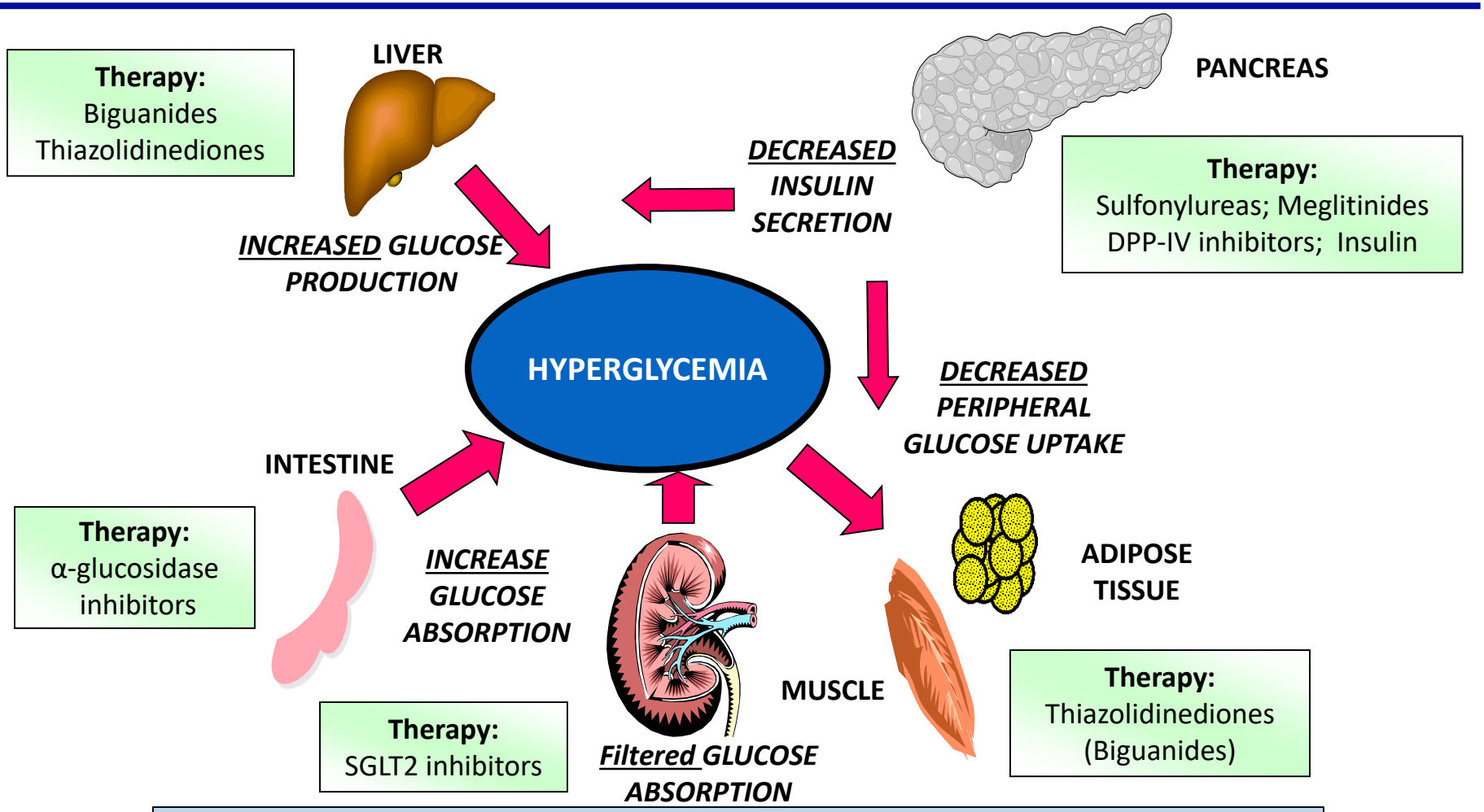
GKM-001

A Novel Liver-Selective Glucokinase Activator with Robust Glucose Lowering and No Hypoglycemia

