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CB4211, a Novel Analog of MOTS-c, Improves Markers of Liver Injury and Metabolism in Obese Subjects with Nonalcoholic Fatty Liver Disease: a Multicenter, Double-Blind, Randomized, Placebo-Controlled Study.

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INTRODUCTION

- CB4211 is an analog of the natural mitochondrially encoded peptide MOTS-c (mitochondrial open-reading-frame of the twelve S rRNA-c), which has shown regulatory effects on metabolism in animal models of disease.[1]
- CB41211 has a unique mechanism of action, enhancing insulin signaling in cultured adipocytes, hepatocytes, and muscle cells.[2]
- CB4211 and related analogs were shown to reduce NAFLD activity score, markers of livery injury, body weight, and fat mass in animal models of NASH or obesity.[3]

AIM

This multicenter, double-blind, randomized, placebo-controlled trial was designed to examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of CB4211 in obese subjects with NAFLD.

METHODS

Initial CB4211 dose selection was performed in single and 7-day multiple ascending dose cohorts in 65 healthy adults (dose range 0.2 to 3.0 mg/kg/day or placebo) using prototype or modified formulations. The proof-of-concept trial enrolled 23 high-risk NAFLD subjects with ≥10% liver fat content (LFC) by MRI-PDFF, body mass index ≥30 kg/m2, and Fibroscan CAP ≥300 dB/m at baseline, randomized 1:1 to receive once daily subcutaneous CB4211 25 mg (modified formulation) or placebo for 4 weeks. One diabetic subject was enrolled on a stable metformin regimen and medications affecting body weight or NAFLD biomarkers were excluded. All subjects were monitored in an in-patient unit during the entire 4-week treatment period and received a standardized diet based on energy expenditure at baseline. Endpoints included safety and tolerability (Primary) and pharmacokinetics (Secondary). Exploratory endpoints included changes from baseline to week-4 in ALT, AST, glucose, liver fat content, and body weight.

RESULTS

Baseline Characteristics

Parameter	Placebo (n=9)	CB4211 (25 mg) (n=11)
Age (years)	47 (11)	48 (10)
Male/Female	6/3	7/4
Body Weight (kg)	101 (10.6)	99.3 (11.4)
BMI (kg/m^2)	34.9 (3.2)	36.5 (2.8)
ALT (IU/L)	30 (20)	37 (17)
AST (IU/L)	26 (11)	27 (12)
Fatty Liver Index	91.6 (6.5)	92.6 (6.0)
LFC (MRI-PDFF) (%)	15.9 (5.6)	21.1 (7.6)
Fibroscan Cap (dB/m)	334 (19.7)	366 (29.5)
Liver Stiffness (kP)	5.4 (1.9)	6.1 (1.9)

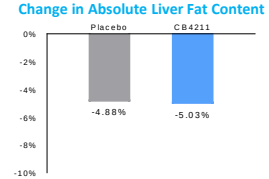
Data are Mean (SD)

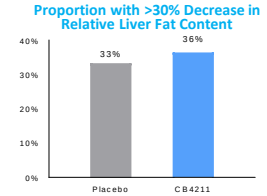
Other Baseline Assessments

Biomarker	Placebo (n=9)	CB4211 (25 mg) (n=11)
Glucose (mg/dL)	90 (7.3)	98 (9.3)
Insulin (mIU/L)	12.3 (6.6)	17.1 (6.6)
HOMA2-IR	2.69 (1.30)	4.20 (1.74)
HbA1c (%)	5.7 (0.2)	5.9 (0.4)
Free Fatty Acid (mEq/L)	0.51 (0.15)	0.42 (0.15)
TG (mg/dL)	126 (38.5)	121 (44.0)
Adiponectin (mg/L)	3.7 (1.4)	4.3 (2.9)
C Reactive Protein (mg/L)	4.3 (2.8)	5.7 (4.7)
Hyaluronic Acid (ng/mL)	20.7 (8.65)	33.3 (16.7)
PIIINP (ng/mL)	10.2 (4.58)	9.09 (2.03)
TIMP-1 (ng/mL)	196 (61.5)	225 (43.6)
IL-6 (ng/L)	3.92 (3.15)	5.29 (6.96)
TNF (ng/L)	1.33 (0.33)	1.39 (0.28)

Data are Mean (SD)

Change in LFC at Week 4

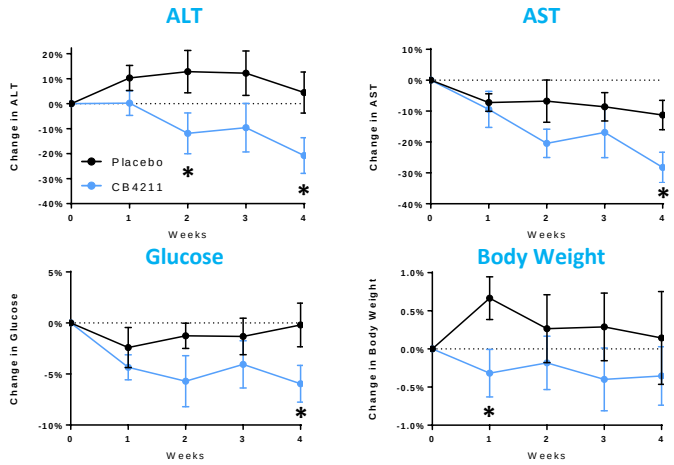




Changes in Markers of Liver Injury, Fasting Glucose Levels, and Body Weight

Biomarker	Placebo (n=9)	CB4211 (25 mg) (n=11)	Change vs Placebo
ALT (% reduction from baseline)	4%	-21%	-25%*
Proportion of subjects with >17 U/L decrease in ALT[4]	11%	27%	16%
AST (% reduction from baseline)	-11%	-28%	-17%*
Fasting Glucose (% reduction from baseline)	0%	-6%	-6%*

Mean data at week 4. *Statistically significant, p<0.05 vs. placebo



Data are Mean + SEM % change from baseline. *Statistically significant, p<0.05 vs. placebo

CONCLUSIONS

- In obese NAFLD subjects, 4 weeks of CB4211 treatment produced statistically significant reductions compared to placebo in biomarkers of liver injury, ALT and AST, independent of effects on liver fat content.
- CB4211 reduced fasting glucose levels, with a trend to reduced body weight, corroborating previous preclinical data in disease models.
- Liver fat content was reduced substantially in both CB4211 and placebo arms, likely due to a healthier diet during confinement for the study.
- CB4211 treatment was safe and well tolerated with no serious adverse events. Three subjects discontinued the study: 2 for positive COVID-19 tests and 1 withdrew consent. Generally mild to moderate injections site reactions were the only treatment related AE in >10% of subjects.
- These data support the further development of CB4211, a first in class MOTS-c analog, as a potential treatment for NASH.

REFERENCES

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DISCLOSURES

RL – disclosures on file with AASLD; MH – employee, Prosciento, Inc.; HS – employee, Endeavor Clinical Trials, LLC; EL - disclosures on file with AASLD, Jeanelle Kam – employee, LabCorp Clinical Research Unit, Inc.; KC – employee and stockholder, CohBar, Inc.