

# PBI-4050 Protects Against Pancreatic Fibrosis in Type II Diabetes



PROMETIC

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## INTRODUCTION

PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in CKD patients, displays antifibrotic activities via a novel mechanism of action. In a double-blind single ascending dose (400 to 2400 mg) in healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in CKD patients with no SAEs observed at 800 mg.

In the present study, we examined whether PBI-4050 affected hyperglycemia, insulin resistance and the development of pancreatic fibrosis in two models of type II diabetes (db/db and eNOS<sup>-/-</sup> db/db).

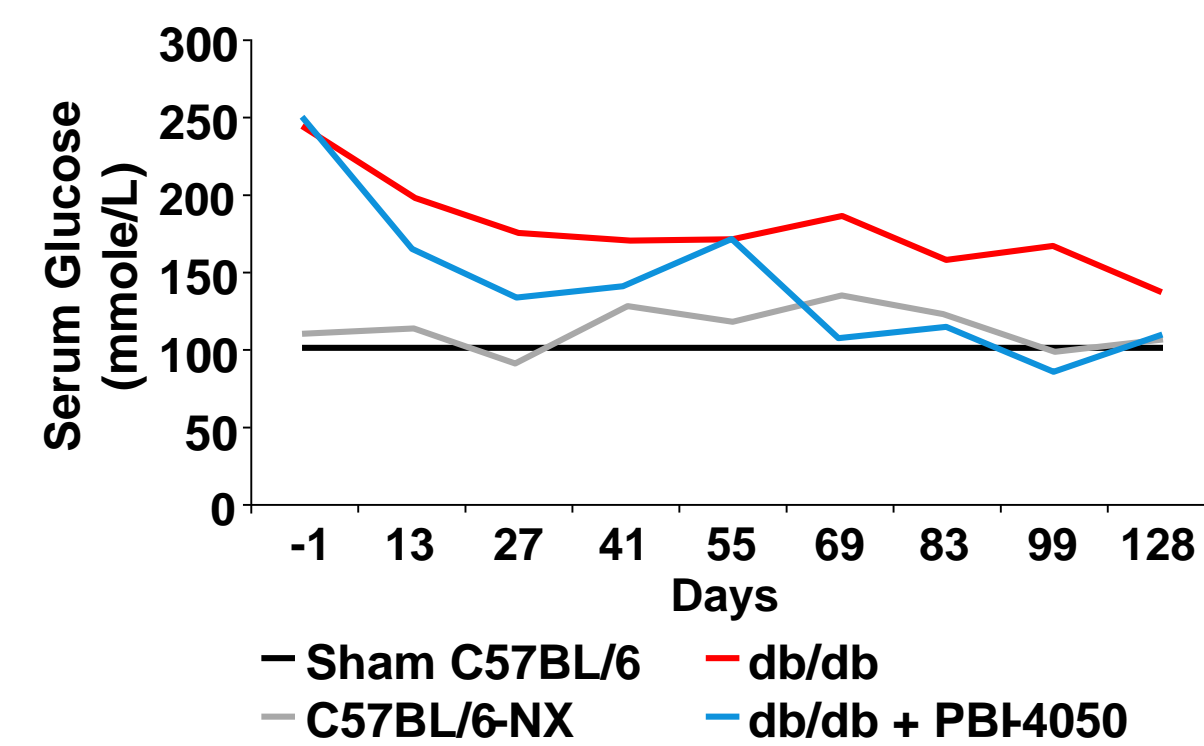
## STUDY DESIGN

Six-week old db/db or C57BL/6 mice were subjected to uninephrectomy (NX) or sham operations. Sham operated mice underwent exposition of the kidney and removal of the perirenal fat. NX animals were treated by gastric gavage with vehicle or PBI-4050 administered once daily at 100 mg/kg. Animals were treated from day 1 to 130. BKS db/db with eNOS knockout (eNOS<sup>-/-</sup> db/db) mice received vehicle (water) or PBI-4050 (200 mg/kg/day) by daily gastric gavage either from 8 to 20 weeks of age (early treatment) or from 16-24 weeks of age (late treatment).

