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An open-label, active-controlled phase 2 evaluation of novel GLP-1 analog ecnoglutide (XW003) in adults with obesity

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BACKGROUND

Obesity is a chronic disease that can increase the risk of serious health complications, including type 2 diabetes (T2DM), heart disease, and stroke[1].

GLP-1 analogs, such as semaglutide (Wegovy®) and liraglutide (Saxenda®), have recently been developed as effective treatments for weight loss. These drugs mimic the activity of GLP-1, a naturally produced incretin hormone that is released by intestinal cells after a meal. GLP-1 acts on various tissues, including the gastrointestinal tract, pancreas, and central nervous system to slow gastric emptying, promote a sense of fullness, reduce appetite, and regulate blood sugar[2].

Ecnoglutide (XW003) is a novel, long-acting GLP-1 analog being developed for the treatment of obesity and T2DM.

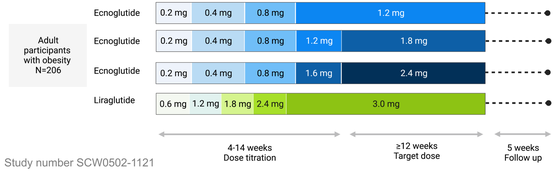
METHODS

We performed a randomized, open-label, active controlled, Phase 2 study to evaluate the effects of ecnoglutide once weekly versus liraglutide once daily on body weight in adult participants with obesity (BMI ≥30.0 to ≤40.0 kg/m^2). The trial was conducted at nine sites in Australia and New Zealand. Eligible male and female participants were aged 18 to 70 years, inclusive, with HbA1c <6.5% and weight stable for at least 3 months.

Participants were randomized (1:1:1:1) to receive target doses of 1.2, 1.8, or 2.4 mg ecnoglutide as once weekly subcutaneous (SC) injections or liraglutide (Saxenda®) at 3.0 mg as once daily SC injections for 26 weeks, including a dose titration period.

The primary endpoint was percent change in body weight at Week 26. Secondary endpoints included proportion of participants reaching pre-defined weight loss targets, as well as changes in waist and hip circumference, BMI, and lipid profiles.

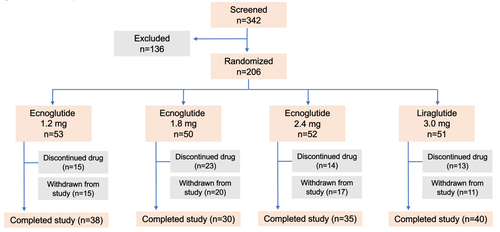
Study design



Study number SCW0502-1121

RESULTS

Subject disposition



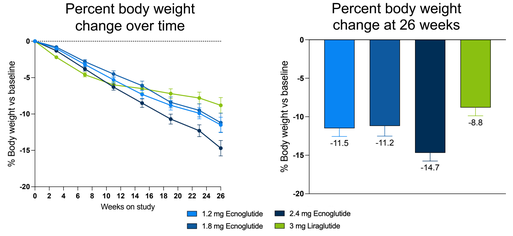
The most common reason for treatment discontinuation was AEs; 18.7% for ecnoglutide and 13.7% for liraglutide.

Demographics and baseline characteristics

Characteristic*		Ecnoglutide (once weekly) 1.2 mg (N=53)	1.8 mg (N=50)	2.4 mg (N=52)	Overall (N=155)	Liraglutide (once daily) 3 mg (N=51)
Age (years)		48.5 (10.90)	47.6 (11.04)	49.8 (11.84)	48.7 (11.23)	47.3 (12.62)
Sex, n (%)	Female	39 (73.6%)	39 (78.0%)	39 (75.0%)	117 (75.5%)	38 (74.5%)
	Male	14 (26.4%)	11 (22.0%)	13 (25.0%)	38 (24.5%)	13 (25.5%)
Race, n (%)	Asian	1 (1.9%)	2 (4.0%)	1 (1.9%)	4 (2.6%)	0
	Black or African American	0	1 (2.0%)	0	1 (0.6%)	0
	Native Hawaiian or Pacific Islander	8 (15.1%)	5 (10.0%)	3 (5.8%)	16 (10.3%)	6 (11.8%)
	White	41 (77.4%)	38 (76.0%)	43 (82.7%)	122 (78.7%)	39 (76.5%)
	Other	1 (1.9%)	3 (6.0%)	3 (5.8%)	7 (4.5%)	3 (5.9%)
	Multiple	2 (3.8%)	1 (2.0%)	2 (3.8%)	5 (3.2%)	3 (5.9%)
Weight (kg)		98.52 (11.921)	102.23 (12.873)	98.62 (13.719)	99.75 (12.884)	103.45 (15.180)
Height (cm)		167.15 (8.920)	169.44 (8.201)	167.00 (8.477)	167.84 (8.561)	171.10 (11.111)
BMI (kg/m^2)		35.18 (2.649)	35.52 (2.888)	35.24 (2.761)	35.31 (2.751)	35.22 (2.802)