Liver-Selective GK Activation is a Novel Mechanism of Glucose Lowering

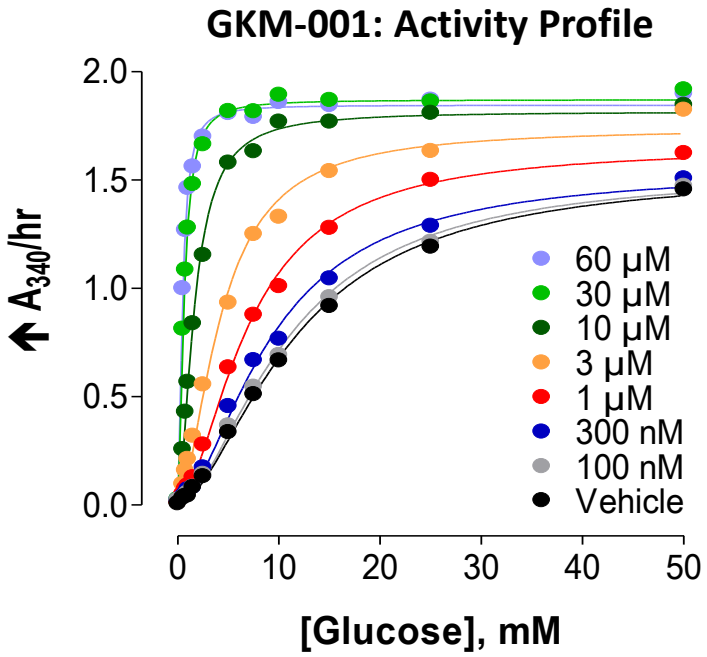


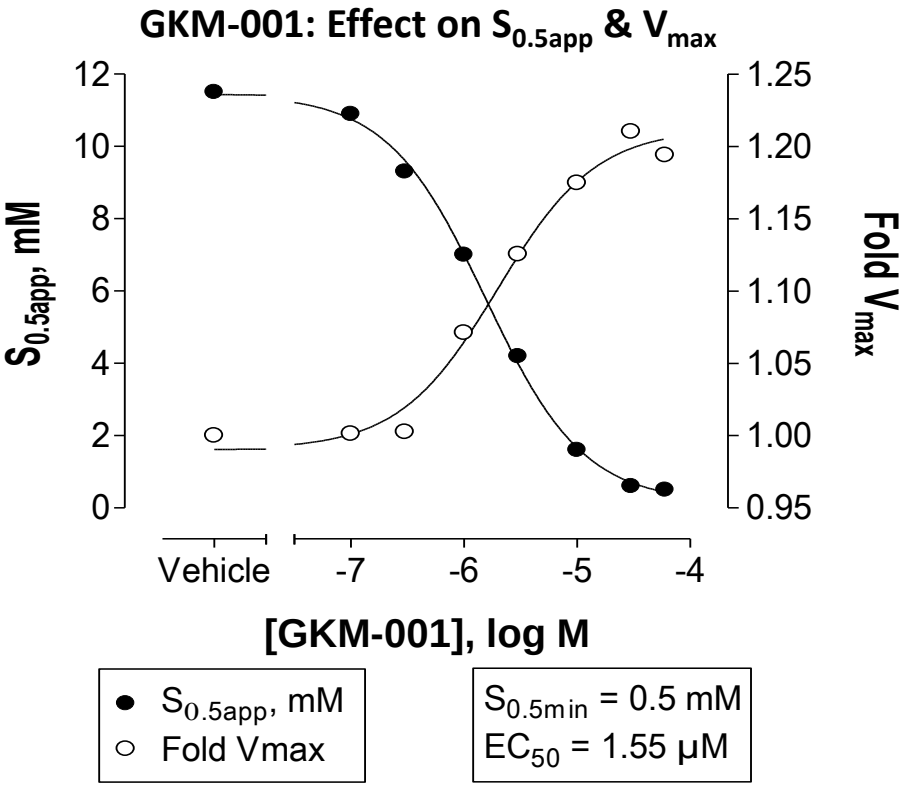
Liver Selective GKAs increase glycogen storage, substrate cycling in the liver and reduce Hepatic Glucose Output: Combination with many other mechanisms

GKM-001: A Potential "First-in-Class" Glucokinase Activator

- GKM-001 is a novel, liver-selective Glucokinase activator (GKA)
- Demonstrated glucose Lowering without hypoglycemia in normal and Type II Diabetes Mellitus (T2DM) subjects in single ascending dose study and in T2DM in a 14 day multiple ascending dose (MAD) study despite an apparent 21 hours half life – early but strong evidence of proof of concept in humans
- Robust fasting and post-prandial glucose lowering achieved without hypoglycemia validating pre-clinical efficacy and safety data – right balance of potency, liver selectivity and PK providing efficacy without hypoglycemia associated with pan GK activators
- Unlike pan active GKAs, GKM-001 appears to have no effect on insulin secretion as evident from *in vitro* studies and the lack of increase in C-peptide in T2DM patients
- Ideal Pharmacokinetic properties for the intended indication and patient population
  - Half-life & duration of PD effects support QD dosing
  - Low apparent volume of distribution
  - No food effect
  - Dual routes of elimination
  - Low variability and linear kinetics
  - Not a substrate or inhibitor of any P450
- In the MAD study in T2DM patients, no clinically relevant adverse events, changes in vital signs (including blood pressure) and changes in laboratory values were observed including liver enzymes & lipids – triglycerides, cholesterol and non-esterified fatty acids
- 90-day safety studies successfully completed to initiate additional clinical studies including a 12-week Phase IIb (effect on HbA1c) study
- US, EP Composition of Matter patent granted (US 8501955)

GKM-001: Intrinsic Allosteric Activation of GK

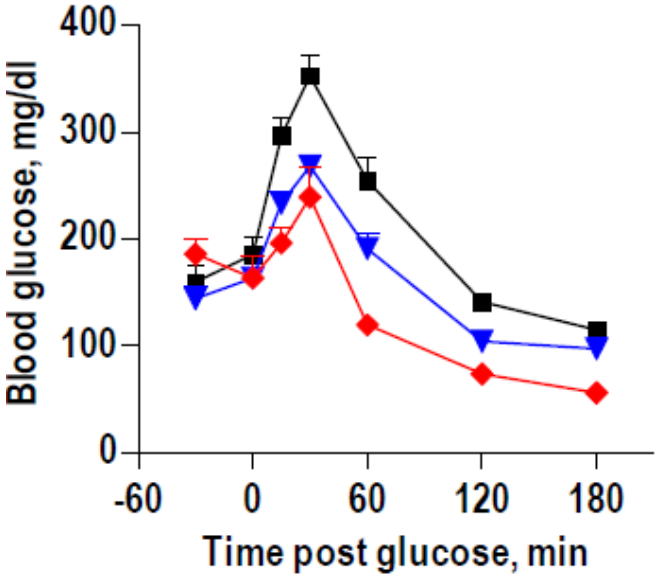




Human GK Enzyme Assay	EC_{50} = 1.55 µM; $S_{0.5}$app = 0.5 mM; V_{max}app = 1.2 fold
Rat GK Enzyme Assay	EC_{50} = 4.3 µM; $S_{0.5}$app = 0.9 mM; ΔV_{max}app = 1.4 fold
Hexokinase Selectivity	No effect at 10 µM compound

