GL0034 (Utreglutide), a long acting, glucagon-like peptide-1 receptor agonist, improves body weight loss, lipid and liver injury markers in individuals with obesity: A phase 1 multiple ascending dose study

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Introduction

- Worldwide, 43% of adults were overweight in 2022, and adult obesity is doubled since 1990[1]. Obesity significantly increases all-cause mortality in affected individuals, largely due to its association with increased risks of cardiovascular disease and diabetes[2-6].
- Glucagon-like peptide-1 receptor agonists effectively decrease body weight in obese individuals, prompting investigation into and implementation of their use for the treatment of obesity[7,8].
- GL0034 (Utreglutide) is a novel incretin analogue with potent, G protein–biased, long-acting agonist activity at the glucagon-like peptide-1 receptor[9]. It is under development for the treatment of metabolic disorders and metabolic dysfunction-associated steatotic liver disease (MASLD).
- Utreglutide has demonstrated significant reductions in body weight up to Day 22 in a single ascending dose study in individuals with obesity[10].

Aim

To assess the safety and MASLD-relevant pharmacodynamic effects of multiple ascending doses of Utreglutide in individuals with obesity.

Method

- Randomized, double-blind, single-center, placebo-controlled, Phase 1 study was conducted to evaluate the safety and tolerability of GL0034; along with key metabolic parameters.
- EudraCT No. 2020-003765-20

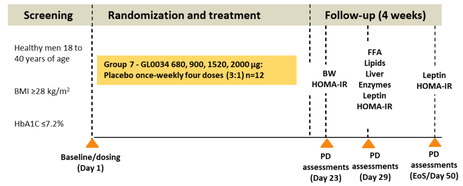


Fig 1 – Schematic representation of the study design
BMI, body mass index; BW, Body weight; HbA1$_c$, glycated hemoglobin; PD, pharmacodynamics

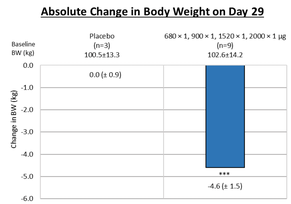
Table 1 - Demographics	Placebo	GL0034
	(n = 3)	680 × 1, 900 × 1, 1520 × 1, 2000 × 1 µg (n=9)
Sex, male, n (%)	3 (100)	9 (100)
Age, years, mean (range)	29.7 (23–36)	29.6 (21–39)
BMI, kg/m²	28.4 ± 1.4	32.2 ± 4.6
Body weight, kg	102.2 ± 13.1	103.1 ± 15.4
Data shown as mean ± SD; at baseline, unless otherwise indicated.		

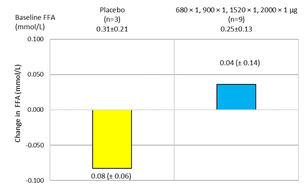
- A total of 12 male subjects were enrolled in 3:1 ratio.
- The most frequent AEs were gastrointestinal with dose-dependent nausea, decreased appetite and vomiting.
- One individual with a gastro-intestinal related serious AE rapidly recovered upon treatment with i.v. rehydration.

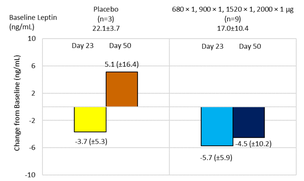
Table 2: Summary of AEs	Placebo	GL0034
	(n = 3)	680 × 1, 900 × 1, 1520 × 1, 2000 × 1 µg (n=9)
nsTEAEs	3 (100)	9 (100)
Related to treatment	2 (66.6)	9 (100)
Leading to discontinuation	0 (0)	0 (0)
SAE	0 (0)	1 (11.1)
Related to treatment	0 (0)	1 (11.1)
Leading to discontinuation	0 (0)	0 (0)
Severity (nsTEAEs)		
Mild	3 (100)	8 (88.9)
Moderate	1 (33.3)	8 (88.9)
Severe	0 (0)	1 (11.1)
Most frequent TEAEs		
Decreased appetite	0 (0)	9 (100)
Early satiety	1 (33.3)	9 (100)
Nausea	0 (0)	5 (55.6)
Dyspepsia	1 (33.3)	4 (44.4)
Vomiting	0 (0)	2 (22.2)
Data shown as n (%), where n represents the number of affected patients.		

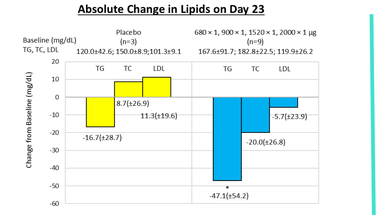
AE, adverse event; ns – non-serious; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.