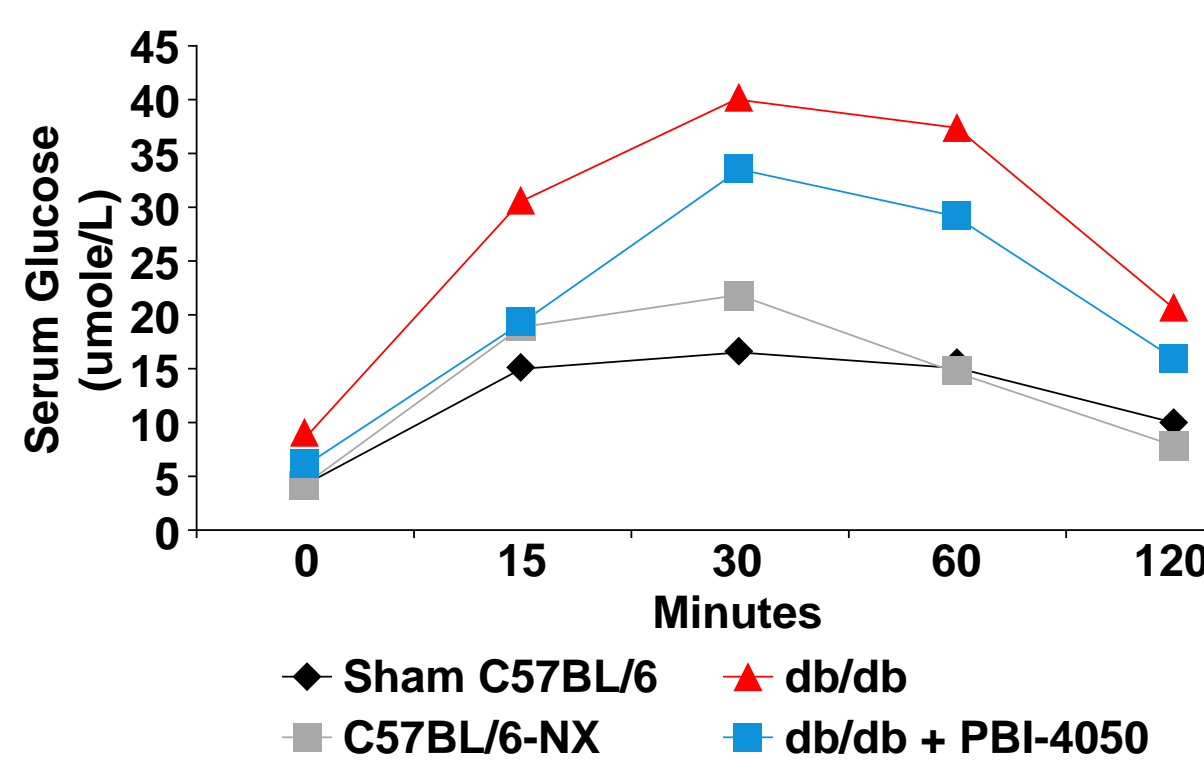
## RESULTS

### UNINEPHRECTOMIZED db/db MICE

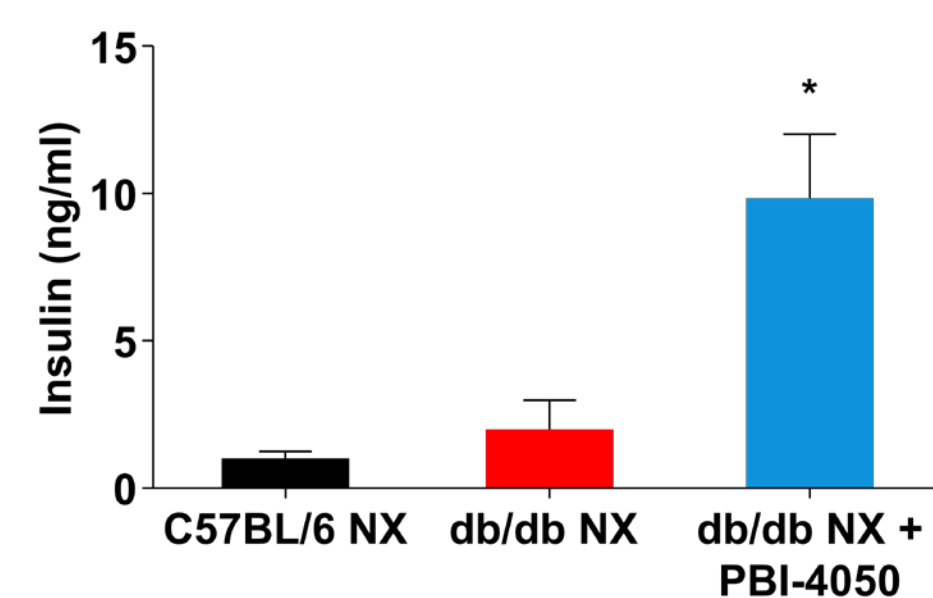
#### 1. PBI-4050 reduces serum glucose measured on 5-hour starved mice



