A Phase I Study to Investigate the Safety, Tolerability and Pharmacokinetics of a Biased GLP-1R Antibody Glutazumab

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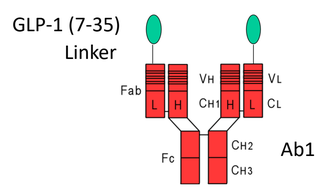
ABSTRACT

GLP-1R is a class B G-protein coupled receptor and a major therapeutic target for type 2 diabetes and obesity. Several GLP-1 analog drugs have been approved for T2DM to achieve good glycemic control and improved β-cell function with hypoglycemia rarely (1, 2). However, the on-target toxicity limited their dosage and any further improvement to the patients.

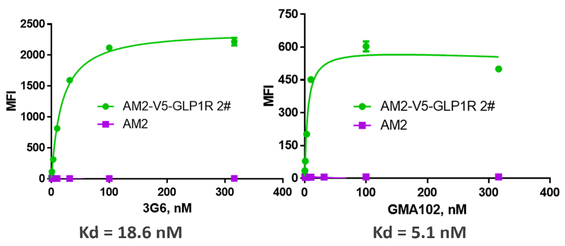
To overcome the shortcomings of the existing drugs, we constructed Glutazumab, a humanized anti-GLP-1R monoclonal antibody carrying a GLP-1 fragment. It could serve as a biased GLP-1 in the hope of having less on-target toxicity. A first-in-human, placebo-controlled, double-blinded, dose-escalation phase 1 study was carried out to investigate the safety, tolerability and pharmacokinetics of a single subcutaneous dose of Glutazumab in healthy male volunteers. Phase 1 data showed that Glutazumab has fewer and milder common adverse effects like nausea and vomiting of GLP-1R agonists, while the maximum tolerated dose is multiple-fold higher than that of dulaglutide (3). On the other hand, similar efficacy were demonstrated in a monkey OGTT study of Glutazumab and dulaglutide at similar molar dosage. Glutazumab, dosing either once a week or two-week, could be the first long-acting GLP-1 drug with the biased activity and the best-in-class with a well-tolerated safety profile.

MOLECULAR DESIGN AND IN VITRO ACTIVITY



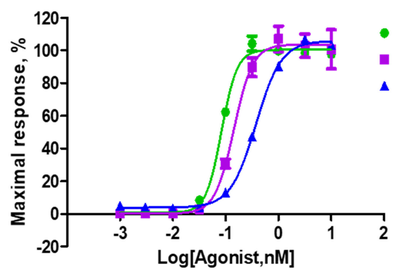
Structure of Glutazumab

A DPP-IV-resistant GLP-1 (7-35) analog fused to the light chain of a humanized GLP-1 receptor antibody (Ab1, IgG2)



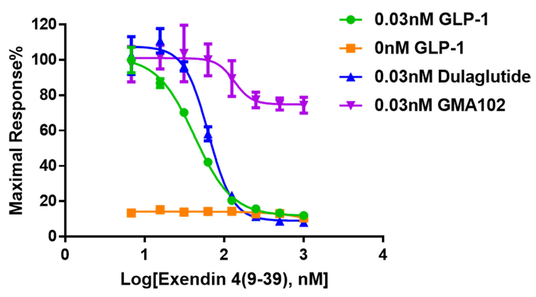
Saturation Binding

A. Binding of Glutazumab to human GLP-1R
B. Binding of Ab1 to human GLP-1R



In Vitro Functional Activity

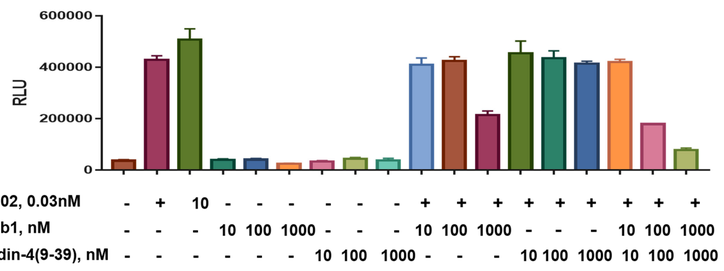
Glutazumab has similar potency to Dulaglutide in *in vitro* cell based assay