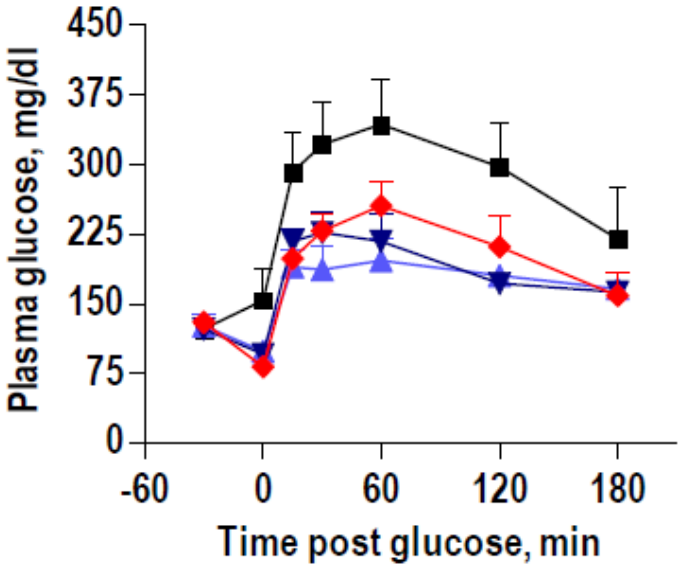
Single Doses of GKM-001 Result in Significant Acute Reduction in Plasma Glucose Following OGTT in Diet-Induced Obese (DIO) Mice and Zucker *fa/fa* Rats

DIO C57BL/6J Mice



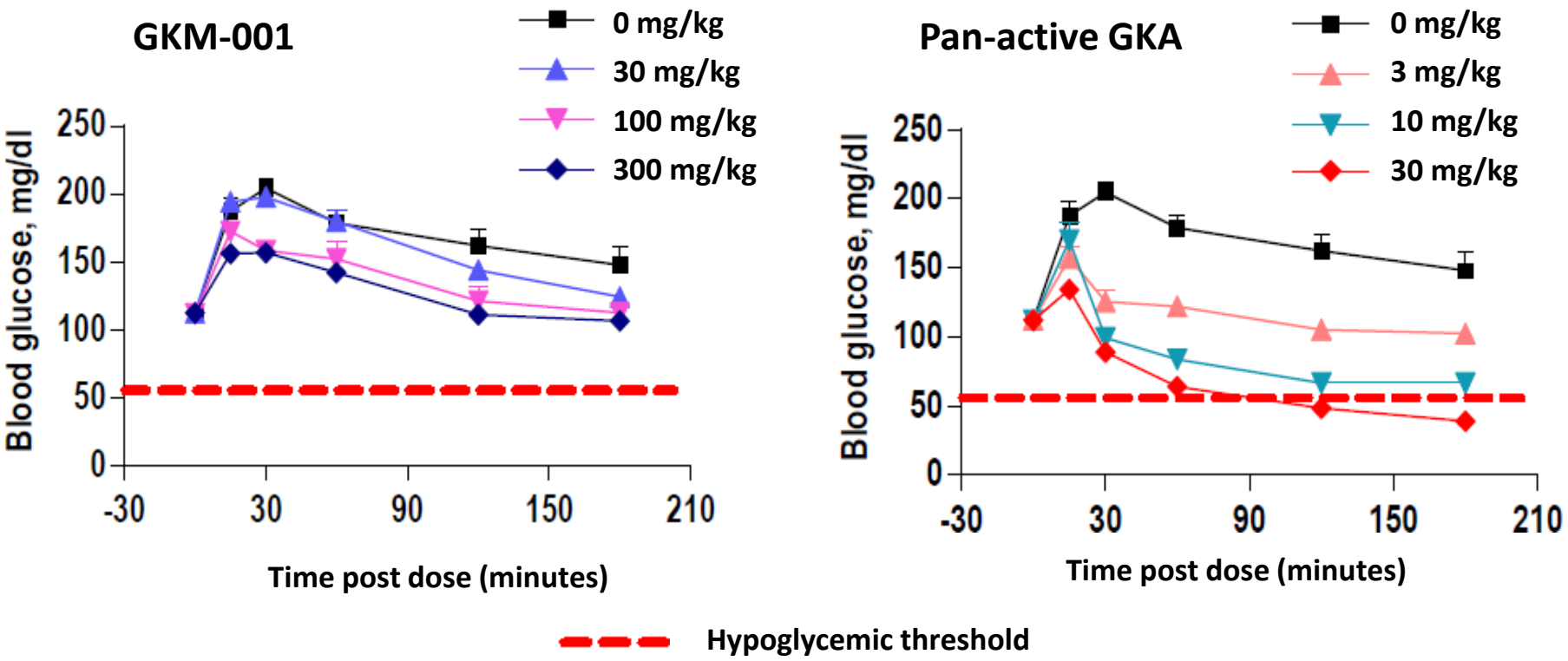
- Vehicle, 10 ml/kg
- GKM-001, 30 mg/kg
- Pan-active GKA, 10 mg/kg

