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A phase 1c evaluation of a novel GLP-1 analog ecnoglutide (XW003) for weight loss in adults with overweight & obesity

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Background

Ecnoglutide (XW003) is a novel, long-acting glucagon-like peptide-1 (GLP-1) analog being developed for the treatment of type 2 diabetes mellitus (T2DM) and obesity.

GLP-1 analogs mimic the activity of the natural incretin hormone, which is released from L-cells in the gut following ingestion of a meal. GLP-1 enhances glucose-stimulated insulin secretion and lowers blood sugar levels, as well as slows gastric emptying and promotes a sense of fullness[1]. Approved GLP-1 analogs include liraglutide (Saxenda®, Victoza®), dulaglutide (Trulicity®), and semaglutide (Ozempic®, Rybelsus® and Wegovy®).

In preclinical models, ecnoglutide showed potent GLP-1 receptor activation, a favorable cAMP signaling bias, as well as significant improvements in glucose control and body weight reduction in rodents compared to semaglutide. In Phase 1 clinical trials in healthy participants, once-weekly injection of ecnoglutide for up to 10 weeks showed a favorable safety, tolerability, and pharmacokinetics profile[2].

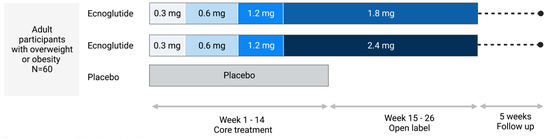
Methods

In this Phase 1c randomized, double-blind, placebo-controlled study of ecnoglutide, we enrolled 60 non-diabetic Chinese adults with overweight or obesity (body mass index [BMI] 24-35 kg/m^2).

Eligible participants were randomized in a 5:1 ratio to receive ecnoglutide (1.8 mg or 2.4 mg) or placebo as once weekly injections for 14 weeks, including a dose escalation period. This core treatment was followed by an open-label extension of the ecnoglutide groups, for a total duration of 26 weeks.

Safety, tolerability, pharmacokinetics, and pharmacodynamics, including change from baseline in body weight-related parameters were evaluated.

Study design



Study number SCW0502-1014

Results

Subject disposition

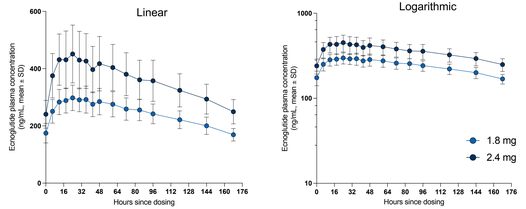
Subject Disposition	Ecnoglutide 1.8 mg	Ecnoglutide 2.4 mg	Ecnoglutide Total	Placebo
Enrolled in study	29	21	50	10
Completed Core Phase	24 (82.8%)	20 (95.2%)	44 (88.0%)	9 (90.0%)
Enrolled in Extension Phase	19 (65.5%)	15 (71.4%)	34 (68.0%)	0
Completed Extension Phase	19 (65.5%)	14 (66.7%)	33 (66.0%)	0
Withdrawn from Core Phase	5 (17.2%)	1 (4.8%)	6 (12.0%)	1 (10%)
Withdrawn from Extension Phase	0	1 (4.8%)	1 (2.0%)	0

Demographics and baseline characteristics

Characteristic*	Ecnoglutide 1.8 mg (n=29)	Ecnoglutide 2.4 mg (n=21)	Placebo (n=10)
Age (years)	27.66 (5.205)	30.00 (5.486)	27.50 (6.536)
Gender, n (%)			
Female	6 (20.7)	7 (33.3)	1 (10)
Male	23 (79.3)	14 (66.7)	9 (90)
Ethnic group, n (%)			
Han	28 (96.6)	21 (100.0)	10 (100)
Other	1 (3.4)	0	0
Body weight (kg)	88.44 (9.858)	79.66 (9.957)	83.87 (9.303)
BMI (kg/m^2)	30.07 (1.655)	29.14 (1.675)	28.77 (1.685)
Waist circumference (cm)	98.61 (5.903)	94.00 (5.497)	96.09 (5.304)
Waist/Hip ratio	0.94 (0.055)	0.92 (0.054)	0.94 (0.024)
HbA1c (%)	5.47 (0.327)	5.31 (0.287)	5.40 (0.194)
FPG (mmol/L)	4.72 (0.550)	4.82 (0.315)	4.88 (0.334)
Fasting insulin (uIU/mL)	12.46 (8.661)	11.39 (5.030)	10.87 (5.310)
HOMA-IR	2.71 (2.095)	2.46 (1.161)	2.36 (1.135)

