Effect of CIN-109, a Novel GDF-15 Analog, on Body Weight and Composition in Subjects with Obesity

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Background

In animal models, increases in GDF-15, a protein that is a member of the transforming growth factor Beta (TGFβ) family, have been associated with decreases in food intake and body weight. GDF-15 also is associated with maintenance of energy expenditure in animal models by increasing β-adrenergic signaling in the muscle. CIN-109 is a novel human serum albumin-growth differentiation factor 15 (HSA GDF15) fusion protein with a long half-life (12-14 days) being developed for weight management. Despite the availability of approved medications for weight management, there is a need for medications which target reductions in fat mass while maintaining lean mass.

Methods

This was a Phase 1 randomized, double-blind, placebo-controlled, multiple ascending dose study assessing the safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of CIN-109.

Otherwise healthy subjects with obesity were randomized to receive placebo or CIN-109 subcutaneously once weekly without titration (at doses of 5 mg, 10 mg, 15 mg, 20 mg, or 40 mg) or once every other week without titration (Q2W; at doses of 20 mg, 40 mg, or 60 mg). The weekly groups were treated for 4-6 weeks and the Q2W groups for 8 weeks. Subjects remained in the study clinic a full day prior to and for 3 days after the first and last dose of study drug.

Safety assessments included clinical laboratory tests, vital signs, physical examinations, 12-lead ECGs, and adverse events. Blood samples to characterize the PK and immunogenicity of CIN-109 and for exploratory biomarkers were collected. PD measures included 24-hour food intake (assessed by weight of meals) on the day prior to the first dose as well as 2 days after the first dose and the last dose), body weight, and body composition (using DEXA).

Results

A total of 68 subjects were randomized in a 3:1 active:placebo ratio; 59 subjects completed the study. Mean weight and BMI of CIN-109-treated subjects were ~100 kg and ~35 kg/m^2, respectively (Table 1).

TABLE 1: SUBJECT DEMOGRAPHICS

		Weekly dosing cohorts						Q2W dosing cohorts			
		Placebo	5 mg	10 mg	15 mg	20 mg	40 mg	Placebo	20 mg	40 mg	60 mg
Mean Age		36.3	44.2	42.7	34.0	38.0	32.8	29.8	40.2	41.1	40.3
Mean Weight		105.26	108.42	102.33	110.79	108.40	89.17	98.75	106.62	98.11	96.02
Mean BMI		34.0	35.7	36.4	34.9	34.3	32.7	33.6	35.7	34.6	33.5
Sex	Female	6	2	3	2	1	3	4	3	4	3
	Male	5	4	3	6	5	3	2	3	3	3
Race	White	4	2	2	2	1	2	2	3	3	2
	Black	7	4	4	6	5	4	3	3	2	3
	Other	0	0	0	0	0	0	1	0	2	1

There were no treatment-related serious adverse events (SAEs). A total of 2 subjects discontinued in association with GI adverse events (AEs) after the first dose. Q2W dosing was associated with fewer, less severe GI AEs as compared to weekly dosing (Table 2).

TABLE 2: NUMBER OF SUBJECTS WITH NAUSEA AND VOMITING ADVERSE EVENTS BY TREATMENT

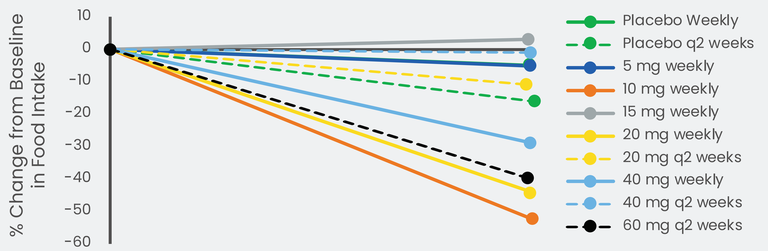
		Placebo qW (n=11)	5 mg qW (n=6)	10 mg qW (n=6)	15 mg qW (n=8)	20 mg		40 mg		60 mg q2W (n=6)	Placebo q2W (n=6)
						qW (n=6)	q2W (n=6)	qW (n=6)	q2W (n=7)		
Nausea	Mild	1	2	1	1	2	2	1	5	4	0
	Moderate	0	0	0	2	2	0	5	1	1	1
	Severe	0	0	0	0	0	0	0	0	0	0