Zucker *fa/fa* Rats



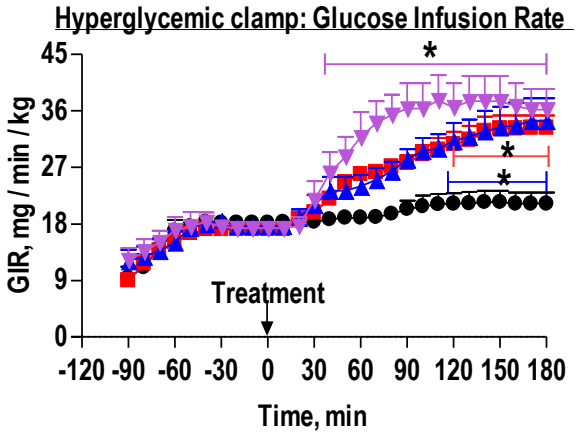
- Vehicle, 10 ml/kg
- GKM-001, 50 mg/kg
- GKM-001, 100 mg/kg
- Pan-active GKA, 10 mg/kg

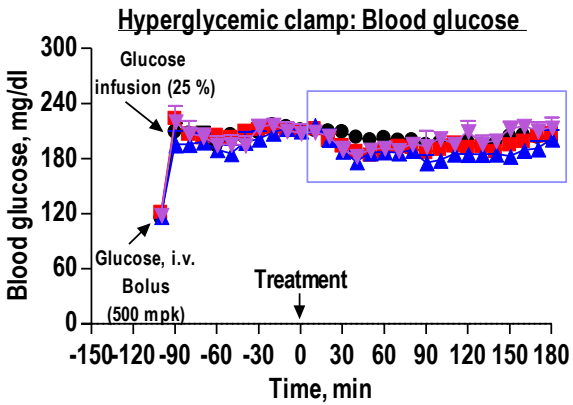
Pre-clinical Evidence: GKM-001 does not Induce Hypoglycemia in Fasted Normoglycemic Mice over a Wide Range of Doses

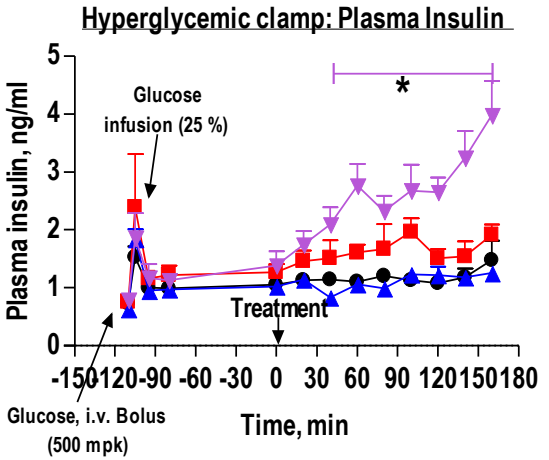


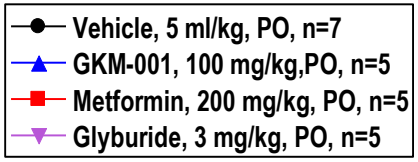
GKM-001 dose of 300 mg/kg did not induce hypoglycemia in mice while a dose of 30 mg/kg of a comparator pan-active GKA induced hypoglycemia in mice

GKM-001 Acts Selectively at the Liver as Shown by a Hyperglycemic Clamp







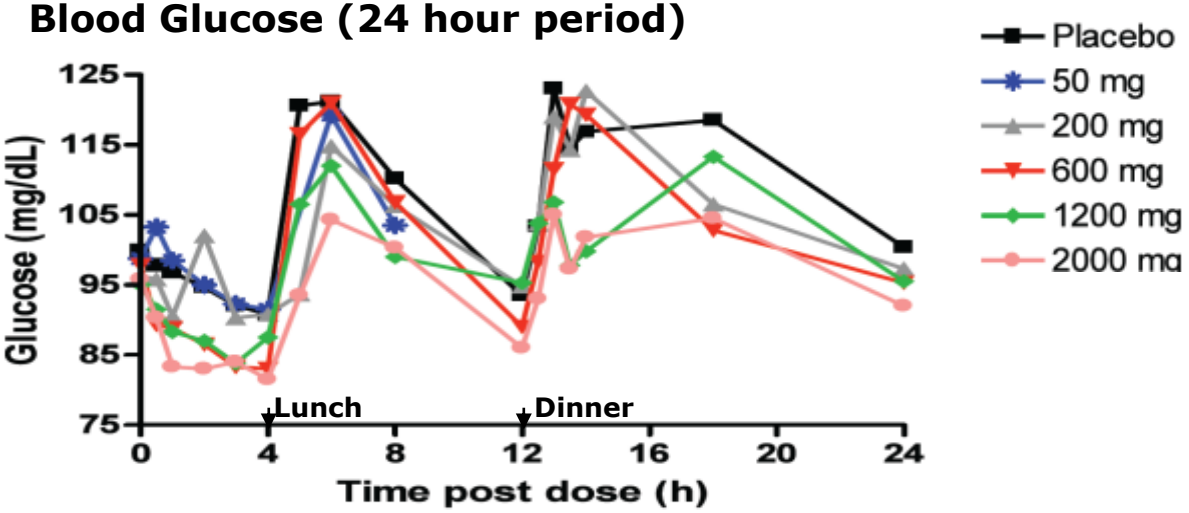


Data is shown as Mean ± S.E.M. Two way ANOVA followed by Bonferroni's test, * P < 0.05

