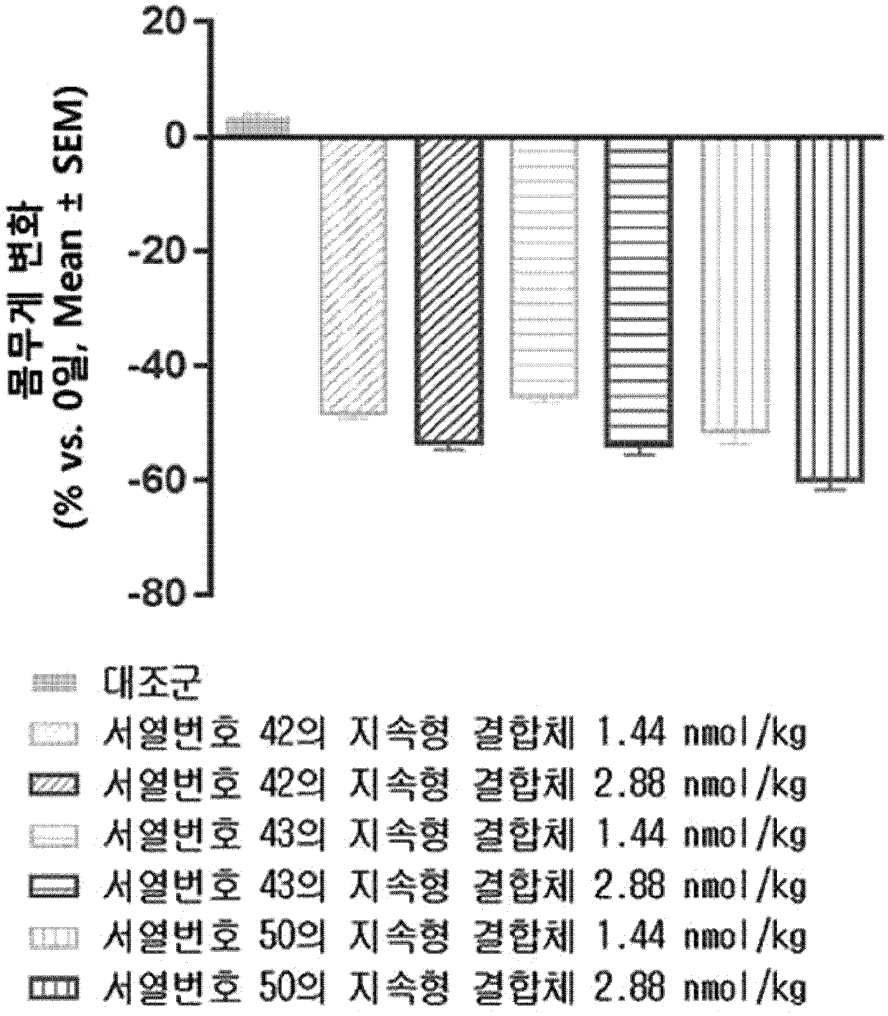
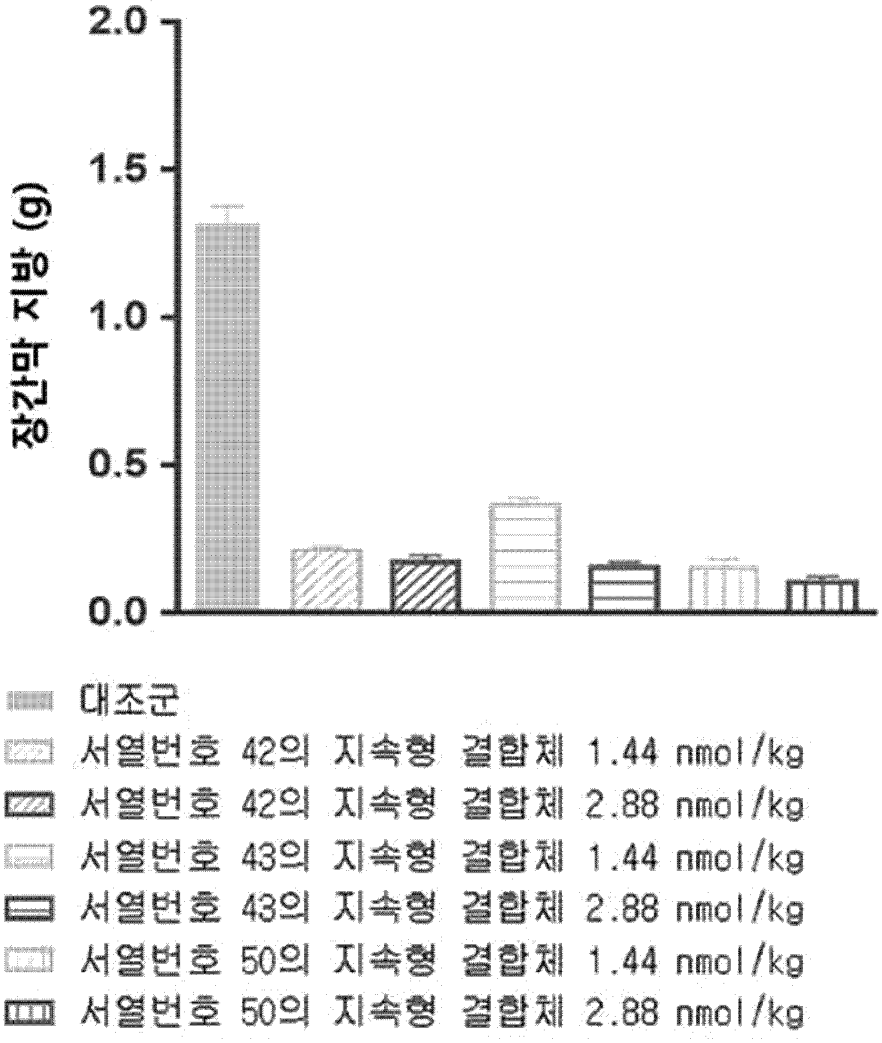
[도1]