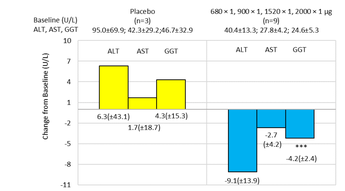
Results











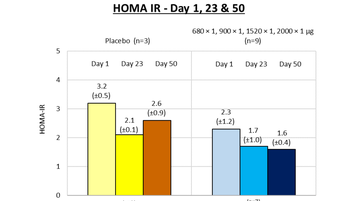


Fig. 2 Absolute change in body weight on Day 29 (top left); lipids (top right), Free Fatty Acids (FFA) (middle left), liver enzymes (middle right), Day 23 ; leptin on Day 23 and Day 50 (bottom left); and actual HOMA-IR on Day 1, Day 23 and Day 50 after treatment with GL0034
For lipids - First bar represents TG; Second bar represents TC ; Third bar represents LDL; For liver enzymes - First bar represents ALT; Second bar represents AST ; Third bar represents GGT; For leptin First bar represents Day 23; Second bar represents Day 50; For HOMA-IR First bar represents Day 1; Second bar represents Day 23; Third bar represents Day 50.
ALT-Alanine transaminase; AST – Aspartate aminotransferase; BL- Baseline GGT - γGlutamyl transferase; TG-Triglycerides; TC-Total cholesterol; LDL-Low density lipoprotein; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance
p<0.05,p<0.01 and ***p<0.001 vs respective D1 (BL); Paired Student's t-test or One-way ANOVA followed by Dunnett's test*

Table 3: Effect of GL0034 treatment on various biomarkers in individuals with obesity

Parameters	Day	Placebo (n=3) Mean ± SD	680 × 1, 900 × 1, 1520 × 1, 2000 × 1 µg (n=9) Mean ± SD
BMI (kg/m^2)	BL	28.4 ± 1.4	32.4 ± 4.6
BW (kg)	Day 1	100.5 ± 13.3	102.6 ± 14.2
	CBL Day 29	0.0 ± 0.9 (-0.02)	-4.6 ± 1.5***(-4.7)
TG (mg/dL)	Day 1	120.0 ± 42.6	167.6 ± 91.7
	CBL Day 23	-16.7 ± 28.7 (-14.3)	-47.1 ± 54.2* (-21.4)
TC (mg/dL)	Day 1	150.0 ± 8.9	182.8 ± 22.5
	CBL Day 23	8.7 ± 26.9 (6.4)	-20.0 ± 26.8 (-10.3)
LDL-C (mg/dL)	Day 1	101.3 ± 9.1	119.9 ± 26.2
	CBL Day 23	11.3 ± 19. 6 (12.4)	-5.7 ± 23.9 (-2.3)
ALT (U/L)	Day 1	95.0 ± 69.9	40.4 ± 13.3
	CBL Day 23	6.3 ± 43. 1 (9.5)	-9.1 ± 13.9 (-21.9)
AST (U/L)	Day 1	42.3 ± 29.2	27.8 ± 4.2
	CBL Day 23	1.7 ± 18.7 (17.7)	-2.7 ± 4.2 (-10.8) (n=7)
GGT (U/L)	Day 1	46.7 ± 32.9	24.6 ± 5.3
	CBL Day 23	4.3 ± 15.3 (-2.6)	-4.2 ± 2.4***(-17.4)
FFA (mmol/L)	Day 1	0.31 ± 0.21	0.25 ± 0.13
	CBL Day 23	-0.083 ± 0.064 (-25.1)	0.036 ± 0.140 (50.3)
HOMA-IR	Day 1	3.2 ± 0.5	2.3 ± 1.2
	Day 23	2.1 ± 0.1 (n=2)	1.7 ± 1.0 (n=7)
	Day 50	2.6 ± 0.9	1.6 ± 0.4
Leptin (ng/mL)	Day 1	22.1 ± 3.7	17.0 ± 10.4
	CBL Day 23	-3.7 ± 5.3 (-17.1)	-5.7 ± 5.9 (-33.0)
	CBL Day 50	5.1 ± 16.4 (24.0)	-4.5 ± 10.2 (-8.3)

ALT-Alanine transaminase; AST – Aspartate aminotransferase; BMI – Body Mass Index; BW- Body Weight; CBL- Change from baseline; GGT – Gamma Glutamyl transferase; FFA – Free fatty acids; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance; LDL-C- Low Density Lipoprotein Cholesterol; TG- Triglycerides; TC – Total cholesterol
Values in parenthesis indicate percent change from baseline.
**P<0.05, **p<0.01, ***P<0.001, vs respective Day 1 Levels; Paired Student's t-test or One-way ANOVA followed by Dunnett's post-hoc test*

Conclusions

- Multiple ascending doses of Utreglutide are safe and generally well tolerated in adults with obesity.
- Utreglutide demonstrated significant body weight reduction along with improvements in lipids, liver injury and metabolic markers in individuals with obesity.
- The observed effects of Utreglutide suggest potential therapeutic benefits in MASLD patients.

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