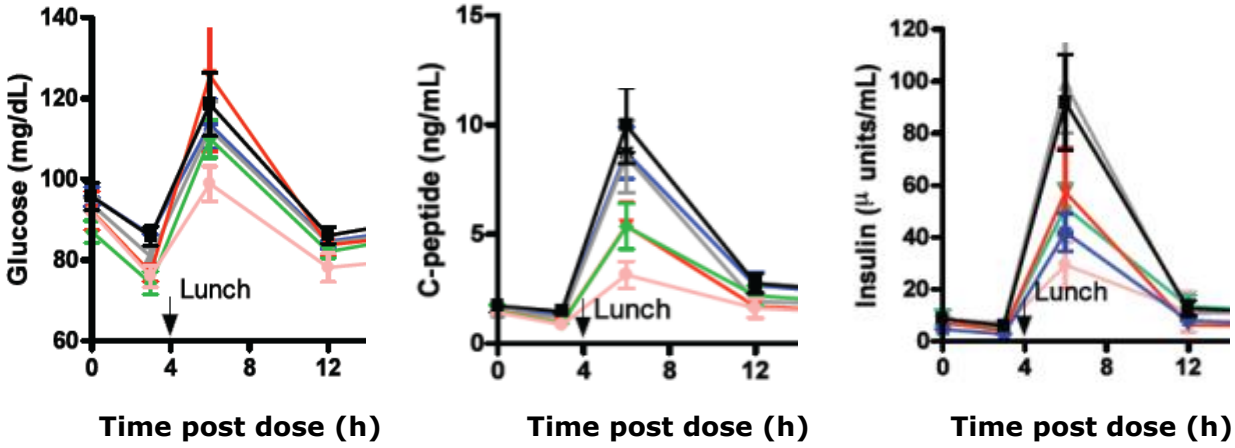
- GKM-001 showed significant increase in Glucose Infusion Rate to maintain similar levels of hyperglycemia as compared to vehicle treatment
- GKM-001 did not show significant change in plasma insulin during hyperglycemic clamp as compared to vehicle treatment
    - Glyburide showed significant increase in plasma insulin during hyperglycemic clamp as compared to vehicle treatment

SAD Study in Healthy Subjects Shows Glucose and Insulin Lowering, No Hypoglycemia

Blood Glucose (24 hour period)



Serum levels (post lunch)

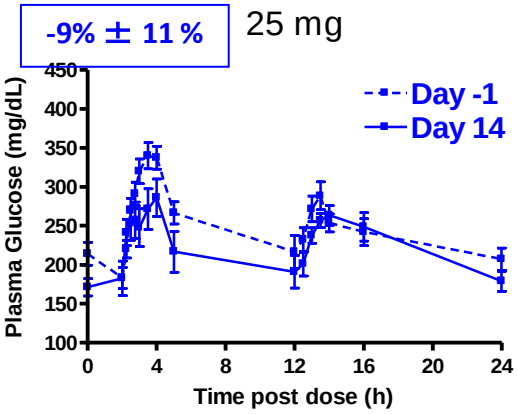


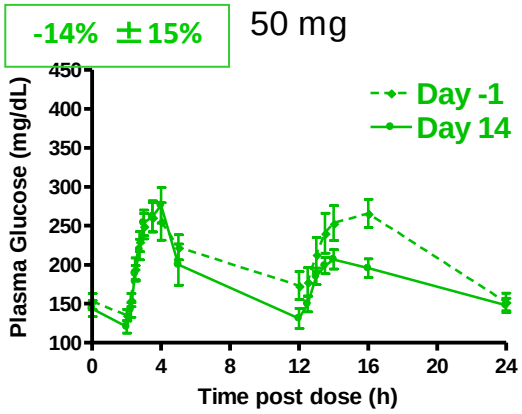
Size of Trial: 30 subjects in 5 panels

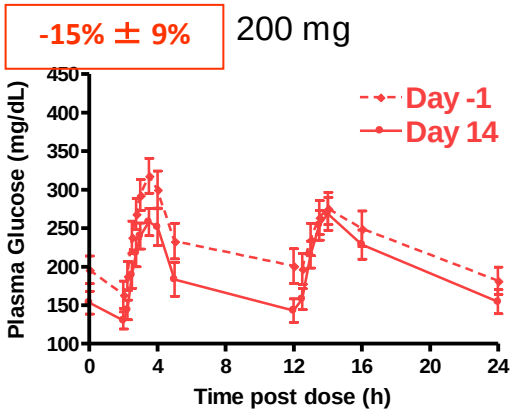
- No hypoglycemia up to 2000 mg in healthy subjects
- Improved post-meal glucose control
- Reduced serum C-peptide and serum insulin excursions

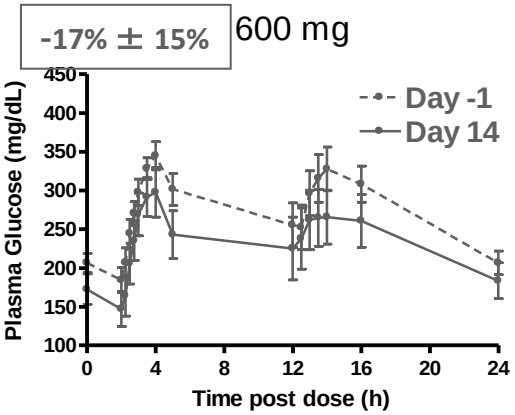
GKM-001 Shows 24-h Plasma Glucose Lowering in T2D Subjects after 14 Days of Dosing

