LGD-6972:

Glucagon Receptor Antagonist

Highly Potent, Orally-Bioavailable, Small Molecule Glucagon Receptor Antagonist for the Treatment of Type 2 Diabetes

Overview

- Diabetes is one of the largest and fastest growing medical markets with major growth projected for future need
  - $33 billion worldwide annual sales in 2012
  - Estimated to grow to $60+ billion by 2020
- Despite existing therapies, significant need for novel mechanism to improve glycemic control
- Glucagon Receptor Antagonists may provide an effective treatment for Type 2 Diabetes Mellitus either alone or in combination with other anti-diabetic drugs
- Clinically validated mechanism
- LGD-6972 is a novel, highly potent and selective Glucagon Receptor antagonist with an attractive preclinical profile

Diabetes: Significant Health Issue

- 371 million people worldwide with diabetes
  - 25.8 million in U.S., 8.3% of population
  - 1.9 million Americans diagnosed with diabetes every year
  - 90-95% of cases have Type 2 diabetes
- Diabetes is leading cause of kidney failure, non-traumatic lower-limb amputations and new cases of blindness among adults in U.S.
  - 7th leading cause of death, with over 71,000 deaths in U.S. each year
  - Will be 7th leading cause of deaths worldwide by 2030
  - More deaths per year from diabetes than breast cancer and AIDS combined
- $245 billion annually attributable to diagnosed diabetes in U.S.
  - $176 billion in direct costs and $69 billion in indirect costs (disability, work loss, premature mortality)

Source: American Diabetes Association "Fast Facts" 2013; CDC "National Diabetes Fact Sheet" 2011; WHO Diabetes Fact Sheet; International Diabetes Federation Atlas, 2012 Update