20
0
-20
-40
-60
-80
몸무게 변화
(% vs. 0일, Mean ± SEM)
대조군
서열번호 42의 지속형 결합체 1.44 nmol/kg
서열번호 42의 지속형 결합체 2.88 nmol/kg
서열번호 43의 지속형 결합체 1.44 nmol/kg
서열번호 43의 지속형 결합체 2.88 nmol/kg
서열번호 50의 지속형 결합체 1.44 nmol/kg
서열번호 50의 지속형 결합체 2.88 nmol/kg

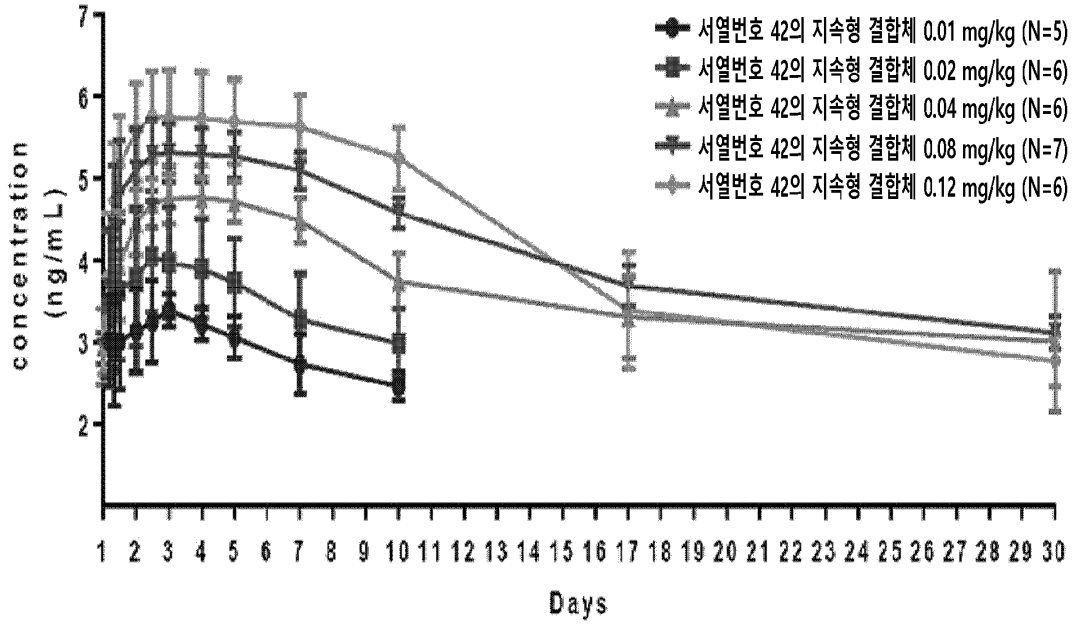
[도2]