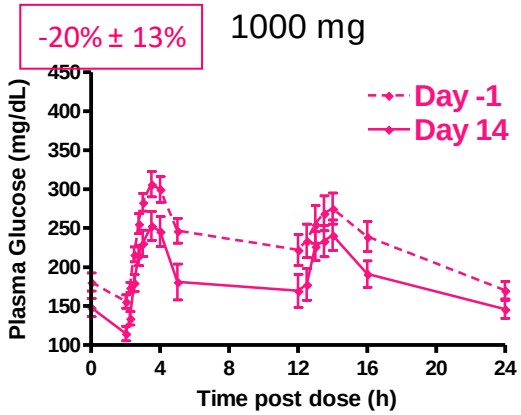
Percent reduction in 24 h glucose AUC on Day 14 relative to Day -1 shown in box within each graph

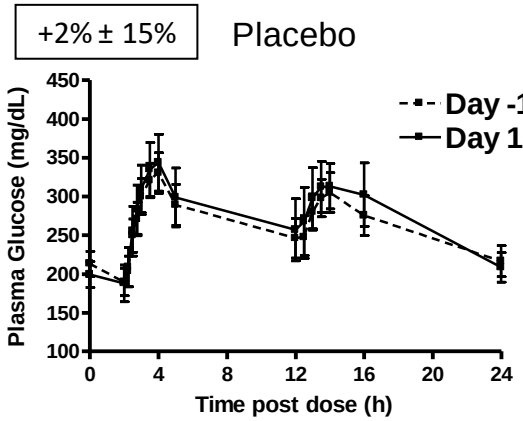




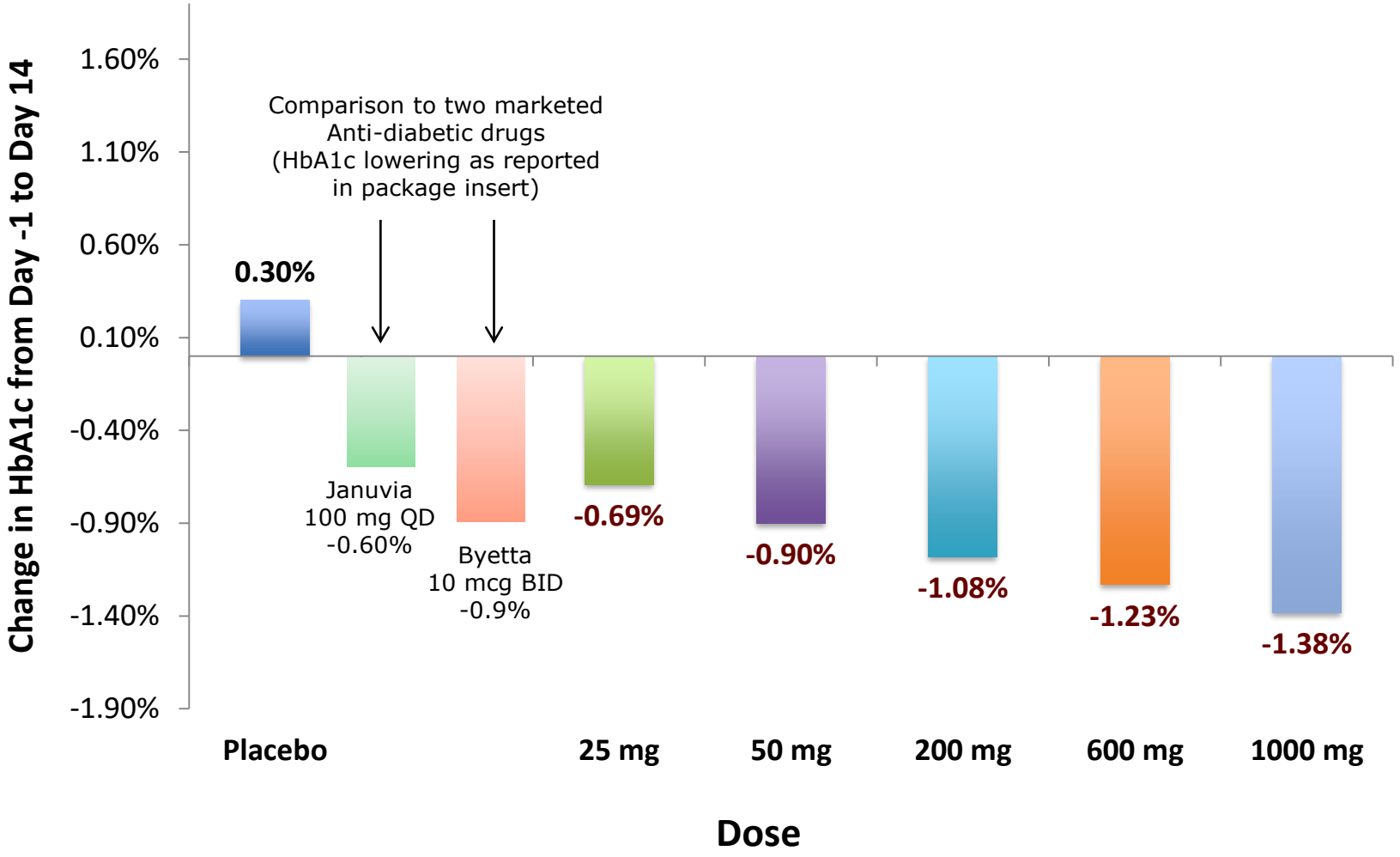




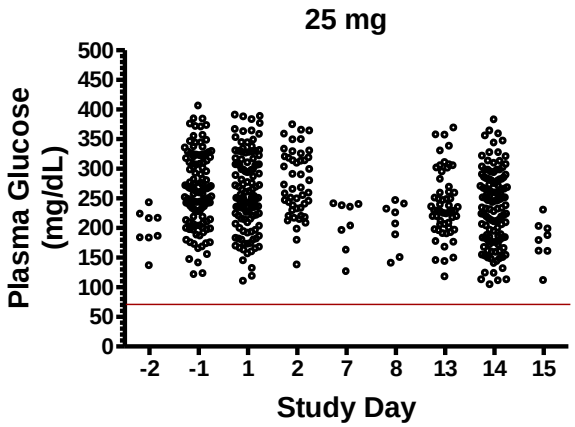


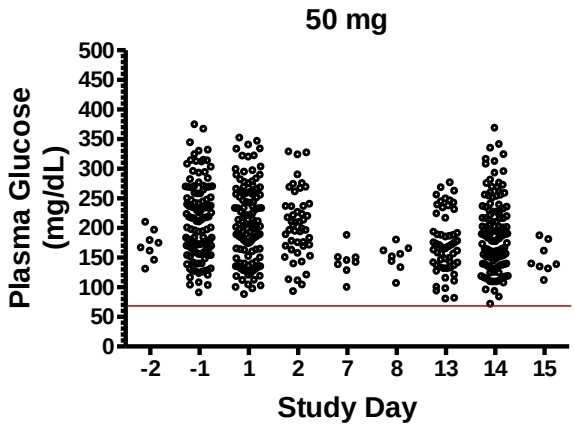


