Novel combination of GLP-1/GIP/Glucagon triple agonist (HM15211) and once-weekly basal insulin offers improved glucose lowering and weight loss in a diabetic animal model

Jung Kuk Kim, Jong Suk Lee, Jaehyuk Choi, Sang Hyun Lee, In Young Choi, and Sun Jin Kim

Hanmi Pharm. Co., Ltd., Seoul, Republic of Korea

Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.

- **This presentation only includes content to scientific data and research results**
- **All treatment options in the therapeutic area will be addressed in this presentation**

PHOTOGRAPHY PROHIBITED

PLEASE DO NOT take photos of this presentation

Efficacy and safety profiles of intensified insulin therapy

Basal Insulin mono

Pros.

- The most potent therapeutics
- Individualized dosing by titration

Cons.

- Little effect on PPG control
- With increasing dose higher risk for
  - Weight gain
  - Hypoglycemia

Efficacy and safety profiles of intensified insulin therapy

Basal Insulin mono

Pros.
- The most potent therapeutics
- Individualized dosing by titration

Cons.
- Little effect on PPG control
- With increasing dose higher risk for
  - Weight gain
  - Hypoglycemia

1. Basal/Bolus insulin

2. Basal insulin/GLP-1RA COMBO

Efficacy and safety profiles of intensified insulin therapy

Basal Insulin mono

Pros.
- The most potent therapeutics
- Individualized dosing by titration

Cons.
- Little effect on PPG control
- With increasing dose higher risk for
  - Weight gain
  - Hypoglycemia

1. Basal/Bolus insulin

DUAL VII (Novo nordisk)

T2DM patient w/
HbA1c: 7.0 ~ 10.0%
IGlar: 20 ~ 50U + metformin
BMI ≤ 40 kg/m^2

- IGlar + IAsp + metformin
- IDegLira + metformin

26 weeks

Ref. *Diabetes Care.* **41**, 1009-16 (2018) for DUAL VII

2. Basal insulin/GLP-1RA COMBO

Efficacy and safety profiles of intensified insulin therapy

Basal Insulin mono

Pros.
- The most potent therapeutics
- Individualized dosing by titration

Cons.
- Little effect on PPG control
- With increasing dose higher risk for
  - Weight gain
  - Hypoglycemia

1. Basal/Bolus insulin

-1.46 %	84.1 U	1.66 episodes/PYE*	2.64 kg
Glycemic control (HbA1c change)	**Total INS dose**	**Hypo. Risk**	**Weight control (BW change)**
-1.48 %	40.4 U	0.13 episodes/PYE	-0.93 kg

Ref. *Diabetes Care.* **41**, 1009-16 (2018) for DUAL VII; IR presentation 2Q, 2017 Novo nordisk

2. Basal insulin/GLP-1RA COMBO

Note. *PYE: Patient years of exposure

Efficacy and safety profiles of intensified insulin therapy

Basal Insulin mono

Pros.
- The most potent therapeutics
- Individualized dosing by titration

Cons.
- Little effect on PPG control
- With increasing dose higher risk for
  - Weight gain
  - Hypoglycemia