2.0
1.5
1.0
0.5
0.0
장간막 지방 (g)
대조군
서열번호 42의 지속형 결합체 1.44 nmol/kg
서열번호 42의 지속형 결합체 2.88 nmol/kg
서열번호 43의 지속형 결합체 1.44 nmol/kg
서열번호 43의 지속형 결합체 2.88 nmol/kg
서열번호 50의 지속형 결합체 1.44 nmol/kg
서열번호 50의 지속형 결합체 2.88 nmol/kg

[도3]

						Placebo
	서열번호 42의 지속형 결합체 0.01 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.08 mg/kg (N=7)	서열번호 42의 지속형 결합체 0.12 mg/kg (N=6)	(N=10)
Ages: years (SD)	41.0 (14.3)	36.3 (11.8)	54.0 (6.1)	49.7 (11.1)	43.8 (13.5)	47.4 (6.6)
Sex: M/F (%)	50/50	33/67	67/33	43/57	67/33	50/50
Race (%)						
White	4 (67)	5 (83)	2 (33)	5 (71)	6 (100)	5 (50)
Black or African American	2 (33)	1 (17)	4 (67)	1 (14)	0 (0)	4 (40)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)
Weight: kg (SD)	95.7 (8.5)	97.1 (16.8)	96.9 (10.3)	92.6 (11.0)	87.3 (14.5)	96.0 (10.7)
BMI: kg/m^2 (SD)	33.2 (1.7)	34.9 (3.4)	33.1 (2.4)	32.7 (1.8)	32.7 (2.6)	34.5 (3.6)

[도4]



[도5]

	서열번호 42의 지속형 결합체 0.01 mg/kg (N=5)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.08 mg/kg (N=7)	서열번호 42의 지속형 결합체 0.12 mg/kg (N=6)
C_{max} (ng/mL)	29.76 (14.707)	70.52 (39.699)	127.52 (34.227)	232.14 (82.495)	383.67 (185.738)
T_{max} (hr)	31.20 (10.733)	42.03 (16.527)	66.01 (25.996)	61.71 (40.652)	68.08 (43.316)
$T_{1/2}$ (hr)	72.09 (44.939)	77.24 (26.196)	89.26 (20.012)	142.10 (54.641)	79.18 (19.989)
AUC_{0-inf} (ng/mL·h)	5034.63 (1322.73)	10189.05 (4584.02)	24603.83 (8530.78)	52575.52 (5808.64)	90903.07 (34897.44)
Dose-normalized C_{max} (ng/mL/mg)	30.73 (13.34)	35.99 (21.21)	33.13 (9.70)	31.46 (11.00)	38.39 (23.25)
Dose-normalized AUC_{inf} (ng/mL·h/mg)	5899.11 (1373.98)	5099.07 (1912.91)	8021.05 (3986.35)	8887.11 (4052.88)	8718.46 (3084.28)

[도6]

TEAE Category No. of Subjects (%)	서열번호 42의 지속형 결합체 0.01 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.08 mg/kg (N=7)	서열번호 42의 지속형 결합체 0.12 mg/kg (N=6)	Placebo (N=10)
Any TEAE	3 (50.0)	2 (33.3)	3 (50.0)	7 (100.0)	4 (66.7)	7 (70.0)
Maximum Severity of TEAE						
Mild	3 (50.0)	2 (33.3)	3 (50.0)	6 (85.7)	3 (50.0)	7 (70.0)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	1[a] (14.3)	1[b] (16.7)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	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)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE Related to Study Medication	0 (0.0)	0 (0.0)	0 (0.0)	5 (71.4)	4 (66.7)	1 (10.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (16.7)	4 (57.1)	4 (66.7)	1 (10.0)
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (16.7)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Abdominal tenderness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	4 (57.1)	4 (66.7)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	2 (33.3)	0 (0.0)

[도7]