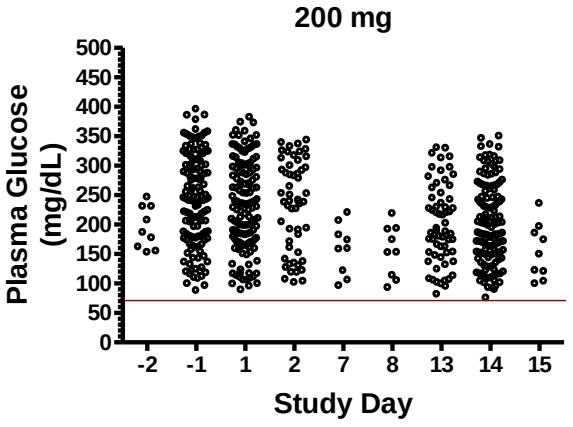
Predicted Change in HbA1c Based on 14d Treatment with GKM-001 Shows a Dose-Dependent Reduction

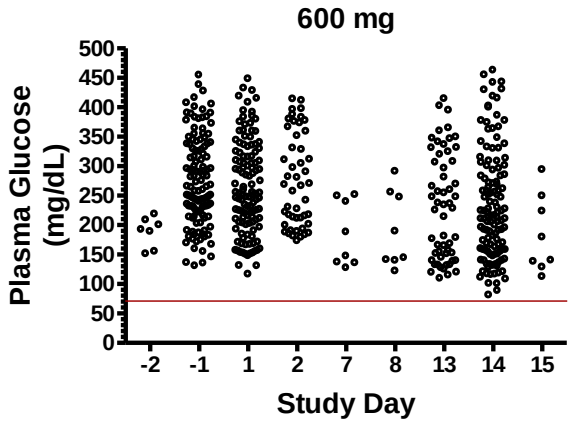


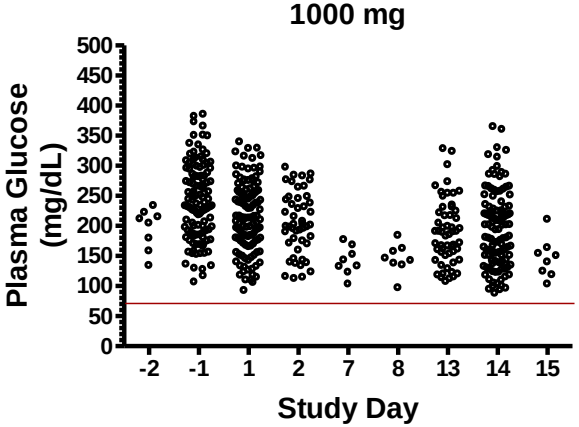
No Hypoglycemia Throughout the MAD Study in T2DM Patients