1. Basal/Bolus insulin

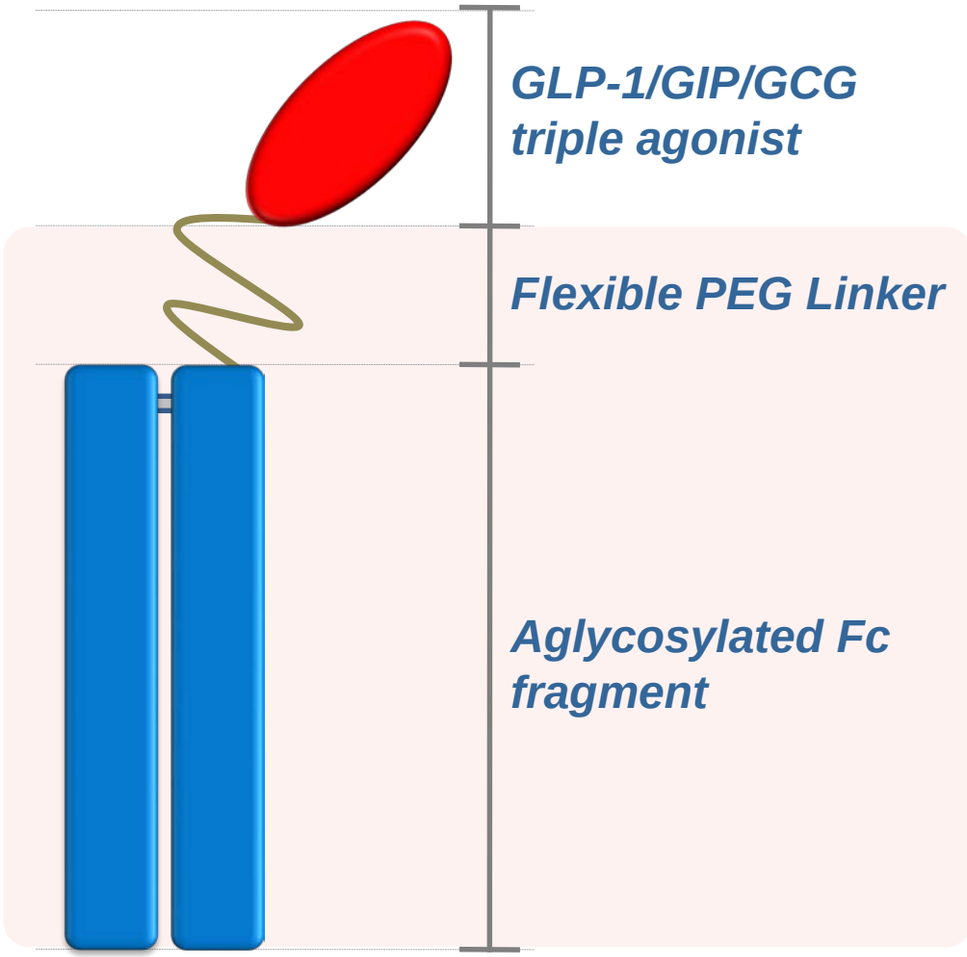
-1.46 %	84.1 U	1.66 episodes/PYE*	2.64 kg
Glycemic control (HbA1c change)	**Total INS dose**	**Hypo. Risk**	**Weight control** (BW change)
-1.3 ~ -2.0 %; -1.48 %	40.4 U	0.13 episodes/PYE	**-2.7 ~ +2.0 kg;** -0.93 kg

Ref. *Diabetes Care.* **41**, 1009-16 (2018) for DUAL VII; IR presentation 2Q, 2017 Novo nordisk