	서열번호 42의 지속형 결합체 0.01 mg/kg	서열번호 42의 지속형 결합체 0.02 mg/kg	서열번호 42의 지속형 결합체 0.04 mg/kg	서열번호 42의 지속형 결합체 0.08 mg/kg	서열번호 42의 지속형 결합체 0.12 mg/kg	Placebo
HR (bpm)	2.0 (3.5)	3.3 (4.1)	-1.5 (4.4)	3.3 (4.8)	1.8 (4.7)	0.4 (4.2)
SPB (mmHg)	-1.5 (10.4)	-0.7 (3.1)	2.3 (15.4)	0.7 (12.3)	-7.9 (10.3)	0.5 (8.2)
DBP (mmHg)	-1.5 (5.6)	-2.3 (4.3)	-2.2 (6.9)	-0.6 (6.3)	-2.9 (7.9)	-3.3 (4.7)
RPP (bpm x mmHg)	146.5 (802.8)	336.5 (661.1)	-123.5 (567.1)	478.0 (936.3)	-299.6 (1090.6)	185.3 (987.1)

[도8]

Visit Result, Subjects (%)	서열번호 42의 지속형 결합체 0.01 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.08 mg/kg (N=7)	서열번호 42의 지속형 결합체 0.12 mg/kg (N=6)	Placebo (N=10)
Day-1						
Tier 1						
Negative	3 (50.0)	5 (83.3)	3 (50.0)	4 (57.1)	6 (100.0)	7 (70.0)
Putative Positive	3 (50.0)	1 (16.7)	3 (50.0)	3 (42.9)	0 (0.0)	3 (30.0)
Tier 2						
Negative	3 (100.0)	1 (100.0)	2 (66.7)	3 (100.0)	0 (0.0)	3 (100.0)
Positive	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Day 17, Out-patient Visit						
Tier 1						
Negative	4 (66.7)	3 (50.0)	2 (40.0)	4 (80.0)	1 (16.7)	8 (80.0)
Putative Positive	2 (33.3)	3 (50.0)	3 (60.0)	1 (20.0)	5 (83.3)	2 (20.0)
Tier 2						
Negative	0 (0.0)	1 (33.3)	1 (33.3)	1 (100.0)	0 (0.0)	1 (50.0)
Positive	2 (100.0)	2 (66.7)	2 (66.7)	0 (0.0)	5 (100.0)	1 (50.0)
Day 30, Follow-up Visit						
Tier 1						
Negative	4 (66.7)	3 (50.0)	2 (40.0)	4 (80.0)	1 (20.0)	8 (80.0)
Putative Positive	2 (33.3)	3 (50.0)	3 (60.0)	1 (20.0)	4 (80.0)	2 (20.0)
Tier 2						
Negative	1 (50.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive	1 (50.0)	3 (100.0)	0 (0.0)	1 (100.0)	4 (100.0)	2 (100.0)

[도9]

Visit Result, Subjects (%)	서열번호 42의 지속형 결합체 0.01 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.08 mg/kg (N=7)	서열번호 42의 지속형 결합체 0.12 mg/kg (N=6)	Placebo (N=10)
Anti-PEG Screening						
Baseline						
NA	6 (100.0)	6 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	10 (100.0)
Day 17, Out-patient Visit						
Negative	5 (83.3)	4 (66.7)	4 (80.0)	5 (100.0)	4 (66.7)	9 (90.0)
Positive	1 (16.7)	2 (33.3)	1 (20.0)	0 (0.0)	2 (33.3)	1 (10.0)
Day 30, Follow-up Visit						
Negative	5 (83.3)	4 (66.7)	4 (80.0)	5 (100.0)	2 (40.0)	9 (90.0)
Positive	1 (16.7)	2 (33.3)	1 (20.0)	0 (0.0)	3 (60.0)	1 (10.0)
Anti-PEG Specificity						
Baseline						
NA	6 (100.0)	6 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	10 (100.0)
Day 17, Out-patient Visit						
Negative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)
NA	6 (100.0)	6 (100.0)	5 (100.0)	5 (100.0)	4 (66.7)	10 (100.0)
Day 30, Follow-up Visit						
Negative	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (40.0)	1 (10.0)
NA	6 (100.0)	5 (83.3)	5 (100.0)	5 (100.0)	3 (60.0)	9 (90.0)