Biased Activity

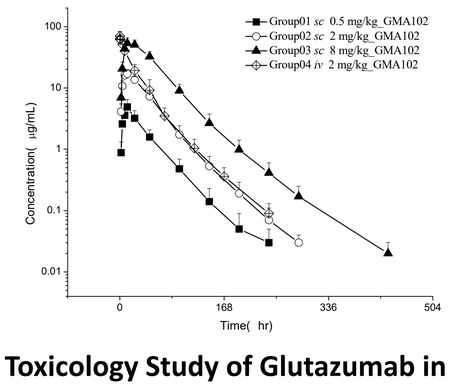
Glutazumab-induced activation of GLP-1R is resistant to the inhibition of Exendin 4(9-39), an antagonist of GLP-1R

Glutazumab-induced activation of hGLP-1R is differentially inhibited by Exendin 4(9-39), Ab1 and both



PK AND SAFETY IN CYNOMOLGUS

Pharmacokinetic Profiles of Glutazumab in Cynomolgus



32 animals (male: female 1:1), divided into 4 groups, 8 animals per group;

Single dose:
sc. 0.5 mg/kg, 2 mg/kg, 8 mg/kg;
iv. 2 mg/kg

Toxicology Study of Glutazumab in Cynomolgus

Control: blank formulation of GMA102

Study	Route of Admin.	Dose	No. of Animals	Dosing Frequency	Major Observations
Impacts on cardiovascular and respiratory system after	Sc.	3.0 mg/kg 10 mg/kg	16 animals, 8 per each dosing group (vs. control)	Single dose	No impact on respiratory system was observed for both groups; the decrease of blood pressure in 10 mg/kg group may relate to pharma-
Single-dose toxicity	Sc.	25 mg/kg 50 mg/kg	6 animals	Single dose observe for	No significant toxicity was observed; MTD≥100 mg/kg
Repeat-dose toxicity	Sc.	3 mg/kg 10 mg/kg 30 mg/kg	40 animals, 10 per dosing group and control	Twice/week, last for 4 weeks, 9 doses	Dose-related reductions in food intake, body weights and blood glucose levels were observed; anti-GMA102 antibodies were detected in some animals; recovery of site-of-injection reaction after dosing. 30 mg/kg as NOAEL in this study

Glutazumab vs. Dulaglutide: Tox in Cynomolgus

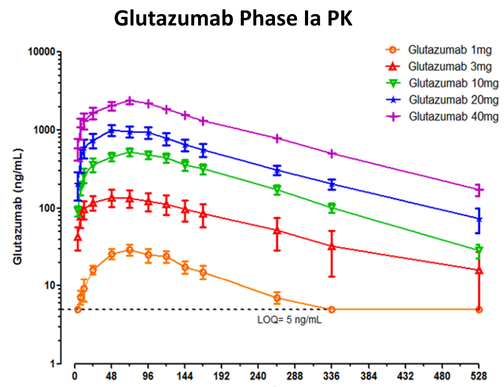
- *No other significant abnormalities observed;*
- *In general, dose related reductions in food intake, body weights and blood glucose levels were observed*

Study	Heart Rate (increase compared with Control Group)		QTc interval (increase compared with Control Group)		GI Disorder (compared with Control Group)	
	Glutazumab 63.2 nmol/kg	**Dulaglutide** 15.8 nmol/kg	**Glutazumab** 63.2 nmol/kg	**Dulaglutide** 15.8 nmol/kg	**Glutazumab**	**Dulaglutide**
Safety Pharm	No statistically significant change	↑ **21% at 3 h*** statistically significant	No statistically significant change	↑ **9% at 24 h*** statistically significant	—	—
	Glutazumab 63.2 nmol/kg	**Dulaglutide** 25.7 nmol/kg	**Glutazumab** 63.2 nmol/kg	Dulaglutide 25.7 nmol/kg	**Glutazumab**	**Dulaglutide**
Tox	no statistically significant change	↑ **8% on day 5***	no statistically significant change	↑ **1% on day 5*** 6.5 nmol/kg ↑ **33% on day 5*** Statistically significant	No nausea or GI related AE observed	1.Number of animals showed nausea and vomiting, a few of them were dehydrated. 2.Dose related. 3.Stronger and more frequent in the first 2 wks.