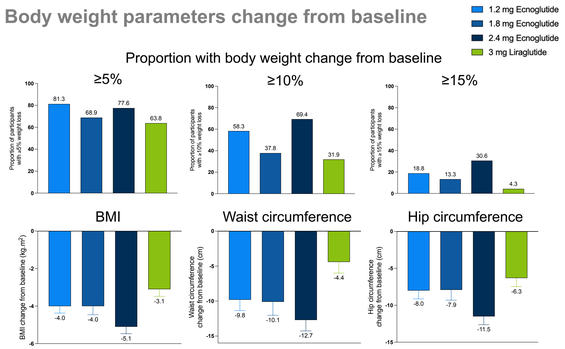
*Mean (SD) unless otherwise noted

Body weight change from baseline



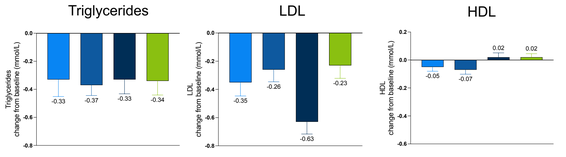
Participants receiving 2.4 mg ecnoglutide showed significantly greater body weight reduction compared to liraglutide at 26 weeks (ITT population; least squares mean difference -5.9, 95% CI -10.4, -1.5; P<0.001).

Body weight parameters change from baseline



Change from baseline at Week 26. Least squares mean and SE is shown for BMI, waist and hip circumference.

Lipid profile change from baseline



Mean and SD change from baseline at Week 26.

Summary of adverse events

Most AEs were GI-related, mild to moderate in severity, and occurred during dose-escalation. Two SAEs of acute cholecystitis were reported, one for 1.2 mg ecnoglutide and one for liraglutide.

AEs, n (%) m*	Ecnoglutide (once weekly) 1.2 mg (N=53)	1.8 mg (N=50)	2.4 mg (N=52)	Overall (N=155)	Liraglutide (once daily) 3 mg (N=51)	Overall (N=206)
One TEAE	49 (92.5%) 389	47 (94.0%) 414	49 (94.2%) 354	145 (93.5%)1157	50 (98.0%) 360	195 (94.7%)1517
One ≥ Grade 3 TEAE	2 (3.8%) 3	0	1 (1.9%) 2	3 (1.9%) 5	4 (7.8%) 5	7 (3.4%) 10
One ≤ Grade 2 TEAE	49 (92.5%) 386	47 (94.0%) 414	49 (94.2%) 352	145 (93.5%)1152	50 (98.0%) 355	195 (94.7%)1507
Study Drug Related TEAE	43 (81.1%) 233	44 (88.0%) 270	44 (84.6%) 222	131 (84.5%) 725	41 (80.4%) 168	172 (83.5%) 893
Injection Site Reaction	8 (15.1%) 18	10 (20.0%) 13	9 (17.3%) 16	27 (17.4%) 47	17 (33.3%) 23	44 (21.4%) 70
Serious TEAE**	2 (3.8%) 2	0	0	2 (1.3%) 2	3 (5.9%) 3	5 (2.4%) 5
Gastrointestinal Disorder	40 (75.5%) 174	42 (84.0%) 208	45 (86.5%) 202	127 (81.9%) 584	41 (80.4%) 137	168 (81.6%) 721
TEAE Leading to Drug Discontinuation	7 (13.2%) 8	15 (30.0%) 28	7 (13.5%) 10	29 (18.7%) 46	7 (13.7%)12	36 (17.5%) 58
TEAE Leading to Study Discontinuation	5 (9.4%) 7	12 (24.0%) 25	6 (11.5%) 8	23 (14.8%) 40	5 (9.8%) 9	28 (13.6%) 49
TEAE Leading to Death	0	0	0	0	0	0

