HM15211, a Novel GLP-1/GIP/Glucagon Triple-Receptor Co-Agonist Significantly Reduces Liver Fat and Body Weight in Obese Subjects with Non-alcoholic Fatty Liver Disease: A Phase 1b/2a, Multicenter, Randomized, Placebo-Controlled Trial

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ABSTRACT

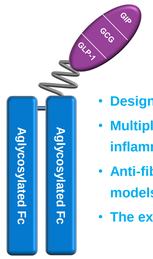
Nonalcoholic fatty liver disease (NAFLD) is increasingly prevalent cause of chronic liver disease globally. HM15211, a novel GLP-1/GIP/Glucagon triple receptor co-agonist has potential for therapeutic benefit in obese subjects with NAFLD. We present the results of a 12 week, phase1b/2a, multicenter, randomized placebo-controlled, multiple ascending dose study to investigate the safety, tolerability, PK and PD of subcutaneous (SC) weekly doses of HM15211 for non-diabetic, obese subjects with NAFLD (MRI-PDFF ≥ 10%). Five different doses of HM15211 (0.01, 0.02, 0.04, 0.06, and 0.08 mg/kg) were tested. Subjects were randomized to HM15211 or placebo in a ratio of 3:1 with 12 subjects per cohort. 50% of the enrolled subjects were women and the baseline age, BMI and liver fat by MRI-PDFF were 46 (11.4) years, 36 (4.96) kg/m^2 and 19.2 (6.5) %, respectively. The relative changes in liver fat [mean (SD)] from baseline to week 8 and 12 were for 0.01 mg/kg was -14.9 (12.2) and -19.6 (12.2) % (p = 0.13 and 0.30); for 0.02 mg/kg was -43 (23.5) and -36 (28.1) % (p < 0.0001 and 0.06); for 0.04 mg/kg was -44.5 (46.6) and -38 (53.5) % (p = 0.0005 and 0.12), for 0.06 mg/kg was -71(23.8) and -59.3 (27.6) % (p < 0.0001 / 0.0020), and for 0.08 mg/kg was -80.3 (13.2) and -81.2 (7.6) % (p < 0.0001 and p < 0.0001), respectively vs. -1.2 (24.5) and -5.7 (37.8) % for placebo group. A dose-dependent reduction in liver fat with escalating doses of HM15211 was observed with the maximum (88%) liver fat reduction noted with HM15211 0.08 mg/kg at 12 weeks. HM15211 decreased body weight compared with placebo across all treatment groups. Placebo-corrected kg and % reduction of body weight were -1.3, -1.8*, -2.1*, -3.1*, and -4.3* kg (-1.2, -1.9*, -2.2*, -2.9*, and -4.4*%) at week 8 and -2.1, -3.1*, -1.9, -4*, and -5.3* kg (-1.9, -3.4*, -2.1, -3.8*, and -5.1* %) at week 12 in 0.01 to 0.08 mg/kg dose cohorts, respectively (*p < 0.05). HM15211 was shown to be well tolerated. The most common dose-dependent adverse events were mild gastrointestinal symptoms. Two subjects developed hyperglycemia which readily resolved with discontinuation of HM15211. No serious adverse events related to HM15211 occurred in any dose cohort.

BACKGROUND

HM15211 has shown therapeutic potential in animal models of obesity, NASH (AS015) and safe profiles in a previous first in human study (FRI115).

[General Profile of HM15211]

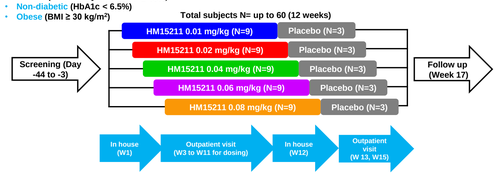
HM15211 is GLP-1/GIP/GCG triple agonist, conjugated with a human IgG Fc fragment via a flexible PEG linker



- Designed and optimized for liver targeted distribution
- Multiple mode of actions to manage steatosis, inflammation and fibrosis
- Anti-fibrosis effect is confirmed in various animal models
- The extended half life is sufficient for weekly dosing

[Study Design]

- NAFLD (Liver fat by MRI-PDFF ≥ 10%)
- Non-diabetic (HbA1c < 6.5%)
- Obese (BMI ≥ 30 kg/m^2)



[Study Objective]

- **Primary objectives**
  - To assess safety and tolerability of HM15211 after administration of multiple SC doses
  - To assess the pharmacokinetic (PK) profile of HM15211 after administration of multiple SC doses
  - To assess a reduction of liver fat after administration of multiple doses
- **Exploratory objectives**
  - To assess additional pharmacodynamic (PD) properties of HM15211 after multiple SC doses