*: time after administration

Pharmacology Reviews 125469Orig1s000, FDA

Glutazumab vs. Dulaglutide: PK in Phase Ia Clinical Studies



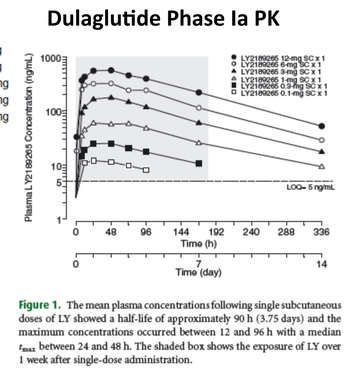


Figure 1. The mean plasma concentrations following single subcutaneous doses of LY showed a half-life of approximately 90 h (3.75 days) and the maximum concentrations occurred between 12 and 96 h with a median t_{max} between 24 and 48 h. The shaded box shows the exposure of LY over 1 week after single-dose administration.

	T1/2 (hr)	Median Tmax (hr)	Cmax (nM)
Glutazumab	98 (at 10 mg)	80	3.46 (at 10 mg)
Dulaglutide	90 (at 3 mg)	36	~3.00 (at 3 mg)

FIRST-IN-HUMAN STUDY

Study Objectives

Primary Objectives

- Assess the safety and tolerability of Glutazumab following single escalating subcutaneous (SC) doses of Glutazumab in healthy volunteers

Secondary Objectives

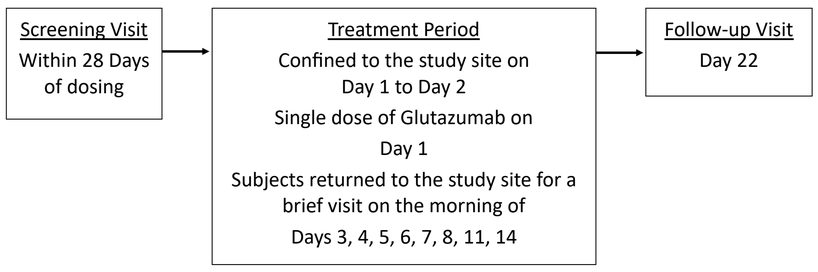
- Assess the PK of Glutazumab following single SC doses in healthy volunteers