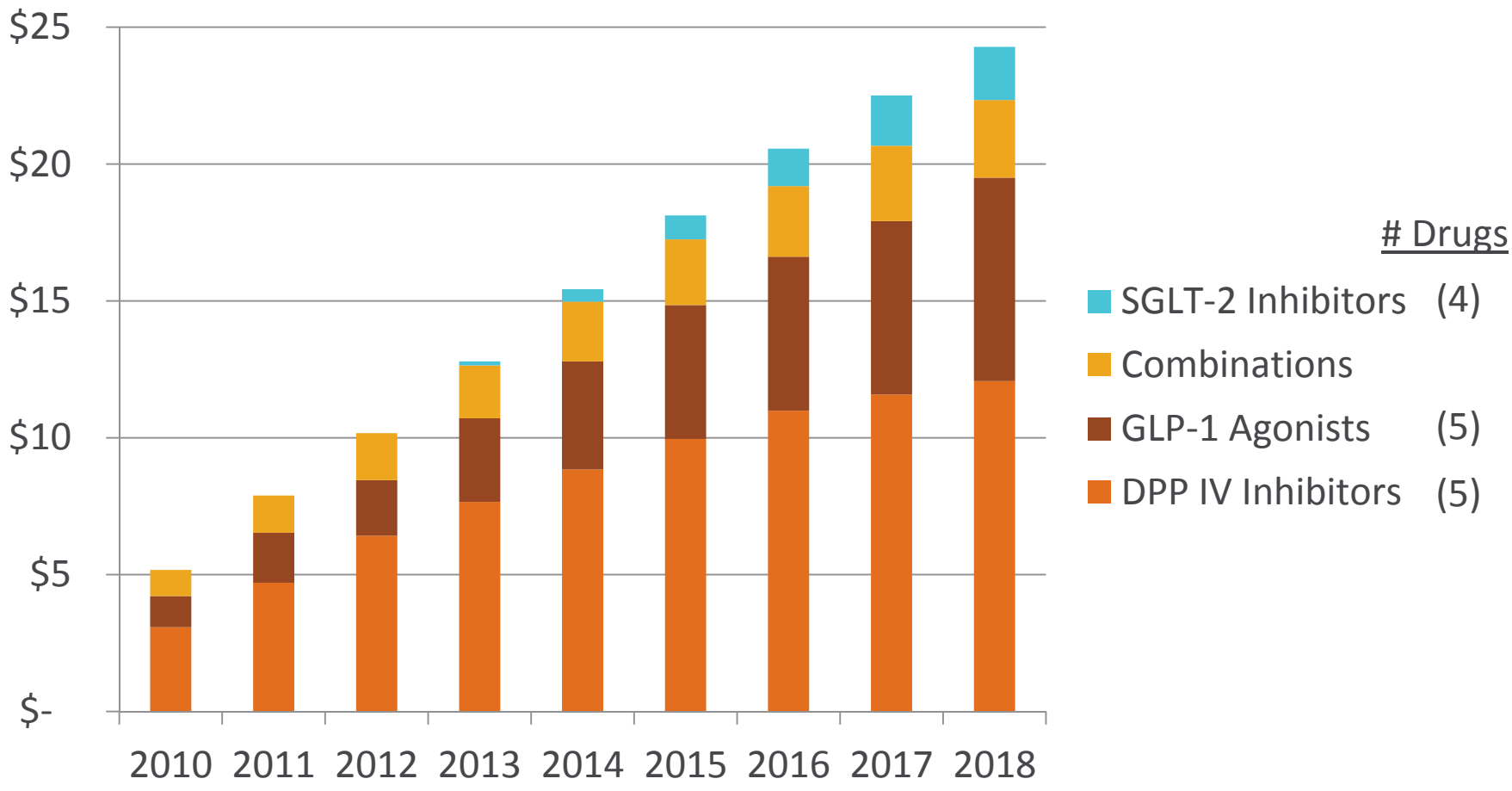
Glucagon Antagonists: Opportunity

- Large patient population with diabetes
  - Despite availability of multiple medications and practice of combination therapy, the majority of T2DM patients fail to achieve glycemic goals
  - New diabetes drugs, DPPIV inhibitors and GLP-1, are under scrutiny for potential risks of pancreatitis and thyroid cancer
- GCGR antagonists are expected to be effective across a broad population of patients with T2DM
  - Lean and obese T2DM patients with elevated hepatic glucose production
  - Advanced T2DM patients with increased glucagon-to-insulin ratio
  - Increased GLP-1 levels may benefit beta cell function
- $33B market for novel therapeutics in 2012, projected to grow to over $60B in 2020
  - Possible that 20% of market in 2020 could be from novel MOAs

Source: Brinson Patrick MNKD report 12/3/12; SunTrust LLY report 6/25/13

Significant Opportunity for Branded Therapies

$Billions



Source: Thomson Reuters, annual reports

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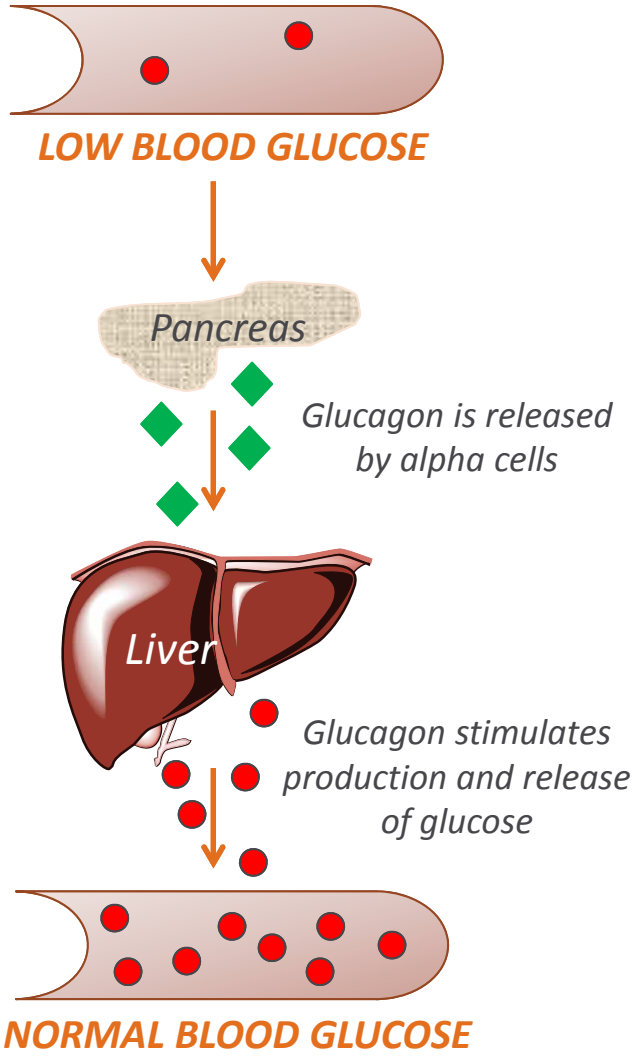
LGD-6972: Glucagon Receptor Antagonist