RESULTS

Table 1. Baseline Characteristics

	HM15211 0.01 mg/kg (N=9)	HM15211 0.02 mg/kg (N=10)	HM15211 0.04 mg/kg (N=12)	HM15211 0.06 mg/kg (N=9)	HM15211 0.08 mg/kg (N=9)	Placebo (N=17)
Ages: years (SD)	44.2 (12.5)	46.5 (9.3)	49.3 (13.5)	45.8 (10.3)	47.3 (11.7)	43.7 (11.9)
Sex: M/F (%)	66.7/33.3	30.0/70.0	33.3/66.7	66.7/33.3	66.7/33.3	47.1/52.9
Race (%)						
White	8 (88.9)	10 (100.0)	10 (83.3)	9 (100.0)	6 (66.7)	15 (88.2)
Black or African American	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	2 (22.2)	2 (11.8)
Asian	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Weight: kg (SD)	101.4 (10.7)	88.0 (13.5)	99.7 (20.1)	112.2 (18.0)	103.3 (16.9)	96.6 (18.3)
BMI: kg/m^2 (SD)	35.4 (3.8)	32.9 (2.8)	37.0 (6.1)	40.1 (7.1)	35.7 (3.8)	35.5 (4.3)
HbA1c: % (SD)	5.9 (0.3)	5.73(0.2)	5.9 (0.3)	5.7 (0.3)	5.7 (0.3)	5.6 (0.3)
FPG: mg/dL (SD)	97.9 (8.8)	102.3 (9.0)	102.2 (8.4)	103.6 (10.8)	103.3 (7.7)	98.1 (8.6)
Liver Fat: % (SD)	19.6 (6.0)	18.2 (4.9)	18.8 (6.2)	17.9 (8.7)	23.6 (8.0)	18.2 (5.3)
Liver aminotransferases						
AST: IU/L (SD)	24.4 (11.4)	21.7 (7.3)	30.4 (12.2)	22.2 (9.0)	23.1 (10.5)	30.2 (22.9)
ALT: IU/L (SD)	39.3 (25.3)	33.8 (14.1)	51.2 (24.2)	31.4 (16.7)	38.6 (27.2)	45.9 (44.1)

Figure 1. Serum PK Exposure of HM15211

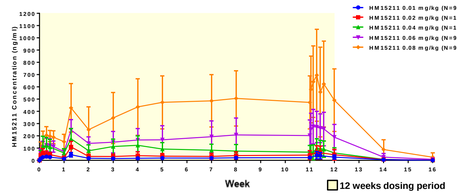


Table 2. Pharmacokinetic parameters

	HM15211 0.01 mg/kg		HM15211 0.02 mg/kg		HM15211 0.04 mg/kg		HM15211 0.06 mg/kg		HM15211 0.08 mg/kg	
	W1 (N=9)	W12 (N=9)	W1 (N=10)	W12 (N=8)	W1 (N=12)	W12 (N=7)	W1 (N=9)	W12 (N=9)	W1 (N=9)	W12 (N=9)
C_{max} (ng/mL)	31.22 ± 13.47	41.79 ± 29.23	66.32 ± 32.93	83.59 ± 42.86	135.46 ± 84.48	131.06 ± 53.74	129.59 ± 56.59	306.44 ± 147.39	227.56 ± 62.14	820 ± 399.77
T_{max} (hr)	48.00 ± 12.00	53.33 ± 10.58	40.80 ± 19.76	48.00 ± 22.22	50.00 ± 19.03	44.57 ± 16.56	61.33 ± 21.17	59.56 ± 40.42	74.67 ± 42.33	46 ± 31.06
$T_{1/2}$ (hr)	62.02 ± NA	NA ± NA	93.85 ± 38.73	NA ± NA	125.21 ± 66.73	175.53 ± 110.9	257.47 ± 292.75	152.44 ± 81.16	118.2 ± 51.78	191.25 ± 75.6
AUC_{0-168h} (ng/mL·hr)	3579.7 ± 1333.0	5554.5 ± 3638.8	6538.7 ± 2488.6	11770.3 ± 7192.4	14859.8 ± 8099.8	17938.87 ± 6840.48	16512.43 ± 6781.51	41053.9 ± 19947.12	28130.17 ± 6965.5	97616.05 ± 42147.89

- Parameters are mean with standard deviation (SD)