#### 2. PBI-4050 ameliorates oral glucose tolerance test (OGTT)

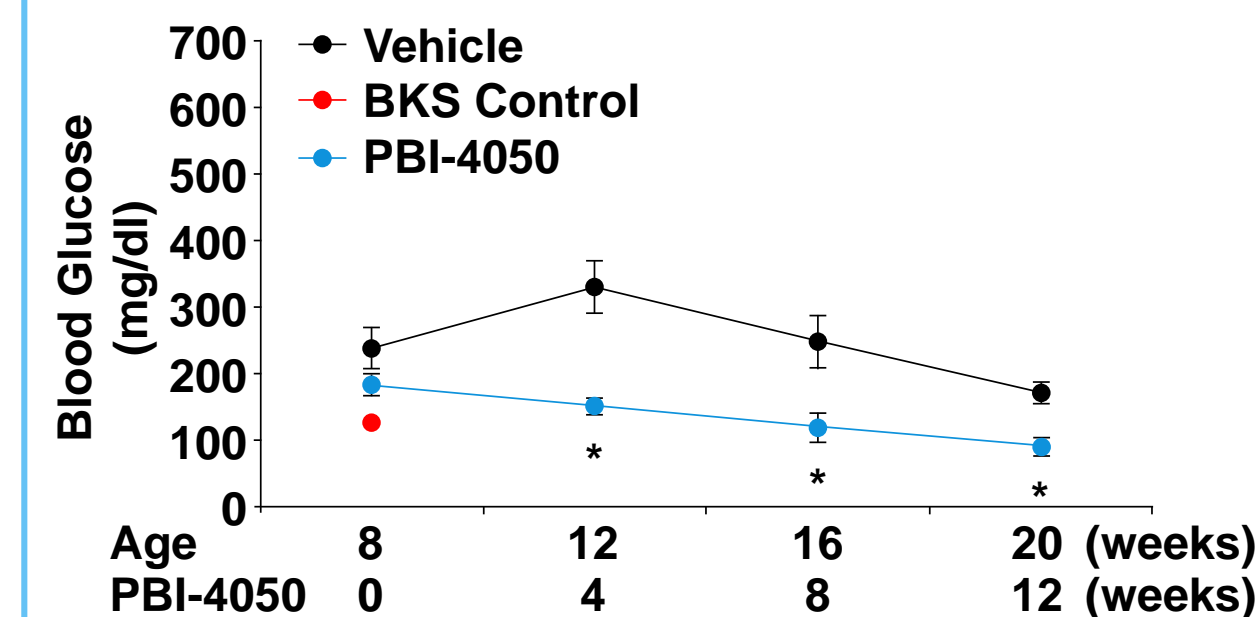