Scientific Background



- Glucagon, acting on its receptor, increases glucose production by opposing the actions of insulin
- In type 2 diabetes, high levels of glucagon exacerbate hyperglycemia
- Reducing glucagon action markedly lowers plasma glucose and triglycerides
- Applicability for **both** fasting and post-prandial hyperglycemia

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LGD-6972: Pre-Clinical Profile

- Highly potent and selective antagonist of the human glucagon receptor (hGCGR)
  - IC50 ~ 1 nM
- Potent and efficacious in animal models of T2DM and T1DM
- Good oral bioavailability and low clearance rate in animals predict low, once-a-day dose in humans
- No safety issues observed in preclinical GLP safety pharmacology or genotoxicity core batteries (ICH guidance S7A and S2(R1))
- Well tolerated with large safety margin in 28-day GLP toxicity studies in rat and monkey
- Efficient scale-up route developed and GMP API manufactured

LGD-6972: *In Vitro* Pharmacology

- Highly potent glucagon receptor binding
- Potent antagonist in functional assay
  - More potent in primates vs. rodents
- Selective activity vs. related GPCRs

GCGR Inhibition Across Species

Species	cAMP IC_{50} (nM)
Human	0.5
Monkey	0.7
Rat	103
Mouse	150

Selectivity vs. Related Receptors

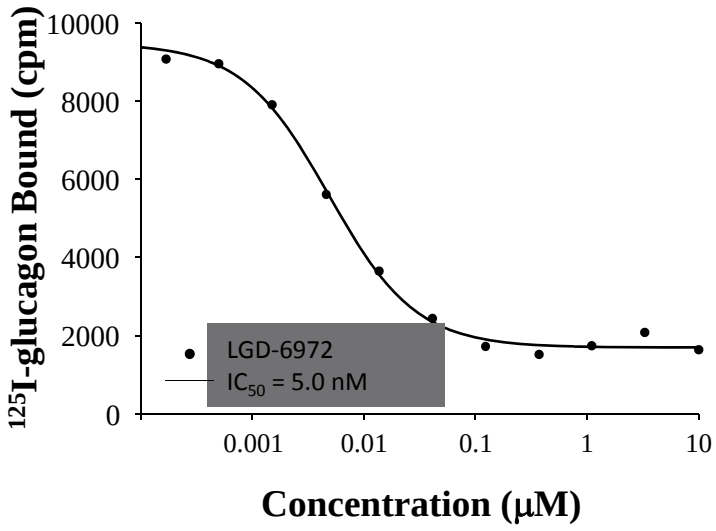
Receptor	cAMP IC_{50} (nM)
hGCGR	0.5
hGLP-1R	>10,000
hGIPR	3,000

American Diabetes Association (ADA) 72nd Scientific Sessions; Philadelphia, PA, USA; June 8-12, 2012

