Pharmacokinetics and pharmacodynamics of the glucagon receptor antagonist LGD-6972 in a multi-dose clinical trial

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INTRODUCTION

- Glucagon and insulin play counter-regulatory roles in glucose homeostasis.
- In normoglycemic subjects, glucagon is elevated during periods of fasting to mobilize glucose stores. In type 2 diabetes mellitus (T2DM), glucagon can be inappropriately elevated potentially playing a role in hyperglycemia.
- Antagonism of glucagon action has been proposed as a mechanism to reduce blood glucose levels in T2DM.
- We have discovered a novel, selective, orally bioavailable glucagon receptor antagonist and investigated its pharmacokinetics, safety, and pharmacodynamics in a Phase 1 multi-dose clinical trial.

CLINICAL TRIAL DESIGN

Primary Objective:

To assess the safety and tolerability of multiple oral doses of LGD-6972 in normal healthy volunteers (NHV) and T2DM subjects.

Secondary Objectives:

- To characterize the pharmacokinetics of LGD-6972.
- To assess the effects of LGD-6972 on glycemic response.

Study Design: This was a multi-center, randomized, double-blind, placebo-controlled multiple ascending dose study in both NHV (n=12) and T2DM subjects (n=36). Subjects were confined to the clinical pharmacology unit and received standardized meals throughout the 14 day dosing period. The NHV cohort was dosed prior to the T2DM cohorts. Dose escalation occurred in the T2DM subjects after review of safety, tolerability, and preliminary PK data from previous dose levels (n=12/cohort; 3-placebo & 9-LGD-6972). T2DM subjects were on a stable dose of metformin and remained on metformin throughout the trial. All subjects were administered once daily placebo or LGD-6972 as a solution formulated with CAPTISOL® prior to morning breakfast.

Pharmacokinetics: Plasma concentrations of LGD-6972 were measured by a validated LC-MS/MS method. A time-exposure profile was measured throughout a 24 hour period on day 1 and day 14 . Additional trough concentrations were measured at several time points to investigate steady state pharmacokinetics and clearance rates.

Pharmacodynamics: Plasma glucose, glucagon, glucagon-like peptide-1, and insulin were measured. In the 10 mg T2DM cohort, an oral glucose tolerance test was performed on day -1 and day 14. 7-point plasma glucose measurements were performed on day -1 and day 14 for all T2DM cohorts.

SUBJECT DEMOGRAPHICS

Normal Healthy Volunteers		LGD-6972 Dose Level	
		Placebo	15 mg
Number of subjects		3	9
Age (yrs)		47.3 (8.7)	42.3 (10.6)
Gender (n)	Female	0	0
	Male	3	9
Ethnicity (n)	Hispanic or Latino	1	3
	Not Hispanic or Latino	2	6
Race (n)	White	1	4
	African American	2	5
BMI (kg/m^2)		27.4 (1.7)	24.4 (2.9)

Data presented as number of subjects or Mean (SD)

Type 2 Diabetes Mellitus Subjects		LGD-6972 Dose Level			
		Placebo	5 mg	10 mg	15 mg
Number of subjects		9	9	9	9
Age (yrs)		52.2 (6.2)	55.1 (6.0)	58.9 (6.7)	53.6 (8.7)
Gender (n)	Female	6	2	4	5
	Male	3	7	5	4
Ethnicity (n)	Hispanic or Latino	7	5	6	6
	Not Hispanic or Latino	2	4	3	3
Race (n)	White	8	8	7	6
	African American	1	1	2	3
BMI (kg/m^2)		31.0 (4.7)	33.6 (4.2)	32.0 (4.9)	31.3 (5.1)
Baseline HbA1c (%)		8.5 (0.9)	8.2 (0.7)	8.2 (1.1)	8.5 (0.9)

Data presented as number of subjects or Mean (SD)

SAFETY

LGD-6972 was well tolerated with no clinically significant or dose dependent changes in hematology, clinical chemistry, urinalysis, ECG, or vital signs. There were no serious adverse events and no study discontinuations. All treatment emergent adverse events (TEAE) were of mild or moderate severity (grade 1 or 2).

Normal Healthy Volunteers		LGD-6972 Dose Level	
		Placebo	15 mg
Number of subjects		3	9
Any TEAE		1 (33.3)	4 (44.4)
Any study drug related TEAE		0 (0)	2 (22.2)
Detail of study drug related TEAE			
Nervous systems disorders	Headache	0 (0)	2 (22.2)

Data presented as: n(%)

Type 2 Diabetes Mellitus Subjects		LGD-6972 Dose Level			
		Placebo	5 mg	10 mg	15 mg
Number of subjects		9	9	9	9
Any TEAE		4 (44.4)	2 (22.2)	6 (66.7)	4 (44.4)
Any study drug related TEAE		1 (11.1)	1 (11.1)	5 (55.6)	2 (22.2)
Detail of study drug related TEAE					
Gastrointestinal disorders		1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)
	Diarrhoea	1 (11.1)	1 (11.1)	0 (0)	0 (0)
	Nausea	1 (11.1)	0 (0)	0 (0)	1 (11.1)
	Constipation	0 (0)	0 (0)	1 (11.1)	0 (0)
Investigations		0 (0)	1 (11.1)*	0 (0)	0 (0)
	ALT increased	0 (0)	1 (11.1)*	0 (0)	0 (0)
	AST increased	0 (0)	1 (11.1)*	0 (0)	0 (0)
	Blood urine present	0 (0)	1 (11.1)*	0 (0)	0 (0)
	GGT increased	0 (0)	1 (11.1)*	0 (0)	0 (0)
	Neutrophil count increased	0 (0)	1 (11.1)*	0 (0)	0 (0)
	WBC count increased	0 (0)	1 (11.1)*	0 (0)	0 (0)
Nervous systems disorders	Headache	0 (0)	0 (0)	3 (33.3)	1 (11.1)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	0 (0)	0 (0)	1 (11.1)	0 (0)