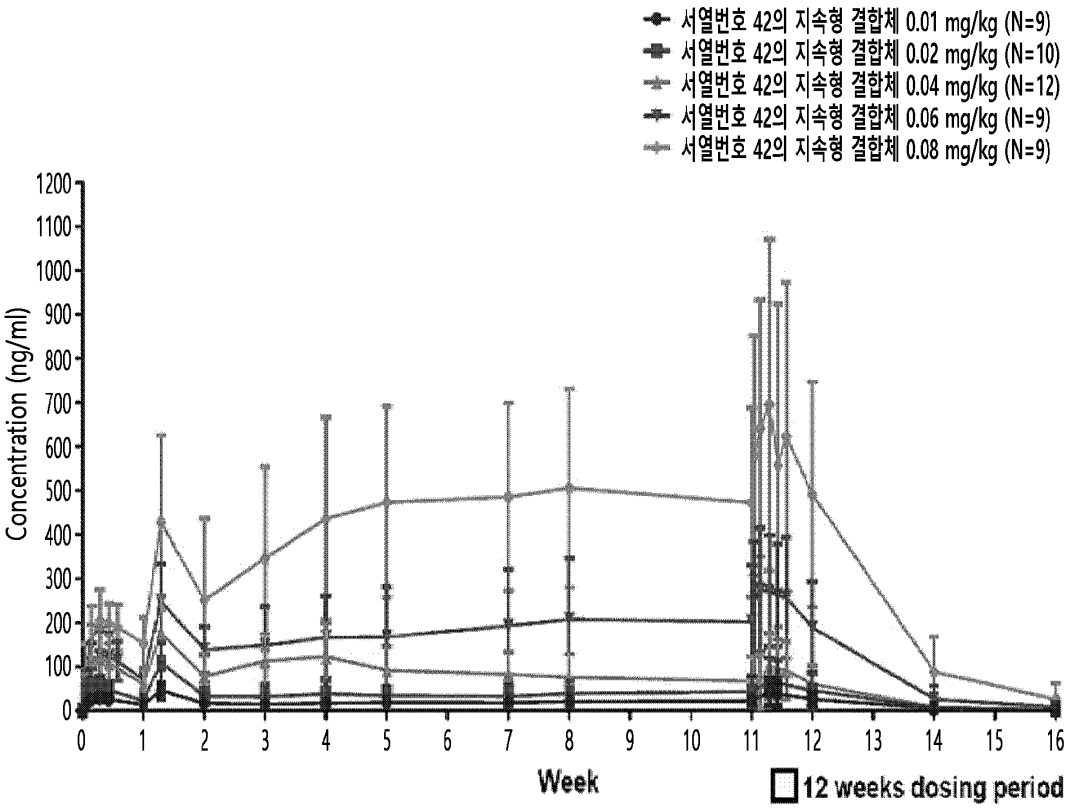
[도10]

Visit Result, Subjects (%)	서열번호 42의 지속형 결합체 0.01 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=6)	서열번호 42의 지속형 결합체 0.08 mg/kg (N=7)	서열번호 42의 지속형 결합체 0.12 mg/kg (N=6)	Placebo (N=10)
Evaluable for neutralizing antibodies	2 (33.3)	3 (50.0)	2 (33.3)	1 (14.3)	5 (83.3)	3 (30.0)
Screening						
Positive for neutralizing GLP-1 activity	1 (50.0)	1 (33.3)	1 (50.0)	0 (0.0)	2 (40.0)	0 (0.0)
Negative for neutralizing GLP-1 activity	1 (50.0)	2 (66.7)	1 (50.0)	1 (100.0)	3 (60.0)	3 (100.0)
Positive for neutralizing GIP activity	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Negative for neutralizing GIP activity	2 (100.0)	2 (66.7)	2 (100.0)	1 (100.0)	4 (80.0)	3 (100.0)
Positive for neutralizing Glucagon activity	2 (100.0)	1 (33.3)	1 (50.0)[a]	0 (0.0)	4 (80.0)	2 (66.7)
Negative for neutralizing Glucagon activity	0 (0.0)	2 (66.7)	1 (50.0)	1 (100.0)	1 (20.0)	1 (33.3)
Confirmatory						
Positive for neutralizing GLP-1 activity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative for neutralizing GLP-1 activity	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)
Positive for neutralizing GIP activity	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Negative for neutralizing GIP activity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive for neutralizing Glucagon activity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative for neutralizing Glucagon activity	2 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	3 (75.0)[a]	2 (100.0)
Cross-reactivity						
Positive for GLP-1 cross-reactivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative for GLP-1 cross-reactivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive for GIP cross-reactivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative for GIP cross-reactivity	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Positive for Glucagon cross-reactivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative for Glucagon cross-reactivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[도11]