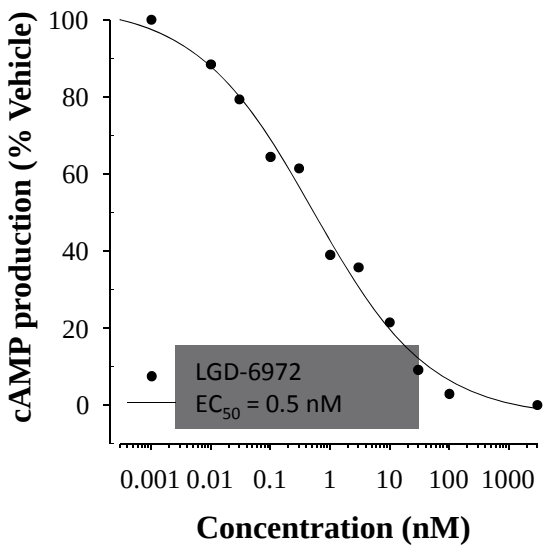
LGD-6972: Antagonism of Glucagon Action

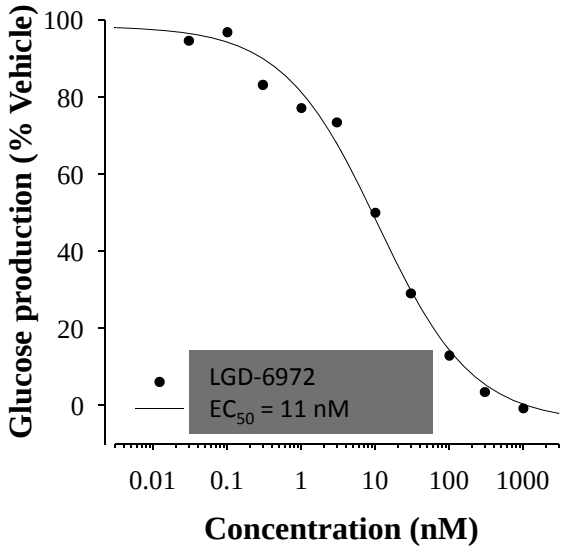
LGD-6972 demonstrates high potency in antagonizing hGCGR

Glucagon Displacement (Recombinant hGCGR)



cAMP & Glucose Production (Human Hepatocytes, 0.1 nM Glucagon)