Study Design

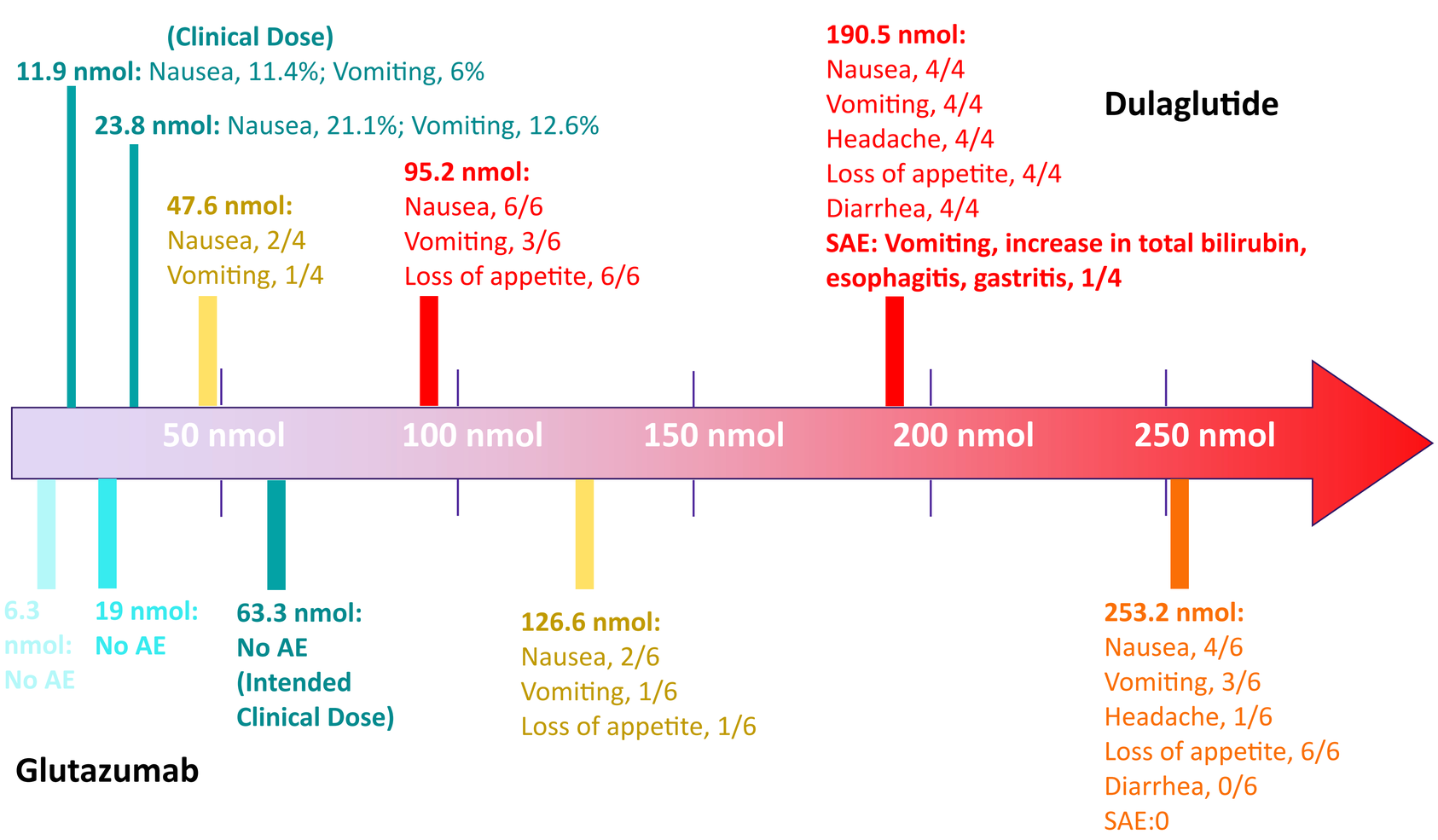
This was a randomized, placebo-controlled, double-blind, single dose escalation study to evaluate the safety, tolerability and PK of Glutazumab. This study was the first time that Glutazumab had been administered to humans.

The study was designed to investigate 5 different doses of Glutazumab. Five cohorts of 8 healthy subjects were planned to be investigated. Subjects were randomized to receive either Glutazumab or placebo (3 glutazumab: 1 placebo) as a single SC injection.

Cohort	Dose	
1	1mg Glutazumab	n=6
	Placebo	n=2
2	3mg Glutazumab	n=6
	Placebo	n=2
3	10mg Glutazumab	n=6
	Placebo	n=2
4	20mg Glutazumab	n=6
	Placebo	n=2
5	40mg Glutazumab	n=6
	Placebo	n=2



Glutazumab vs. Dulaglutide: Tox in Phase Ia Clinical Studies



ON-GOING PHASE IB/IIA

A Randomized, Placebo-controlled, Double-blind, Semi-sequential Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Repeated Escalating Subcutaneous Doses of Glutazumab in Subjects with Type 2 Diabetes

Study Design and Subjects

Multi-center, double-blind, semi-sequential group, randomization, placebo-control; Diabetics (n=44) in Australia and New Zealand

Cohorts and Treatment

GMA102 5，10，20，30 mg and X (depend on results of preceding cohorts) with subcutaneous injection for weekly*8 weeks

Clinical Outcome

Efficacy of Glutazumab on blood glucose and HbA1c as well as BMI
Pharmacokinetics profile, safety and tolerance

CONCLUSION

- Glutazumab is a novel GLP-1 analog of GLP-1/GLP-1R antibody fusion with biased activity towards GLP-1R.
- In FIH study, Glutazumab had a mono-exponential pharmacokinetics with half-life (T½) varying from 70 hours（at 1mg）up to 118 hours (at 40mg).
- In the dose range of 1 to 40 mg, Glutazumab was safe and well tolerated by healthy volunteers and demonstrated superior safety profile comparing with Dulaglutide. This is consistent with the cynomolgus study.
- Glutazumab is being tested in the on-going phase IB/IIA clinical studies.
- Glutazumab may be a safe and effective treatment for type 2 diabetes in the future.

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- 3. Trulicity Assessment Report, European Medicines Agency (EMA) , 2014

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