#### 3. PBI-4050 increases serum insulin level

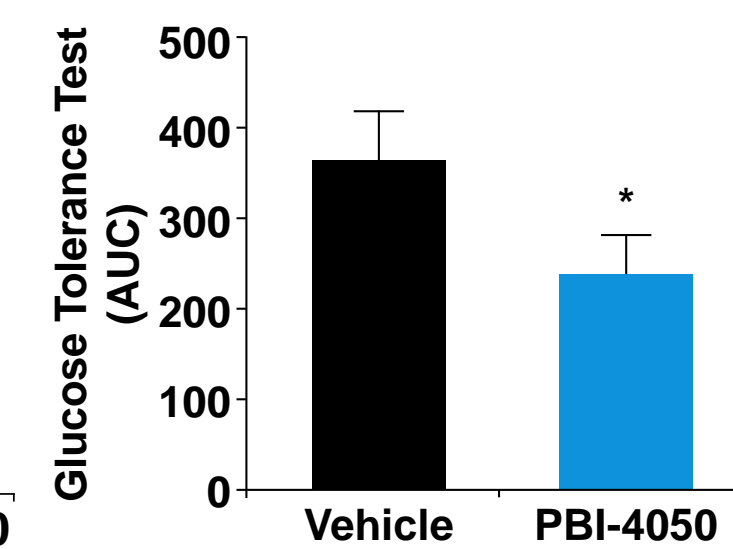
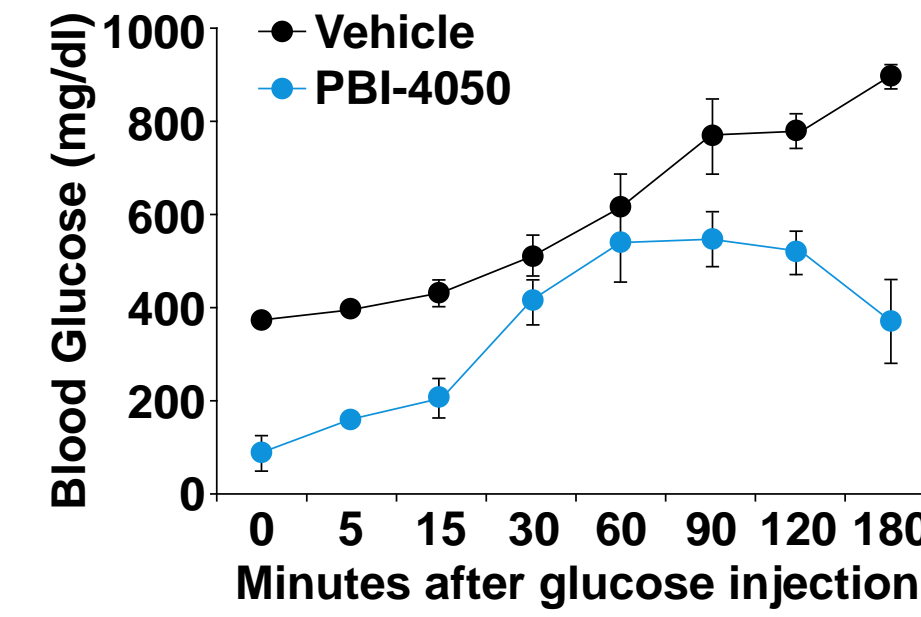