*Mean (SD) unless otherwise noted

Pharmacokinetics



Steady state absorption of ecnoglutide was slow and consistent, with a median T_{max} of 24 hours for both dose groups. The C_{trough}, C_{max}, and AUC increased dose proportionally. Ecnoglutide showed an extended $T_{1/2}$ of 138.9 to 161.9 hours.

Summary of adverse events

AEs, n (%)	Ecnoglutide 1.8 mg (N=29)	Ecnoglutide 2.4 mg (N=21)	Ecnoglutide Total (N=50)	Placebo (N=10)
Any TEAE	29 (100.0)	20 (95.2)	49 (98.0)	9 (90.0)
Any Study Drug Related TEAE	23 (79.3)	20 (92.5)	43 (86.0)	1 (10.0)
TEAE ≥Grade 3	0	1 (4.8)	1 (2.0)	0
Study Drug Related TEAE ≥Grade 3	0	0	0	0
Serious TEAE	0	1 (4.8)	1 (2.0)	0
Study Drug Related Serious TEAE	0	0	0	0
TEAE Leading to Study Discontinuation*	1 (3.4)	1 (4.8)	2 (4.0)	0
TEAE Leading to Death	0	0	0	0

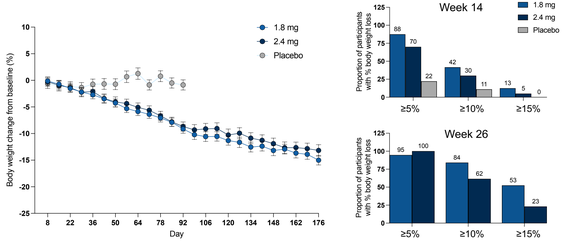
*One participant in the 1.8 mg group withdrew due to respiratory infection and one in the 2.4 mg group withdrew due to acute appendicitis. Both were considered unrelated to the study drug.

TEAEs ≥5% incidence in any group by preferred term

TEAE by preferred term, n (%) m*	Ecnoglutide 1.8 mg (N=29)	Ecnoglutide 2.4 mg (N=21)	Ecnoglutide Total N=50	Placebo N=10
Diarrhea	12 (41.4) 28	10 (47.6) 16	22 (44.0) 44	1 (10.0) 1
Decreased appetite	10 (34.5) 21	6 (28.6) 9	16 (32.0) 30	0
Abdominal distension	11 (37.9) 20	5 (23.8) 6	16 (32.0) 26	0
Vomiting	7 (24.1) 16	9 (42.9) 23	16 (32.0) 39	0
Nausea	6 (20.7) 9	8 (38.1) 16	14 (28.0) 25	0
Abdominal pain	8 (27.6) 11	4 (19.0) 6	12 (24.0) 17	0
Proteinuria	8 (27.6) 9	5 (23.8) 6	13 (26.0) 15	2 (20.0) 3
Elevated serum uric acid	9 (31.0) 11	3 (14.3) 3	12 (24.0) 14	3 (30.0) 3
Hypertension	0	0	0	2 (20.0) 2
Tachycardia	6 (20.7) 9	2 (9.5) 2	8 (16.0) 13	0
Elevated WBC count	0	1 (4.8) 1	1 (2.0) 1	1 (10.0) 1
Pulpitis	1 (93.4) 1	0	1 (2.0) 1	1 (10.0) 1
Hypotension	0	0	0	1 (10.0) 1
Upper respiratory tract infection	4 (13.8) 4	1 (4.8) 1	5 (10.0) 5	0
Dizziness	2 (6.9) 2	3 (14.3) 3	5 (10.0) 1	0
Elevated serum creatinine	2 (6.9) 2	2 (9.5) 2	4 (8.0) 4	1 (10.0) 1
RBC in urine	1 (3.4) 1	3 (14.3) 3	4 (8.0) 4	0
Headache	1 (3.4) 1	2 (9.5) 3	3 (6.0) 4	0
First degree AV block	1 (3.4) 1	2 (9.5) 2	3 (6.0) 3	0
Constipation	0	2 (9.5) 6	2 (4.0) 6	0
Dyslipidemia	2 (6.9) 2	0	2 (4.0) 2	0

