Supporting Information

Discovery of an orally efficacious positive allosteric modulator of the glucagon-like peptide-1 receptor

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SUPPLEMENTARY MATERIAL

1. oGTT of LSN3318839 in GLP-1R KO mice
2. Selectivity data for LSN3318839

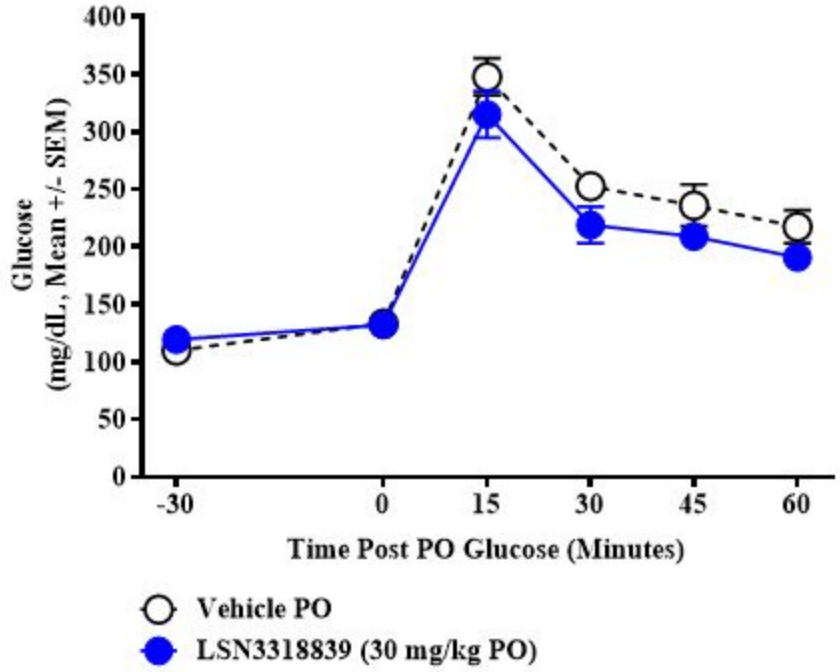

Figure S1. Time course of glucose levels in overnight-fasted GLP-1R KO mice treated orally with LSN3318839 alone followed 30 minutes later by an oral dose of dextrose (3 g/kg). Results are expressed as mean ± S.E.M. No statistical significance was observed for any time point versus vehicle.

Selectivity data for LSN3318839

Selectivity data was obtained at Eurofins (Luxembourg). All assays were using human receptors and channels. Assays tested: Cav1.2 (antagonist mode functional), ERG

(Dofetilide binding), NET (Nisoxetine binding), 5HT2B (agonist, PAM, and antagonist functional), ADORA3 (agonist, PAM, antagonist), ADRA1A (agonist, PAM, antagonist), ADRA2A (agonist, PAM, antagonist), ADRB1 (agonist, PAM, antagonist), ADRB2 (agonist, PAM, antagonist), D1 (agonist, PAM, antagonist), D2L (agonist, PAM, antagonist), H1 (agonist, PAM, antagonist), and OPRM1 (agonist, PAM, antagonist).

All tested assays were inactive (<50% inhibition at 1mM and 10 mM or EC_{50}/IC_{50} > 10 mM) with the exceptions of: 5HT2B (PAM mode 14 % stimulation at 1 uM and 94 % stimulation at 10 mM), ADORA3 (Agonist mode 5% stimulation at 1 mM, 86% stimulation at 10 mM), D2L (Agonist mode 37% stimulation at 1 mM, 69% stimulation at 10 mM), D2L (PAM mode 31% stimulation at 1 mM, 51% stimulation at 10 mM), M2 (Agonist mode 40% stimulation at 1 mM, 59% stimulation at 10 mM).

Internal assays testing LSN3318839 in PAM mode using human receptors: 1uM or 10 uM concentration of LSN3318839 did not shift the EC_{50} of GIP (2-42) or Gcg (2-29) in the GIP-R and the Gcg-R respectively.