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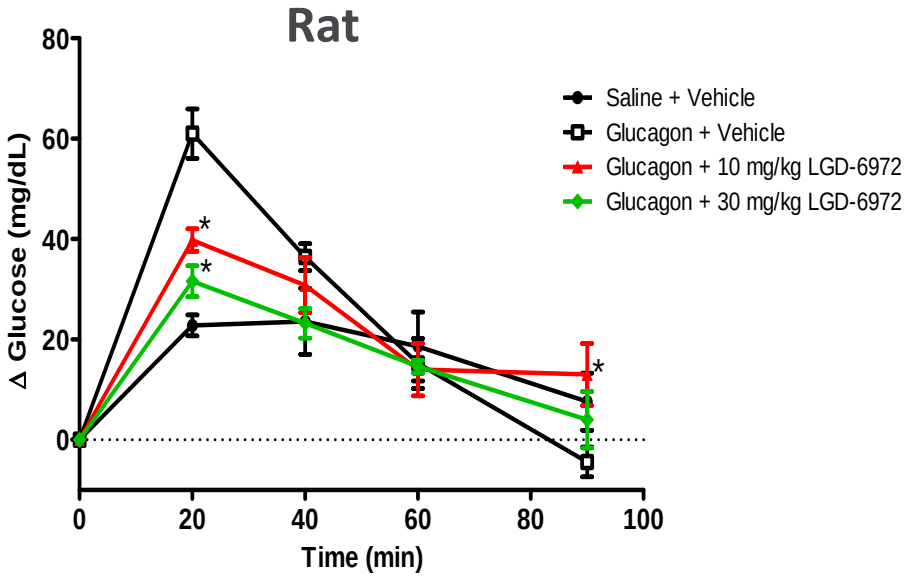
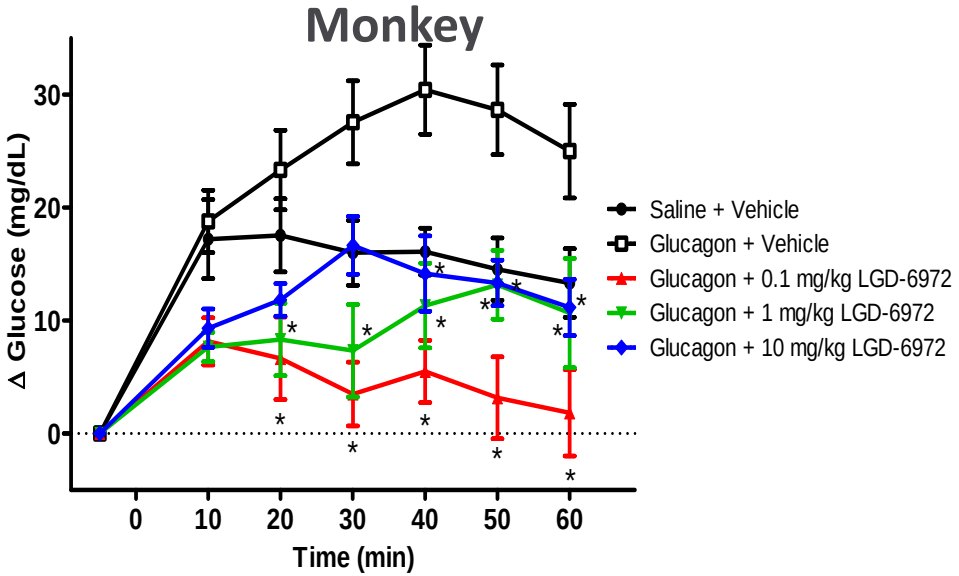
LGD-6972: Acute *in vivo* Glucagon Antagonism

- SD Rats and cynomolgus monkeys dosed p.o. with LGD-6972
- Animals injected with glucagon
- Glucagon-induced elevation of glucose blocked by LGD-6972
  - More potent activity observed in monkey
  - Consistent with in vitro cAMP assay





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LGD-6972: Pharmacokinetics

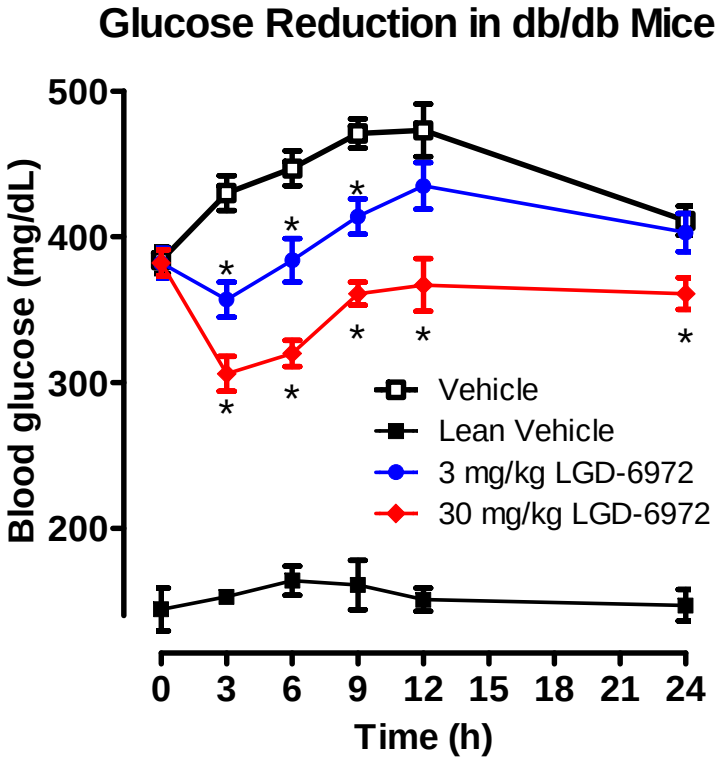
- Good oral bioavailability, slow clearance, and long terminal half-life in multiple species
- Predicted long half-life in humans based on microsomal stability
  - Projections for human dose are very low (2 mg – 30 mg)
  - Lilly glucagon receptor antagonist LY2409021 efficacious starting at 10 mg

