Treatment Efficacy of PBI-4050, an Orally Active Antifibrotic Agent, Can Be Monitored by Following Urinary Biomarkers in 5/6-Nephrectomized Rats



Lyne Gagnon, François Sarra-Bournet, Lilianne Geerts, Brigitte Grouix, Alexandre Laverdure, Jean-Simon Duceppe, Boulos Zacharie and Pierre Laurin

PROMETIC BIOSCIENCES INC., LAVAL, QUÉBEC, CANADA

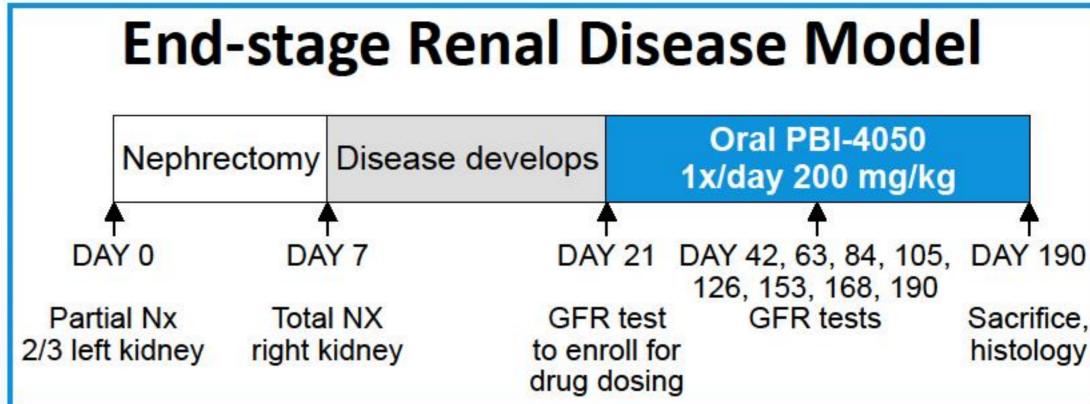
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BACKGROUND AND AIM

PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in Chronic Kidney Disease (CKD) patients, displays antifibrotic activities via a novel mechanism of action. In the present study, we examined the antifibrotic effect of PBI-4050 by evaluating urinary biomarkers in the 5/6-nephrectomized (NX) rats.

METHODS

Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4050 (200 mg/kg, once a day) or vehicle was initiated at day 21, following randomization based on glomerular filtration rate (GFR) results. GFR was measured at day 21 and assessed every 3 weeks up to day 190. Urinary markers were analyzed with Bio-Plex Pro™ rat kidney toxicity panels 1 and 2 (Bio-Rad). Statistics: Student's t-test.



the 5/6-nephrectomized (NX) rats. panels 1 and 2 (Bio-Rad). Statistics: Student's t-test. RESULTS **PBI-4050 Improves Renal Function and Structure GFR URINARY PROTEIN** HISTOLOGY OF KIDNEY LESIONS 1.2-0.45 € 0.40 1.0 ₹ 0.35 0.8 0.6 NX + PBI-4050 Days * p < 0.05*p < 0.05NX NX + PBI-4050 NX NX + PBI-4050 * p < 0.05**Urinary Biomarkers in 5/6-NX Rats β-2-MICROGLOBULIN** NX + PBI-4050 Day 126 Day 153 Day 190 25000-20000-(m) 20000 **20000**-0.0302 15000-0.0002 10000-10000 Conce 5000-NX + PBI-4050 NX NX + PBI-4050 NX NX + PBI-4050 NX (200 mg/kg) (200 mg/kg) (200 mg/kg) **CLUSTERIN** CYSTATIN C Day 190 Day 126 Day 126 **Day 153** Day 190 Day 153 5007 2500 25007 25007 800-1000 Concentration (pg/ml) 1500 - 10 (m/gd) (Jm/600-(m/gd) (m/gd) 0.059 800 0.02 0.006 Concentration (F <u>_</u> 1500-Concentration (0.0043 1000 0.0092 500 NX + PBI-4050 NX + PBI-4050 NX NX + PBI-4050 NX NX NX NX + PBI-4050 NX NX NX + PBI-4050 NX + PBI-4050 (200 mg/kg) (200 mg/kg) (200 mg/kg) (200 mg/kg) (200 mg/kg) (200 mg/kg) KIM-1 CALBINDIN Day 190 Day 153 **Day 126 Day 153** Day 190 100-807 1007 0.8-(Jm/gd) (pg/ml) (lm/gd) 0.0077 Concentration 2.0 Concentration 0.09 0.0035 0.03 20-0.0 NX + PBI-4050 NX + PBI-4050 NX NX + PBI-4050 NX + PBI-4050 NX NX NX + PBI-4050 NX NX (200 mg/kg) (200 mg/kg) (200 mg/kg) (200 mg/kg) (200 mg/kg) MCP-1 **NGAL** Day 190 Day 153 **Day 153** Day 126 Day 190 80007 30007 25007 Concentration (pg/ml) 1500 - 500 - 500 -(Jm/gd) (lm/gd) (Jm/6000-2000-0.0748 4000 0.0041 1000-0.0431 0.0766 2000 0.0944

CONCLUSIONS

NX + PBI-4050

(200 mg/kg)

NX

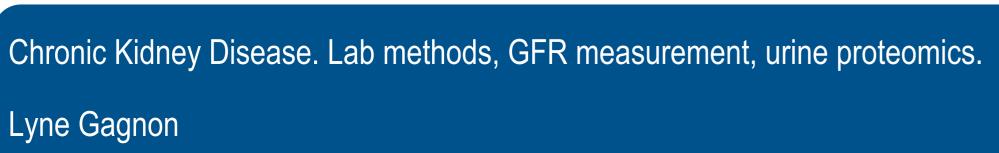
These results suggest that PBI-4050 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and improvement of kidney function. Treatment efficacy can be monitored with urinary biomarkers.



NX

NX + PBI-4050

(200 mg/kg)



NX

NX + PBI-4050

(200 mg/kg)

NX

0.0



NX + PBI-4050

(200 mg/kg)



NX



NX + PBI-4050

(200 mg/kg)