*Data presented as: n(%); *occurred in one subject starting on day 28, two weeks after treatment ended*

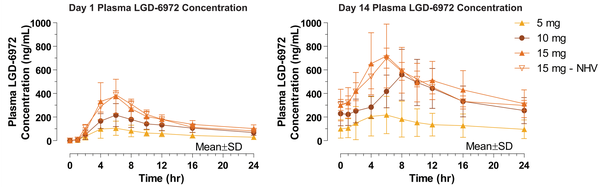
Hypoglycemia: There were no cases of symptomatic hypoglycemia. A single asymptomatic fasting plasma glucose measurement of 69 mg/dL was recorded on day 5 for a T2DM subject receiving 10 mg LGD-6972.

Liver transaminases: Baseline mean ALT was 25.1, 21.2, and 16.0 U/L in the 5, 10, and 15 mg cohorts respectively. Small increases in ALT from baseline were observed by day 14 (15.6, 2.6, and 5.6 U/L, respectively), however the increases were not dose dependent and group means remained within the normal range. One ALT measurement (5 mg dose) was >3x ULN which occurred during the follow up period, 14 days after dosing had stopped. Changes in AST were generally smaller than ALT and there were no changes in bilirubin or violations of Hy's Law.

LDL-cholesterol: No clinically meaningful or dose dependent changes in LDL-cholesterol were observed.

PHARMACOKINETICS

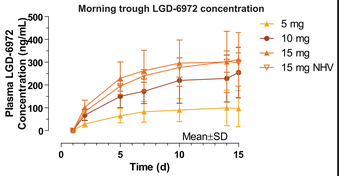
Figure 1. Plasma levels of LGD-6972 were measured by validated LC-MS/MS method. Day 1 LGD-6972 plasma PK profiles were consistent with profiles observed in a previous single ascending dose study. Clearance was slow with a $t_{1/2}$ of approximately 50 hours consistent with a 2-3 fold accumulation upon repeat dosing. AUC and C_{max} increased linearly with dose. At the 15 mg dose, PK parameters were essentially equivalent in NHV and T2DM subjects.



Pharmacokinetic parameters on day 14.

Subjects	Dose (mg)	C_{max} (ng/mL)	d14/d1 C_{max} Ratio	T_{max} (hr)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	d14/d1 AUC Ratio	$t_{1/2}$ (hr)
Normal healthy volunteer	15	708	1.8	6.7	30,519	2.5	51
type 2 diabetes mellitus	5	220	1.9	5.3	11,512	2.4	58
type 2 diabetes mellitus	10	569	2.8	7.8	24,005	3.3	42
type 2 diabetes mellitus	15	759	2.0	5.3	32,787	2.7	51

Figure 2. Morning trough concentrations of LGD-6972 were measured throughout the study. Steady state concentrations were achieved by approximately day 10 in all dosed groups.



PHARMACODYNAMICS

Figure 3. LGD-6972 at 15 mg administered once daily for 14 days reduced fasting plasma glucose in normal healthy volunteers. The reduction in glucose was accompanied by a trend of increasing plasma glucagon.

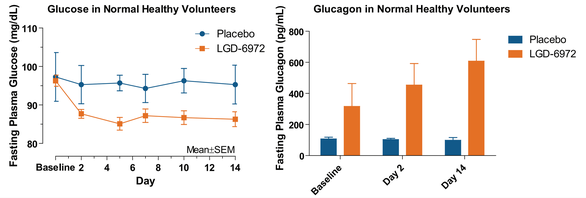


Figure 4. Treatment with LGD-6972 for 14 days reduced fasting plasma glucose in T2DM subjects in a dose dependent manner. LGD-6972 effects were reversible during the follow up period. The maximal baseline adjusted reduction in glucose observed was -60 mg/dL with the 15 mg dose.

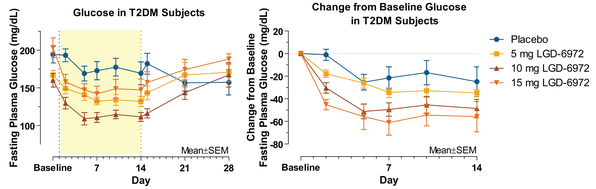


Figure 5. 7 point glucose measurements were performed on day -1 and day 14 in T2DM subjects. LGD-6972 decreased glucose throughout a 24 hour period in both fasting and post-prandial states.

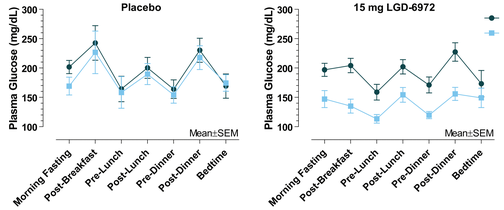
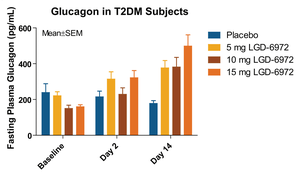


Figure 6. Plasma glucagon concentrations were increased in a dose depedent manner with LGD-6972 treatment in T2DM subjects.



SUMMARY

- LGD-6972 is a potent and selective glucagon receptor antagonist
- In a multiple ascending dose study, LGD-6972 was well tolerated with pharmacokinetics supporting once daily dosing
- LGD-6972 had predictable linear plasma pharmacokinetics
- Pharmacokinetics were comparable in NHV and T2DM subjects
- Dose dependent reductions in fasting plasma glucose were observed
- LGD-6972 reduced glucose in both fasting and postprandial states
- LGD-6972 is a promising agent for the treatment of T2DM

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