### db/db eNOS<sup>-/-</sup> MICE

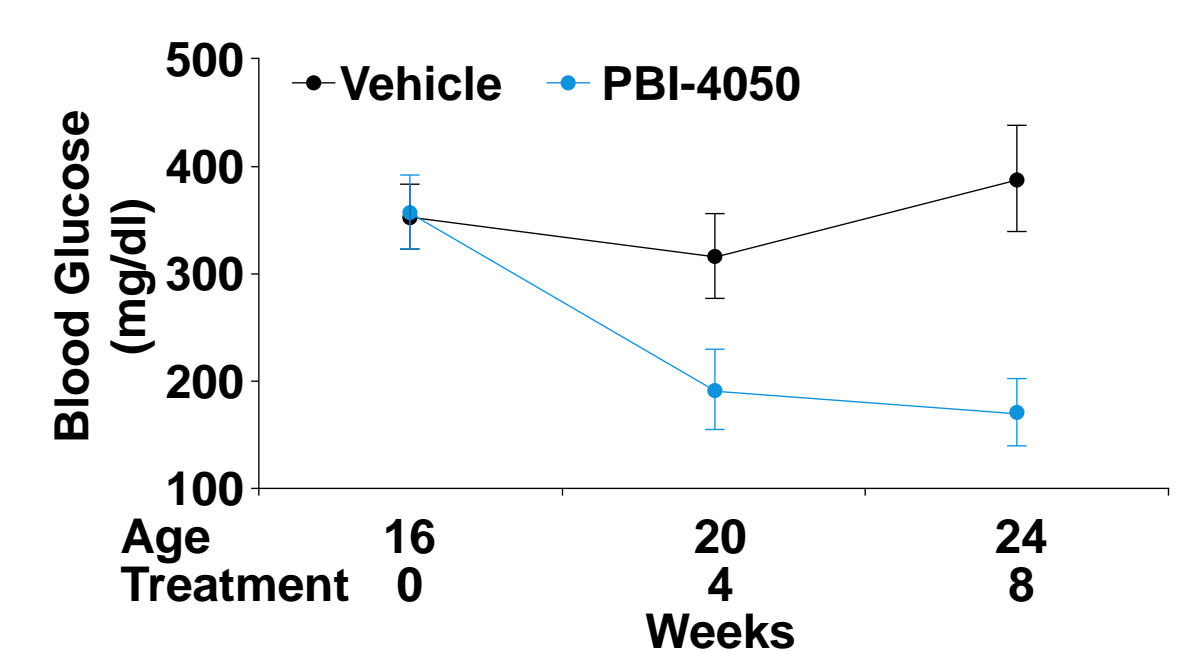
#### 1. Early PBI-4050 treatment decreases blood glucose



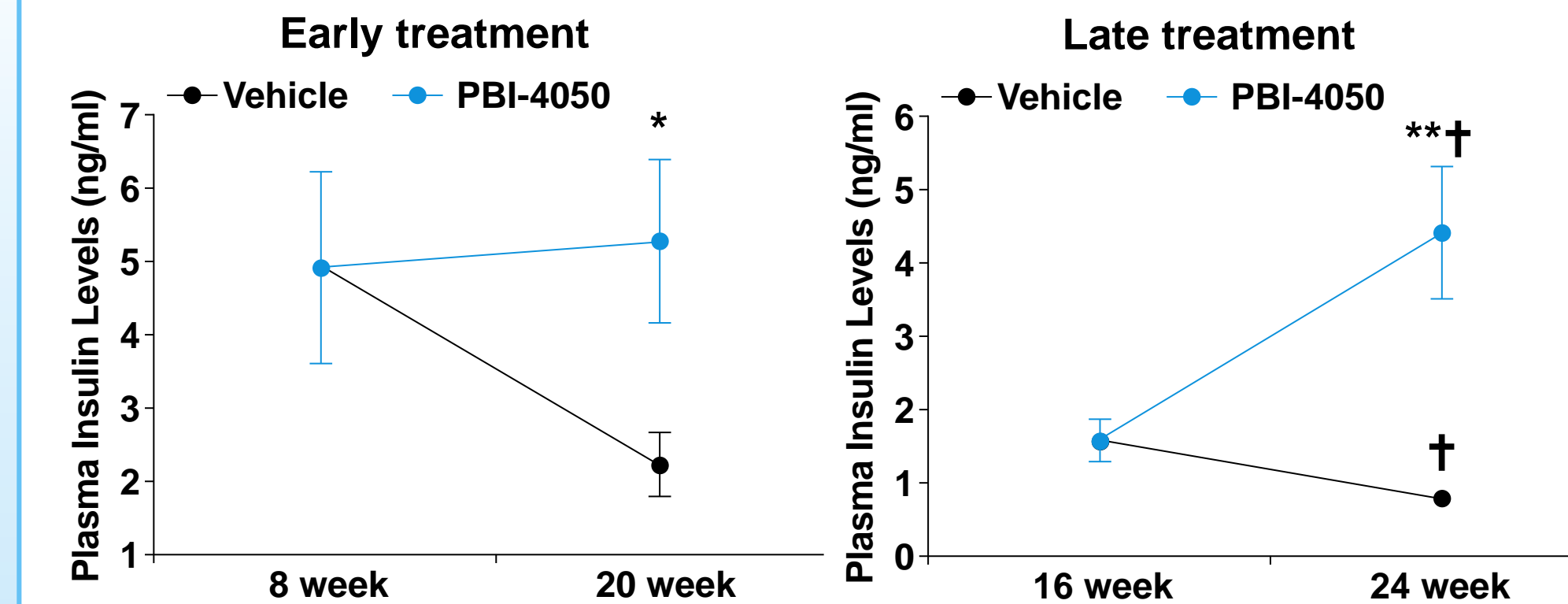
#### 2. Early PBI-4050 treatment ameliorates OGTT