Table 3. Summary of Adverse Events

TEAE Category No. of Subjects (%)	HM15211 0.01 mg/kg (N=9)	HM15211 0.02 mg/kg (N=10)	HM15211 0.04 mg/kg (N=12)	HM15211 0.06 mg/kg (N=9)	HM15211 0.08 mg/kg (N=9)	Placebo (N=17)
Any TEAE	7 (77.8)	9 (90.0)	9 (75.0)	8 (88.9)	6 (66.7)	8 (47.1)
Maximum Severity of TEAE						
Mild	7 (77.8)	3 (30.0)	7 (58.3)	6 (66.7)	2 (22.2)	6 (35.3)
Moderate	0 (0.0)	6 (60.0)	1 (8.3)	2 (22.2)	4 (44.4)	2 (11.8)
Severe	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Any Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE Leading to Study Discontinuation	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (11.1)	0 (0.0)
Any TEAE Related to Study Medication	2 (22.2)	5 (50.0)	3 (25.0)	5 (55.6)	5 (55.6)	1 (5.9)
Gastrointestinal disorders	2 (22.2)	5 (50.0)	4 (33.3)	5 (55.6)	4 (44.4)	5 (29.4)
Abdominal discomfort	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (10.0)	1 (8.3)	1 (11.1)	0 (0.0)	3 (17.6)
Abdominal faeces	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
Diarrhea	1 (11.1)	3 (30.0)	1 (8.3)	1 (11.1)	3 (33.3)	1 (5.9)
Dry mouth	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
Frequent bowel movements	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Gastroesophageal reflux disease	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (5.9)
Nausea	1 (11.1)	1 (10.0)	2 (16.7)	3 (33.3)	3 (33.3)	1 (5.9)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Vomiting	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	1 (5.9)

Figure 2. Representative Liver Fat Reduction by MRI-PDFF

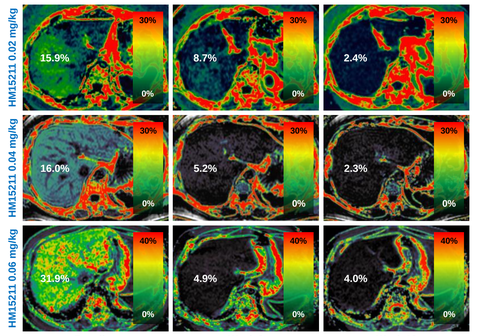
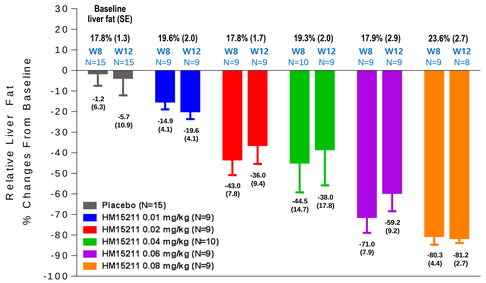


Figure 3. Relative Liver Fat Changes by MRI-PDFF



- Parameters are mean with standard error of mean (SEM)

Table 4. Subjects with Relative Liver Fat Reduction ≥ 30% and ≥ 50%

	Placebo (N=15)	HM15211 0.01 mg/kg (N=9)	HM15211 0.02 mg/kg (N=9)	HM15211 0.04 mg/kg (N=10)	HM15211 0.06 mg/kg (N=9)	HM15211 0.08 mg/kg (N=9)
Patients Achieved ≥ 30% Relative Liver Fat Reduction at						
Week 8	13.3% (2/15)	11.1% (1/9)	77.8% (7/9)	70% (7/10)	88.9% (8/9)	100% (9/9)
Week 12	13.3% (2/15)	33.3% (3/9)	77.8% (7/9)	55.6% (5/9)[1]	88.9% (8/9)	100% (8/8)[1]
Patients Achieved ≥ 50% Relative Liver Fat Reduction at						
Week 8	6.7% (1/15)	0% (0/9)	44.4% (4/9)	60% (6/10)	88.9% (8/9)	100% (9/9)
Week 12	13.3% (2/15)	0% (0/9)	22.2% (2/9)	55.6% (5/9)[1]	66.7% (6/9)	100% (8/8)[1]

[1]One subject in each Cohort 3 and 5 discontinued IP before week 12

CONCLUSION

HM15211 was safe and well tolerated during 12 weeks treatment in non-diabetic obese subjects with NAFLD. Treatment with HM15211 significantly decreased liver fat content and body weight at 8 and 12 weeks. Further development of HM15211 as a treatment for NASH is warranted and Phase 2b trial is currently ongoing.

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