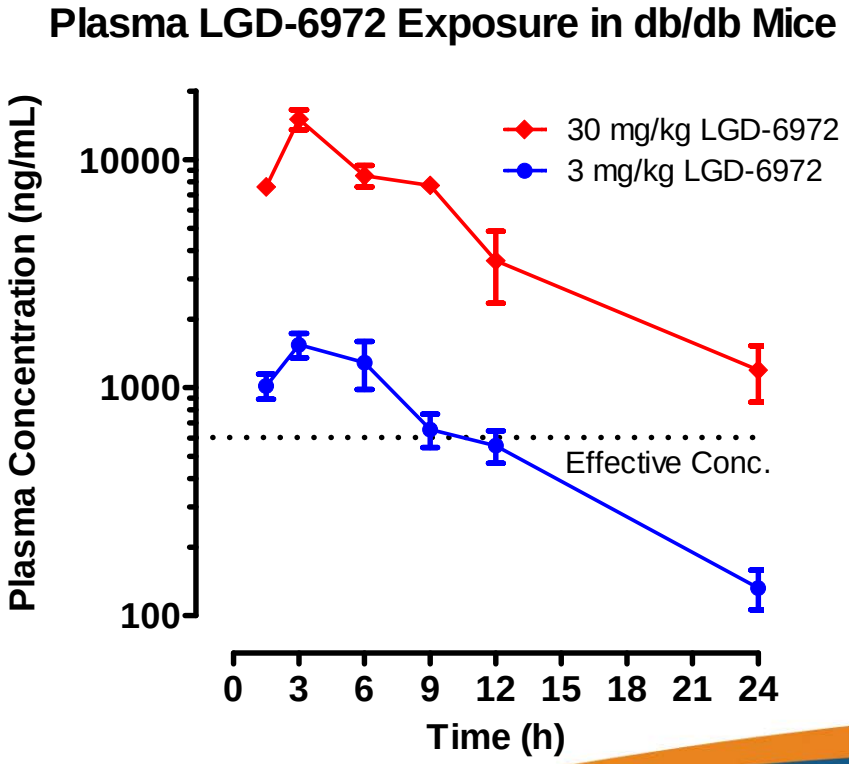
	Dose (mg/kg, po)	C_{max} (µg/mL)	T_{max} (hr)	AUC_{last} (µg•h/mL)	$t_{1/2}$ (hr)	F (%)
Mouse	3	1.71	6.0	16.3	5.9	47
Rat	3	1.33	2.0	7.6	10.9	36
Dog	3	10.9	9.0	225.0	>24	57
Monkey	3	1.10	4.5	9.3	14.9	20

American Diabetes Association (ADA) 72nd Scientific Sessions; Philadelphia, PA, USA; June 8-12, 2012

LGD-6972: PK-PD Relationship

- db/db mice dosed p.o. with LGD-6972
- PK and glucose monitored over 24h interval
- Significant glucose reduction corresponding to plasma concentration of LGD-6972





American Diabetes Association (ADA) 72nd Scientific Sessions; Philadelphia, PA, USA; June 8-12, 2012