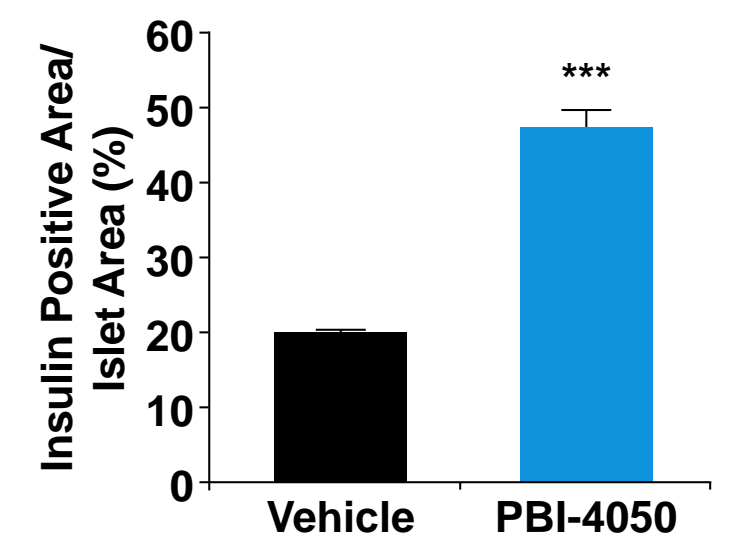
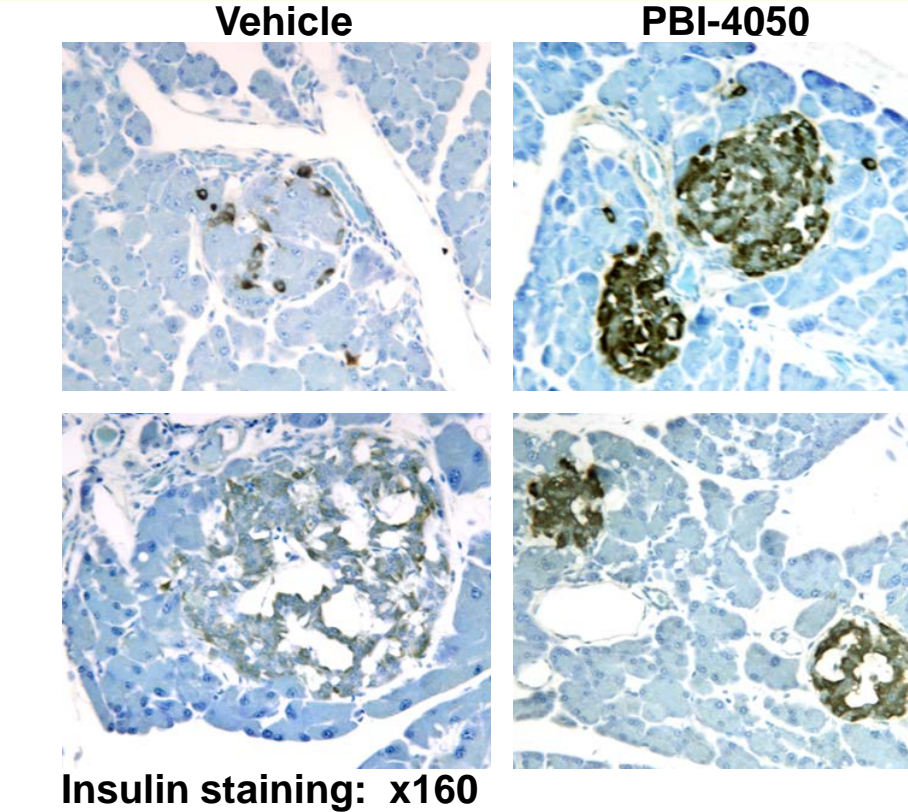
#### 3. Late PBI-4050 treatment decreases fasting hyperglycemia