		Placebo qW (n=11)	5 mg qW (n=6)	10 mg qW (n=6)	15 mg qW (n=8)	20 mg		40 mg		60 mg q2W (n=6)	Placebo q2W (n=6)
						qW (n=6)	q2W (n=6)	qW (n=6)	q2W (n=7)		
Vomiting	Mild	0	0	0	0	1	0	0	2	2	0
	Moderate	0	0	0	1	1	0	4	0	1	1
	Severe	0	0	0	0	0	0	0	0	0	0

CIN-109 exposures increased in a generally dose proportional manner. As expected, given the long half-life of CIN-109, weekly dosing was associated with greater accumulation (approximately 3-5 fold) than Q2W dosing (2-3-fold).

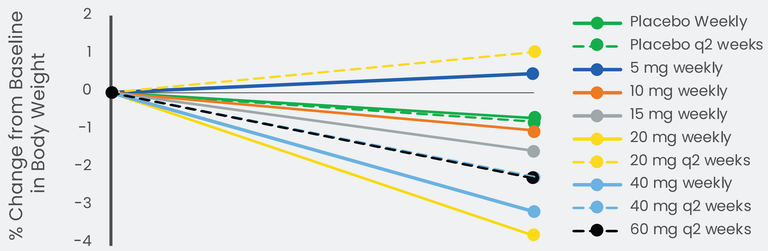
CIN-109 differentiated from placebo with generally dose-dependent decreases in food intake up to ~50% and decreases in body weight up to ~3.7% were observed within 1-2 months of dosing with CIN-109 (Figures 1 and 2).

FIGURE 1: PERCENT CHANGE IN FOOD INTAKE FROM BASELINE TO ENDPOINT



Endpoint is the last measurement prior to discharge from the study center in the final dosing period (2 days post final dose).

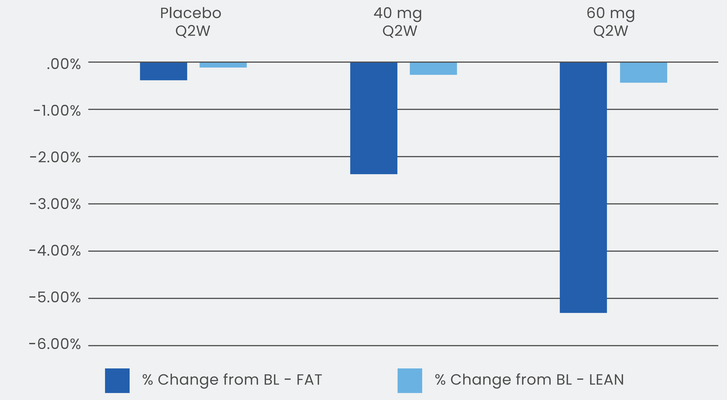
FIGURE 2: PERCENT CHANGE IN BODY WEIGHT FROM BASELINE TO ENDPOINT



Endpoint is the last measurement prior to discharge from the study center in the final dosing period (3 days post final dose).

The majority of the weight lost with each of the Q2W dosing regimens represents fat mass (Figure 3).

FIGURE 3: PERCENT CHANGE IN LEAN AND FAT MASS FROM BASELINE TO ENDPOINT



Conclusions

CIN-109 was well-tolerated and produced meaningful decreases in body weight. At the highest dose tested, the vast majority of the weight loss was from a reduction in fat mass. CIN-109 has the potential to meet an unmet need for medications which target reductions in fat mass while maintaining lean mass.

Disclosures

This study was funded by CinFina Pharma, LLC. a subsidiary of CinRx Pharma LLC. Mary Bond, Brian Murphy, Satya Shreenivas, Mackenzie Pater, Brendan Doran, and Jonathan Isaacsohn are employees of CinRx Pharma and have an equity stake in the company.

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