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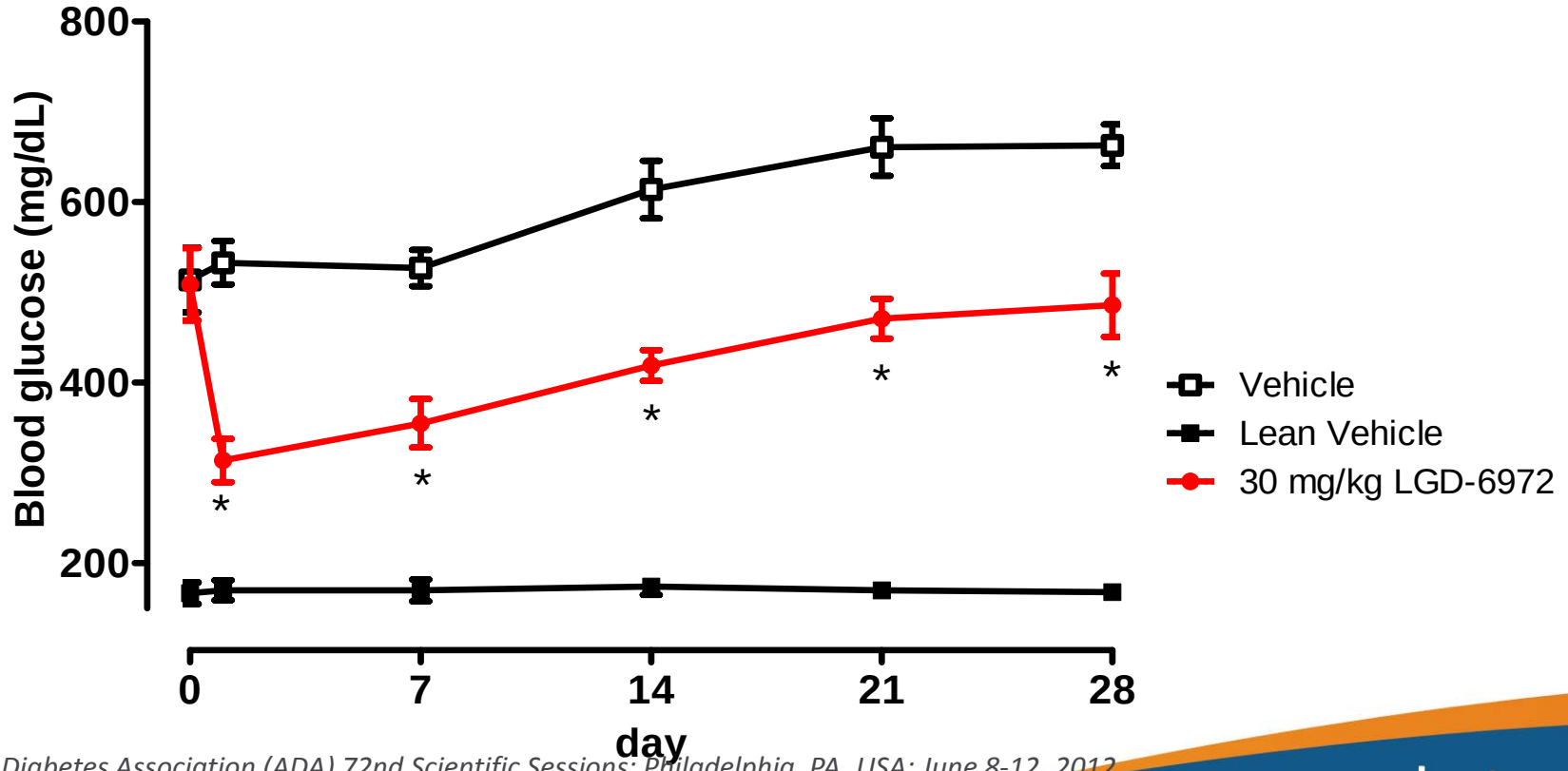
LGD-6972: Chronic glucose reduction in T2DM model

- db/db mice dosed p.o. with LGD-6972
- Glucose monitored weekly for 28 days
- Sustained glucose reduction throughout experiment