*n (%), number and % of participants experiencing an AE ; m, number of incidents of an AE
** Two events of acute cholecystitis were probably related to study drug; other SAEs not related to study drug

Treatment-emergent AEs with total incidence ≥5% by preferred term

TEAE by preferred term, n (%) m*	Ecnoglutide (once weekly) 1.2 mg (N=53)	1.8 mg (N=50)	2.4 mg (N=52)	Overall (N=155)	Liraglutide (once daily) 3 mg (N=51)	Overall (N=206)
Nausea	21 (39.6%) 47	25 (50.0%) 47	32 (61.5%) 88	78 (50.3%) 182	27 (52.9%) 41	105 (51.0%) 223
Headache	18 (34.0%) 41	23 (46.0%) 49	14 (26.9%) 20	55 (35.5%) 110	22 (43.1%) 36	77 (37.4%) 146
COVID-19	15 (28.3%) 15	17 (34.0%) 17	15 (28.8%) 15	47 (30.3%) 47	21 (41.2%) 22	68 (33.0%) 69
Diarrhea	18 (34.0%) 32	20 (40.0%) 46	9 (17.3%) 18	47 (30.3%) 96	18 (35.3%) 26	65 (31.6%) 122
Constipation	15 (28.3%) 31	12 (24.0%) 27	12 (23.1%) 16	39 (25.2%) 74	12 (23.5%) 19	51 (24.8%) 93
Gastroesophageal reflux disease	10 (18.9%) 13	14 (28.0%) 21	10 (19.2%) 11	34 (21.9%) 45	9 (17.6%) 10	43 (20.9%) 55
Vomiting	13 (24.5%) 26	11 (22.0%) 17	11 (21.2%) 31	35 (22.6%) 74	6 (11.8%) 9	41 (19.9%) 83
Injection site bruising	5 (9.4%) 6	8 (16.0%) 11	5 (9.6%) 6	18 (11.6%) 23	14 (27.5%) 18	32 (15.5%) 41
Upper respiratory tract infection	13 (24.5%) 16	3 (6.0%) 3	5 (9.6%) 6	21 (13.5%) 25	6 (11.8%) 7	27 (13.1%) 32
Abdominal pain	5 (9.4%) 5	2 (4.0%) 3	7 (13.5%) 10	14 (9.0%) 18	6 (11.8%) 9	20 (9.7%) 27
Dyspepsia	5 (9.4%) 5	5 (10.0%) 8	5 (9.6%) 9	15 (9.7%) 22	4 (7.8%) 8	19 (9.2%) 30
Fatigue	4 (7.5%) 8	7 (14.0%) 7	6 (11.5%) 6	17 (11.0%) 21	2 (3.9%) 2	19 (9.2%) 23
Dizziness	6 (11.3%) 8	2 (4.0%) 2	4 (7.7%) 5	12 (7.7%) 15	2 (3.9%) 7	14 (6.8%) 22
Arthralgia	2 (3.8%) 2	5 (10.0%) 7	2 (3.8%) 2	9 (5.8%) 11	5 (9.8%) 7	14 (6.8%) 18
Back pain	2 (3.8%) 2	3 (6.0%) 4	1 (1.9%) 1	6 (3.9%) 7	7 (13.7%) 9	13 (6.3%) 16
Gastroenteritis	3 (5.7%) 3	3 (6.0%) 3	1 (1.9%) 1	7 (4.5%) 7	4 (7.8%) 4	11 (5.3%) 11

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

CONCLUSIONS

- Ecnoglutide 1.2, 1.8, and 2.4 mg once weekly resulted in robust weight reductions in adults with overweight and obesity
- Participants receiving ecnoglutide 2.4 mg had significantly greater weight reduction at Week 26 than those receiving once daily liraglutide (-14.7% vs -8.8%, P<0.001).
- Weight loss for 2.4 mg ecnoglutide at 26 weeks (-14.7%) was comparable to 2.4 mg semaglutide at Week 28 (~ -12%)[3] and 15 mg tirzepatide at Week 24 (~ -14%)[4]
- The overall safety profile of ecnoglutide was similar to other GLP-1 based therapies.
- A Phase 3 study of ecnoglutide in patients with obesity has been initiated.

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FINANCIAL DISCLOSURES

Z. Zhu, Y. Li, Q. Zheng, E. Adegbite, S. Ross, L. Telusca, C. L. Jones, M. Fenaux, S. Xu, and M. K. Junaidi are employees of Sciwind Biosciences.