*n (%), number and % of participants experiencing an AE; m, number of incidents of an AE

Body weight change from baseline



Least squares mean (standard error) are plotted for percent weight change from baseline over time.

Changes in body weight-related endpoints between baseline and Week 14

Endpoint	Ecnoglutide 1.8 mg (N=29)	Ecnoglutide 2.4 mg (N=21)	Placebo (N=10)
Body weight (kg)	-8.29 ± 0.52	-7.24 ± 0.56	-0.61 ± 0.82
ETD (95% CI)	-7.68 (-9.57, -5.79)	-6.63 (-8.57, -4.69)	
P value	<0.0001	<0.0001	
Body weight (%)	-9.51 ± 0.61	-8.91 ± 0.66	-0.87 ± 0.96
ETD (95% CI)	-8.64 (-10.86, -6.42)	-8.05 (-10.32, -5.77)	
P value	<0.0001	<0.0001	
Body mass index (kg/m^2)	-2.88 ± 0.18	-2.55 ± 0.19	-0.18 ± 0.28
ETD (95% CI)	-2.71 (-3.35, -2.06)	-2.37 (-3.03, -1.71)	
P value	<0.0001	<0.0001	
Waist circumference (cm)	-6.84 ± 0.68	-6.10 ± 0.77	0.57 ± 1.26
ETD (95% CI)	-7.40 (-10.21, -4.60)	-6.67 (-9.56, -3.78)	
P value	<0.0001	<0.0001	
Waist/Hip ratio	-0.03 ± 0.01	-0.03 ± 0.01	-0.004 ± 0.01
ETD (95% CI)	-0.03 (-0.05, 0.004)	-0.03 (-0.05, 0.002)	
P value	<0.05	<0.05	

Values are expressed as least square means ± standard error, unless indicated otherwise; ETD estimated treatment difference; CI confidence interval.

Changes in body weight-related endpoints between baseline and Week 26

Endpoint	Ecnoglutide 1.8 mg (N=19)	Ecnoglutide 2.4 mg (N=13)
Body weight (kg)	-13.13 (-14.68, -11.57)	-10.73 (-12.59, -8.87)
Body weight (%)	-15.00 (-16.77, -13.24)	-13.18 (-15.29, -11.06)
Body mass index (kg/m^2)	-4.58 (-5.10, -4.05)	-3.80 (-4.43, -3.17)
Waist circumference (cm)	-11.40 (-13.20, -9.59)	-8.49 (-10.76, -6.22)
Waist/Hip ratio	-0.03 (-0.05, -0.02)	-0.02 (-0.03, 0.002)

Values are expressed as least square means (95% confidence interval).

Conclusions

- Ecnoglutide was safe and well tolerated in non-diabetic Chinese adults with overweight or obesity. There were no study drug treatment-related SAEs or ≥Grade 3 AEs.
- Steady state absorption of ecnoglutide was slow and consistent for both doses
- At 14 weeks, ecnoglutide led to significant weight reduction vs placebo (-8.91 to -9.51% vs 0.87%). Weight loss progressively continued, reaching -13.18 to -15.00% at 26 weeks.
- At 26 weeks, 94.7% of participants in the 1.8 mg ecnoglutide cohort and 100% in the 2.4 mg ecnoglutide cohort achieved body weight reductions ≥5% from baseline
- Significant changes were also noted in other weight-related parameters, including BMI, waist circumference & waist to hip ratio

References

1. Heppner and Perez-Tilve (2015) Front. Neurosci. Vol 9
2. Guo et al, in preparation and unpublished results

Financial Disclosures

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