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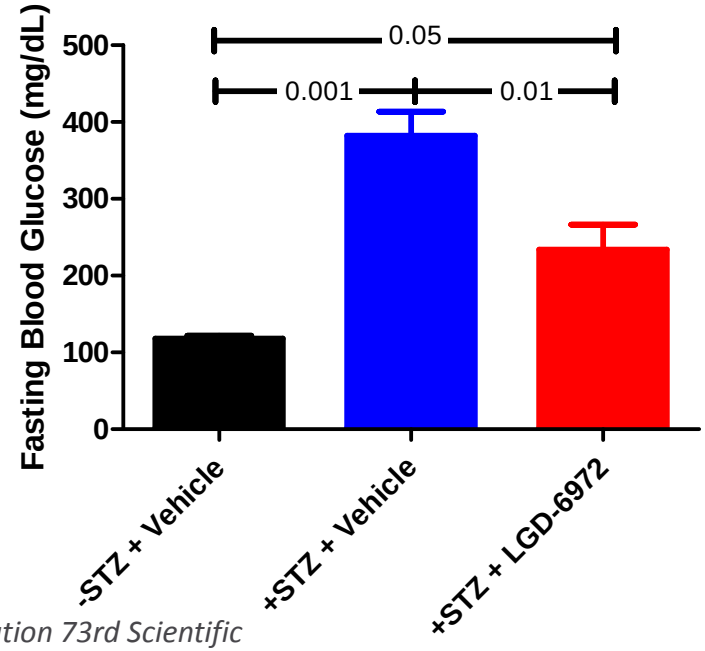
LGD-6972: Glucose Reduction in T1DM Model

- Mice injected with streptozotocin, a beta cell toxin
- Mice dosed p.o. with LGD-6972 after hyperglycemia established
- Significant glucose reduction observed through 28 days



Vajda, et al., *American Diabetes Association 73rd Scientific Sessions; Chicago, IL; June 21-25, 2013*

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LGD-6972: IND-enabling safety and toxicity studies

- No genotoxicity observed in IND-enabling GLP studies
  - Ames Assay
  - CHO cell chromosomal aberration assay
  - In vivo rat micronucleus assay
- No safety pharmacology observations in IND-enabling GLP studies
  - Respiratory safety pharmacology in rats
  - CNS safety pharmacology in rats
  - In vitro hERG patch clamp assay
  - CV safety pharmacology in monkeys
- Well tolerated in 28-day rat and monkey GLP toxicity studies
  - Robust safety margin between NOAEL and efficacious dose

LGD-6972: CMC

- Efficient API manufacturing route has been developed and sufficient drug substance available
  - GMP API synthesized as sodium salt from readily available starting materials
  - Efficient, 6-step synthetic pathway for API
- GMP API made and released sufficient to complete Phase I SAD and MAD studies

LGD-6972: Intellectual Property

- LGD-6972 is covered by two composition-of-matter patent families
  - Nominal patent terms last until 2028-2029 (subject to PTA and terminal disclaimers)
  - Claims allowed or granted in US, Europe and Japan; applications also pending in China, Korea, India, Canada, Mexico, Australia and Brazil

Phase I Clinical Trial Design

- Double-blind, placebo-controlled, randomized ascending single oral dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of LGD-6972 in healthy subjects and subjects with Type 2 Diabetes ("T2DM")
- Enrollment planned for 56 participants with 48 healthy subjects and 8 subjects with T2DM
  - Six groups of healthy subjects and one group of subjects with T2DM
  - n=8 per group (6 LGD-6972 and 2 placebo subjects per group)
- Primary objective: Evaluate the safety and tolerability of single oral doses of LGD-6972 in healthy subjects and subjects with T2DM
- Phase I single-ascending dose study in progress, ClinicalTrials.gov identifier: NCT01919684

Summary

- Glucagon receptor antagonists represent a novel mechanism of action for patients with Type 2 Diabetes, a large, growing market with significant unmet need
- Glucagon receptor antagonism is a clinically-validated mechanism
- LGD-6972 fast follower to Lilly's compound with potentially higher potency
- Commercial precedent for fast followers enjoying superior commercial success to lead program
- Ligand seeking traditional licensing deal comprised of milestones and royalties with experienced partner possessing significant development and commercialization capabilities