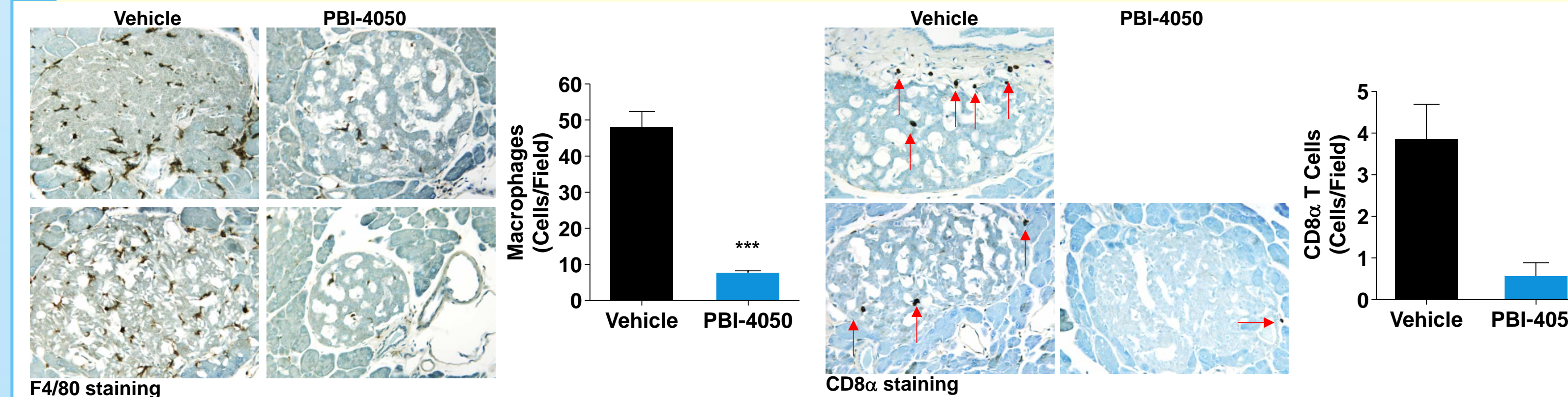
#### 4. Early PBI-4050 treatment preserves and late treatment restores plasma insulin levels



#### 5. Late PBI-4050 treatment preserves islet structure and insulin generation



#### 6. Late PBI-4050 treatment decreases islet leukocyte (macrophage and CD8 cells) infiltration



## CONCLUSION

These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production, and prevents pancreas islet fibrosis in association with a decrease in CD8 and macrophage infiltration.