RGT-075, An Orally Efficacious Small Molecule GLP-1R Full Agonist in Cynomolgus Monkey Models

QILU Regor Therapeutics Inc

Feng Liu[1,2] , Wei Guo[2], Jing Lin[2] and Wenge Zhong[2]

[1] Regor Pharmaceuticals, Inc., 245 Main Street, 2nd floor Cambridge, MA, USA; [2] QILU Regor Therapeutics Inc., 1206 Zhangjiang Road, Pu Dong New District, Shanghai, China

753-P

ABSTRACT

Activation of Glucagon-like peptide-1 receptor (GLP-1R) by peptides has been proven clinically to be a very effective treatment approach for Type 2 diabetes mellitus (T2DM) and obesity. Here we describe a small molecule Glucagon-like peptide 1 receptor (GLP-1R) full agonist RGT-075 with nM potency in G-protein coupled cAMP signaling. RGT-075 displayed much reduced activity in receptor-mediated β-arrestin recruitment and subsequent internalization. It was shown to be selective against other class B G protein-coupled receptors (GPCRs) and was only active for human and monkey GLP-1R. It demonstrated favorable oral bioavailability and pharmacodynamic profile for once-daily oral dosing in monkeys. In food-induced glucose intolerant and prediabetic cynomolgus monkeys, oral administration of RGT-075 improved glucose tolerance by increasing insulin release to a level comparable to injectable liraglutide. In food-induced type 2 diabetic monkeys, once-daily oral administration of RGT-075 reduced food intake and fasting plasma glucose levels. Together, these data support the development and advancement of RGT-075 into the clinic as a potential therapeutic for T2DM and obesity.

BACKGROUND

- Type 2 diabetes mellitus (T2DM) accounts for over 90 percent of subjects with diabetes. In the US, the prevalence of T2DM is rising in parallel with the increasing prevalence of obesity and sedentary lifestyles.[1]
- Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are effective treatments for patients with T2DM through augmenting insulin secretion and suppressing glucagon release via the stimulation of GLP-1Rs. GLP-1RAs have been developed and approved as the injectable medication of choice for most subjects who require glucose lowering treatment added to metformin. However, no small molecular GLP-1RAs are yet approved for use in the US, which could present a desirable alternative treatment of T2DM.[2-3]

EXPERIMENTAL DESIGN

Food Intake Study:

The pharmacodynamics, efficacy, and tolerability of RGT-075 were evaluated in aged, obese, and diabetic cynomolgus monkeys. In this study, ten (10) aged (10-18 years old), obese, diabetic (fasting blood glucose: > 100 mg/dL), male, non-naive cynomolgus monkeys were selected. Seven weeks of animal training/acclimation were followed by a cycle of oral dosing at different dose levels and wash-out periods. During the dosing period, the animals were randomly assigned to 2 groups with five animals per group using a computer-generated randomization method based on body weight, glucose and insulin levels, and stability of training scores.

Clinical observations were done once a day during the training and washout periods and performed twice per day (AM and PM), on dosing days. Food intake measurements were conducted and recorded daily from the training period until the end of the study. Total energy intake (TEI) was calculated in kilocalories (kcal) based on the daily food intake.

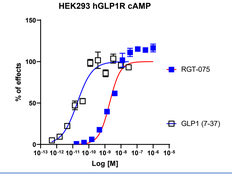
Intravenous Glucose Tolerance Test (IVGTT):

The mechanism of action of RGT-075 was evaluated by a single oral administration to aged, obese, impaired glucose tolerance (IGT) or early diabetic (ED) male cynomolgus monkeys (Macaca fascicularis) in a crossover study design using IVGTT as a quantitative analytical platform. In this study, twelve (12) aged (10~18 years old), obese, IGT or ED, male cynomolgus monkeys were selected. After two weeks of training/acclimation, twelve animals were randomly assigned to a group using a computer-generated randomization method based on their metabolic stages from the baseline/screening IVGTT data [IVGTT rate of glucose disappearance (KG%), IVGTT insulin total area under the curve (AUC) and body weight (BW) results]. The 12 animals were subdivided into 2 groups where the vehicle and RGT-075 were orally administered in a crossover design (i.e., separated by a washout period of 10 days). IVGTT was conducted with the oral administration of the vehicle and RGT-075 one hour before IV bolus glucose injection.

RESULTS

◆ RGT-075 is a selective GLP-1R full agonist with reduced activity of β-arrestin recruitment

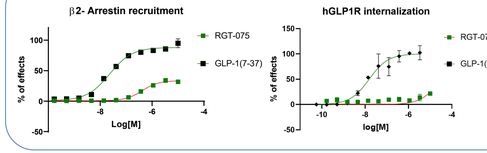
cAMP Functional Assays



Activity (cAMP, HEK293 cells)		RGT-075	GLP-1 (7-37)
		average ± std	average ± std
Human GLP-1R	EC_{50} (nM)	3.9 ± 0.9 (n = 13)	0.023 ± 0.015 (n= 13)
	B_{max} (%)	100	100
Monkey GLP-1R	EC_{50} (nM)	14.0 ± 2.0 (n = 5)	0.026 ± 0.022 (n = 9)
	B_{max} (%)	100	100
Rat GLP-1R	EC_{50} (nM)	>10 μM (n = 3)	0.0047 ± 0.003 (n = 5)
	B_{max} (%)	-	100