	서열번호 42의 지속형 결합체 0.01 mg/kg (N=9)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=10)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=12)	서열번호 42의 지속형 결합체 0.06 mg/kg (N=9)	서열번호 42의 지속형 결합체 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)

[도12]



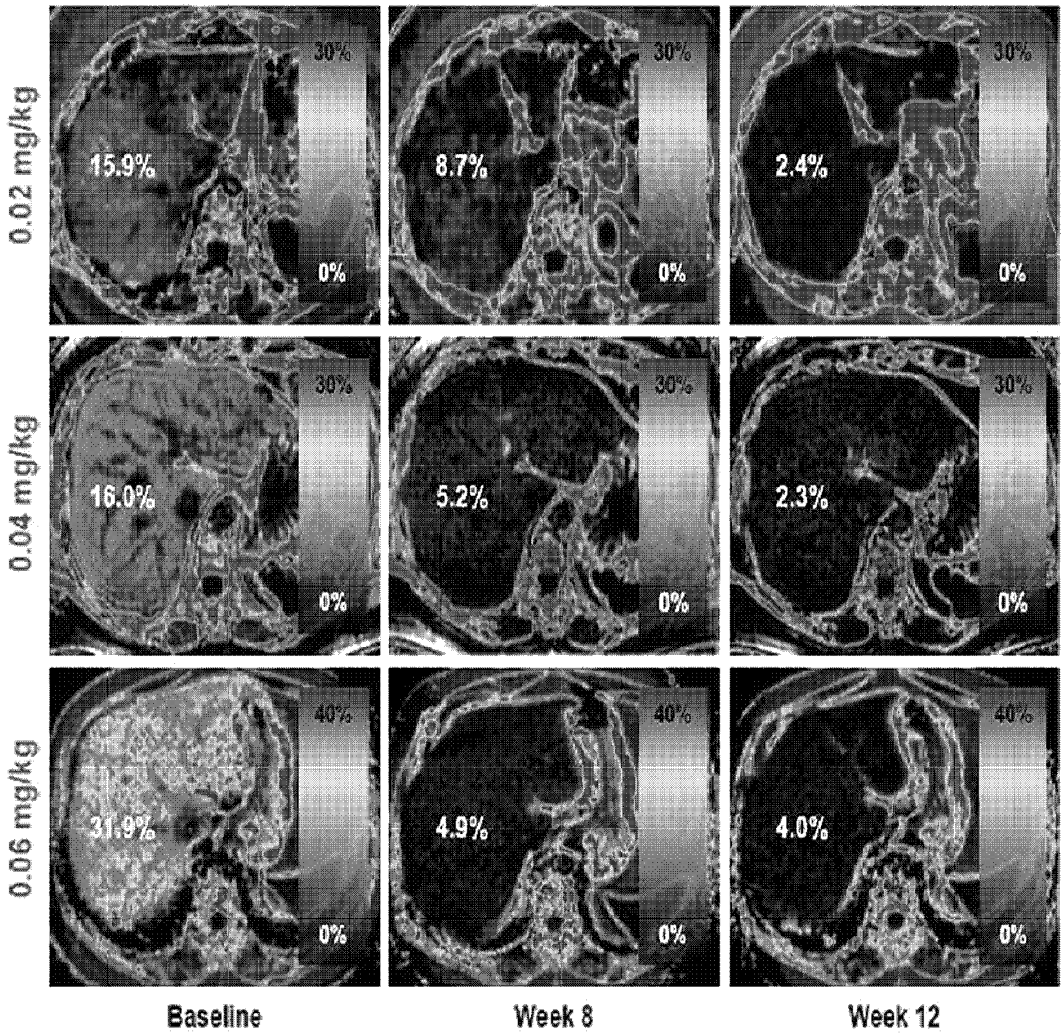
[도13]