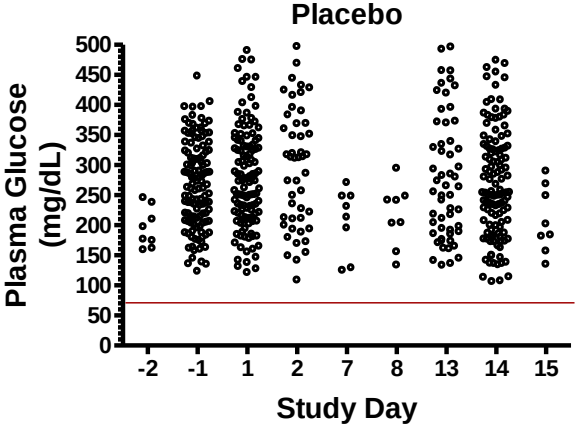








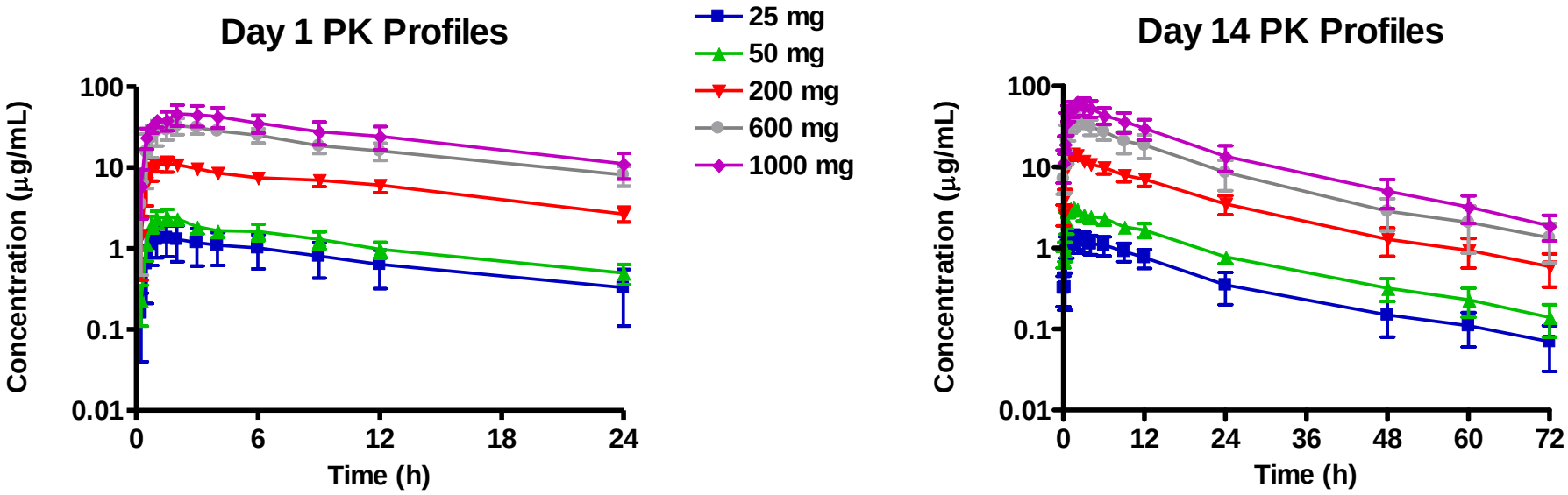




With 12 hours of overnight and 2 hours of post-dose fasting, a total of 14 hours of fasting – no hypoglycemia at steady state

Red line in each graph represents the hypoglycemia threshold of 70 mg/dL

PK Profiles (Human) on Day 1 and Day 14 (Mean ± SD)



- Dose related increase in exposure on Day 1 and Day 14
- About 1.5-fold accumulation after repeated once-daily dosing
- No food effect
- Terminal elimination half-life of about 21 h supports QD dosing
- Dual route of elimination – about 25% of dose recovered unchanged in urine

The Clinical Profile for GKM-001 Generated Positive Feedback from U.S. and EU KOLs

Positive view on liver-selective GKAs

- KOLs generally had a positive response to liver-selective GKAs due to its combination of safety, efficacy, and novel MOA
- Liver-selective GKAs generated more KOL enthusiasm than other future product classes, including SGLT-2s, pan-active GKAs, and generic DPP-IVs
  - Physicians did not view a pan-active GKA favorably as the risk of hypoglycemia would likely prevent significant use
  - KOLs favored GKAs over SGLT-2s as SGLT-2s have the potential to cause urinary tract infections and have an MOA that does not address the root cause of diabetes

Differentiation from DPP-IVs

- Improved efficacy and novel MOA differentiate the class from DPP-IVs
  - GKAs are believed to have superior efficacy to DPP-IVs
  - Independent consultant has projected that availability of generic DPP-IVs will have only a minor impact on GKA sales volume as physicians articulated a significant level of clinical differentiation between GKAs and DPP-IVs

Likely use primarily in combination therapy

- KOLs expect GKAs to be primarily used in combination with metformin
  - KOLs expect GKA use as a monotherapy will be confined to patients that experience side effects with metformin
  - KOLs also anticipate limited combination with insulin-based therapy due to GKAs' insulin-independent MOA

GKM-001: A Recap

- A potential “First-in-Class”
- Liver selective mechanism with potential for b cell sparing
- Safety profile in both pre-clinical and clinical studies support further development – No incidence of hypoglycemia at any dose level
- Robust glucose lowering established in Multiple Ascending Dose studies on T2DM patients without a single incidence of hypoglycemia over a 40-fold dose range
- Favorable Pharmacokinetic properties for the intended indication and patient population – 21 hour half life, text book linear PK, low apparent volume of distribution ,dual route of elimination and no food effect
- Process Chemistry developed, long term stability of API established and Formulation Development of Tablet dosage form underway
- A back up Compound with different Chemistry and clear differentiation identified
- Toxicology studies to support a 12 week Phase IIb (effect on HbA1c) study successfully completed

Thank You