	RGT-075) EC_{50} (μM
	average ± std (n=4)
GCGR	>10 μM
GIPR	>10 μM

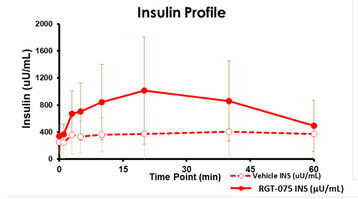
β-arrestin Recruitment and Receptor Internalization

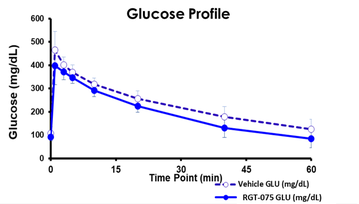


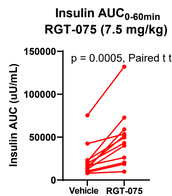
Activity Beta-arresin		RGT-075
		average ± std
β2-arrestin Recruitment	EC_{50} (nM)	490 ± 150 (n = 3)
	B_{max} (%)	28 ± 6 (n=3)
GLP-1R Internalization	EC_{50} (uM)	40.9 ± 56.5 (n = 3)
	B_{max} (%)	17 ± 7 (n = 3)

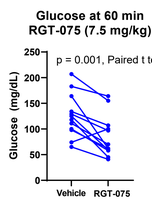
hGLP1R: Human glucagon-like peptide 1 receptor; cAMP: Cyclic adenosine monophosphate; EC_{50}: Half maximal effective concentration; B_{max}: Maximal specific binding; GCGR: Glucagon receptor; GIPR: Glucose-dependent insulinotropic polypeptide receptor.

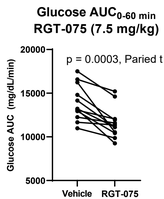
◆ Single-dose oral administrations of RGT-075 to aged, obese, early diabetic cynomolgus monkeys were effective in increasing insulin secretion with improvement in glycemic control on IVGTT









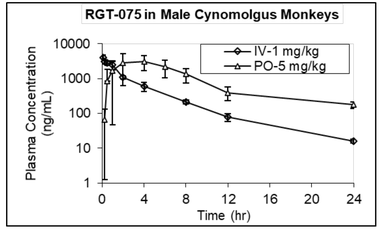


In the IVGTT study, oral dosing of RGT-075

- ❖ **significantly increased Insulin $AUC_{0\text{-}60min}$ levels.**
- ❖ **significantly reduced glucose levels at 60 min after glucose injection.**

RESULTS

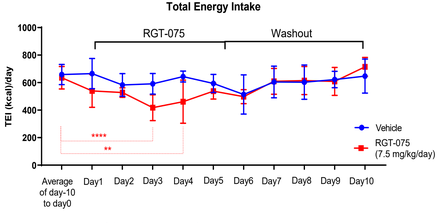
◆ RGT-075 has a favorable oral bioavailability and pharmacodynamic profile for once-daily oral dosing in monkeys



PK Profiles		RGT-075 (PO 5 mg/kg)
In vivo Monkey PK	hGLP1R (EC_{50}, nM)	3.9
	Cl (mL/min/kg) (iv)	1.8
	Vd_{ss} (L/kg) (iv)	0.38
	C_{max} (ng/mL) (po)	3910
	$AUC_{0\text{-}inf}$ (ng·h/mL) (po)	26200
	$t_{1/2}$ (h) (po)	5.3
	F (%) (po)	56
	Parent excreted in urine (po)	<0.1%

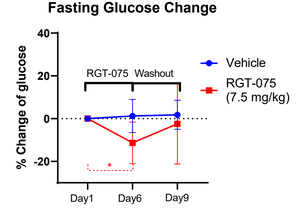
IV: Intravenous; PO: Per Os (oral gavage); PK: Pharmacokinetics; EC_{50}: Half maximal effective concentration; Cl: Clearance; Vd_{ss}: Volume of distribution at steady state; C_{max}: Maximum drug concentration; AUC: Area under the curve; $t_{1/2}$: Terminal half-life; F (%): Percent Bioavailability.

◆ RGT-075 reduces food intake and fasting blood glucose levels in diet-induced obese, diabetic male cynomolgus monkeys



Two-way ANOVA, followed by Dunnett's multiple comparison test, ** p < 0.01, ****p < 0.0001, compared to day-1, n = 5.
TEI: Total Energy Intake.

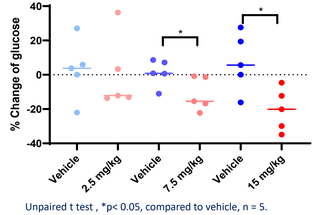
- ❖ **RGT-075 significantly reduced food intake at 7.5 mg/kg PO QD.**
- ❖ **The food intake lowering effect was reversible.**



Paired t test , *p< 0.05, compared to day 1, n = 5

- ❖ **RGT-075 lowered fasting glucose levels significantly and dose dependently.**
- ❖ **The lowering effect of fasting glucose levels was reversible.**

Dose dependence of RGT-075 on fasting glucose levels



Unpaired t test , *p< 0.05, compared to vehicle, n = 5.

Reference

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.
2. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021 Apr;46:101102.
3. Romera I; Cebrián-Cuenca A; Álvarez-Guisasola F; et al. A Review of Practical Issueson the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes. *Diabetes Ther*. 2019, 10: 5–19.