	서열번호 42의 지속형 결합체 0.01 mg/kg		서열번호 42의 지속형 결합체 0.02 mg/kg		서열번호 42의 지속형 결합체 0.04 mg/kg		서열번호 42의 지속형 결합체 0.06 mg/kg		서열번호 42의 지속형 결합체 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 ± 42.66	135.46 ± 84.46	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	176.53 ± 110.9	257.47 ± 292.75	152.44 ± 81.16	118.2 ± 51.78	191.25 ± 75.6
AUC_{0-168h} (ng/mL·h)	3579.7 ± 1333.0	5554.5 ± 3638.8	6638.7 ± 2468.6	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

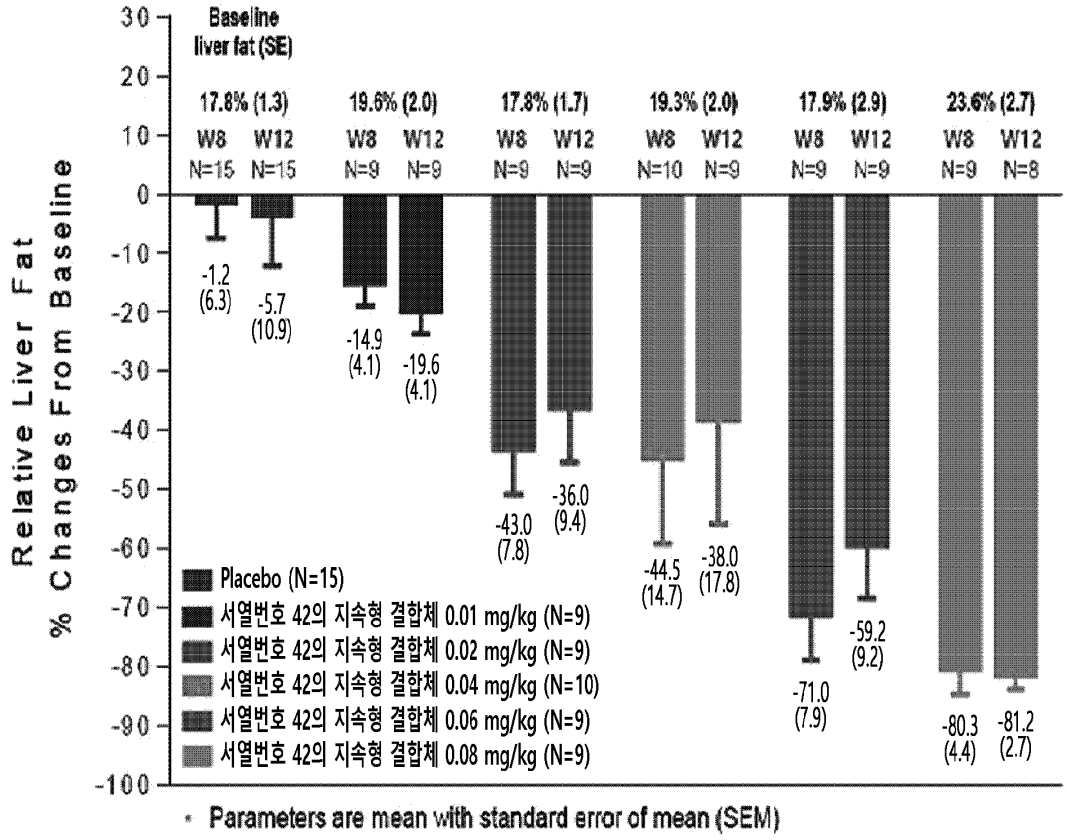
[도14]

TEAE Category No. of Subjects (%)	서열번호 42의 지속형 결합체 0.01 mg/kg (N=9)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=10)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=12)	서열번호 42의 지속형 결합체 0.06 mg/kg (N=9)	서열번호 42의 지속형 결합체 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)

[도15]


0.02 mg/kg
0.04 mg/kg
0.06 mg/kg
15.9%
8.7%
2.4%
16.0%
5.2%
2.3%
31.9%
4.9%
4.0%
30%
0%
40%
0%
Baseline
Week 8
Week 12

[도16]



[도17]

	Placebo (N=15)	서열번호 42의 지속형 결합체 0.01 mg/kg (N=9)	서열번호 42의 지속형 결합체 0.02 mg/kg (N=9)	서열번호 42의 지속형 결합체 0.04 mg/kg (N=10)	서열번호 42의 지속형 결합체 0.06 mg/kg (N=9)	서열번호 42의 지속형 결합체 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]