2. Basal insulin/GLP-1RA COMBO

Note. *PYE: Patient years of exposure

HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist



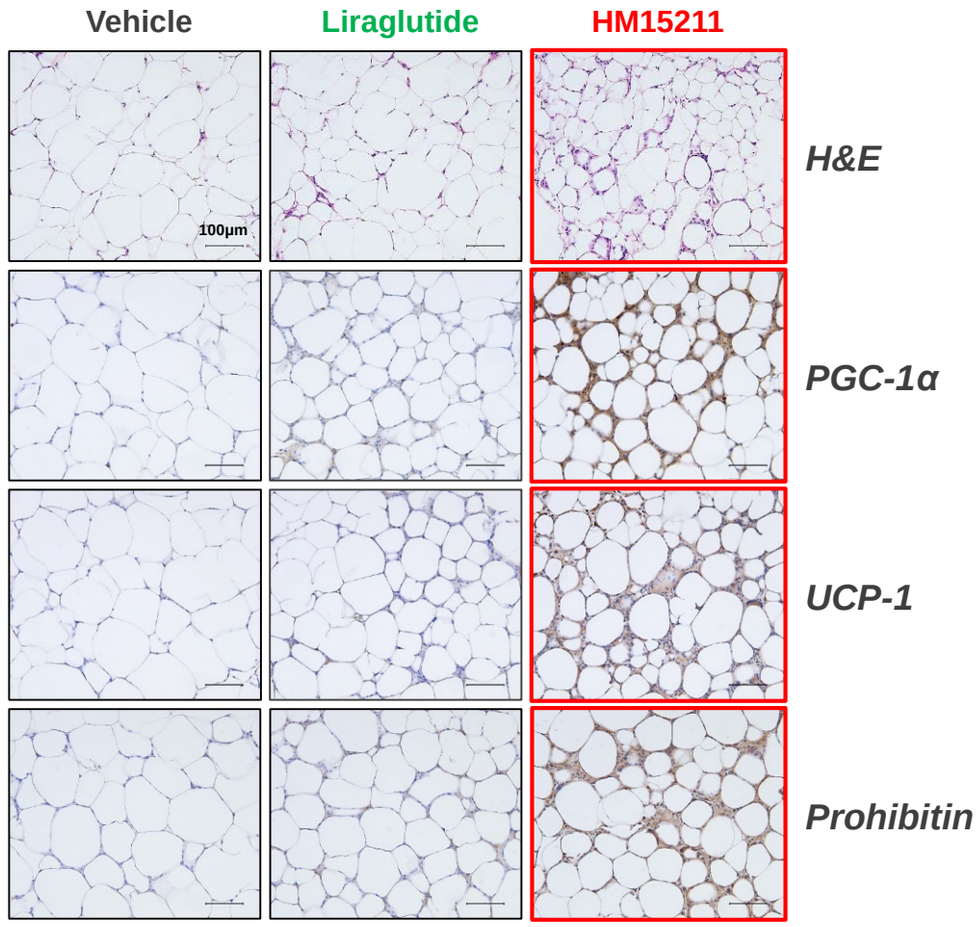
Hanmi's GLP-1/GIP/GCG triple agonist is conjugated with a human IgG Fc fragment *via* flexible linker

[General profiles]

- Extended half-life ($t_{1/2}$ = 42.7 ~ 55 hrs in mice; 82.8 ~ 85.7 hrs in rats)
- High glucagon (GCG) leading to efficient weight loss and NASH improvement [2018 ADA 1105-, 1106-, and 1107-P]
- Balanced GLP-1 and GIP to neutralize hyperglycemic risk of high GCG
- Similar activity profiles at human and rodent receptors
- Under phase 1 clinical evaluation in healthy obese subjects

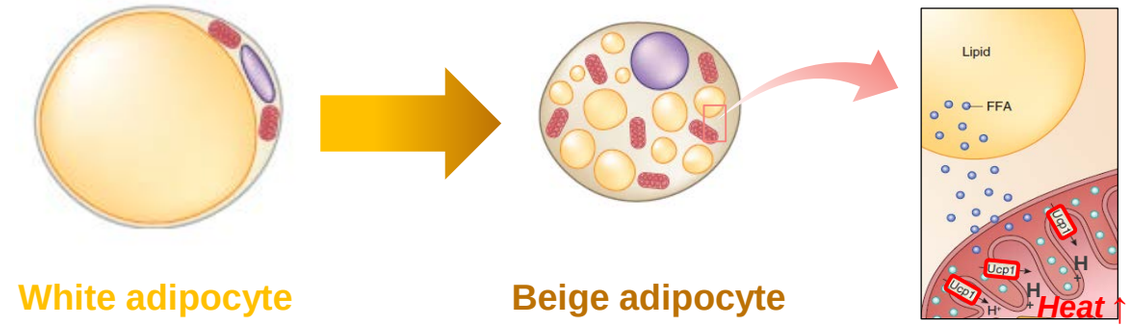
LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

Enhanced energy expenditure by HM15211 via browning of WAT

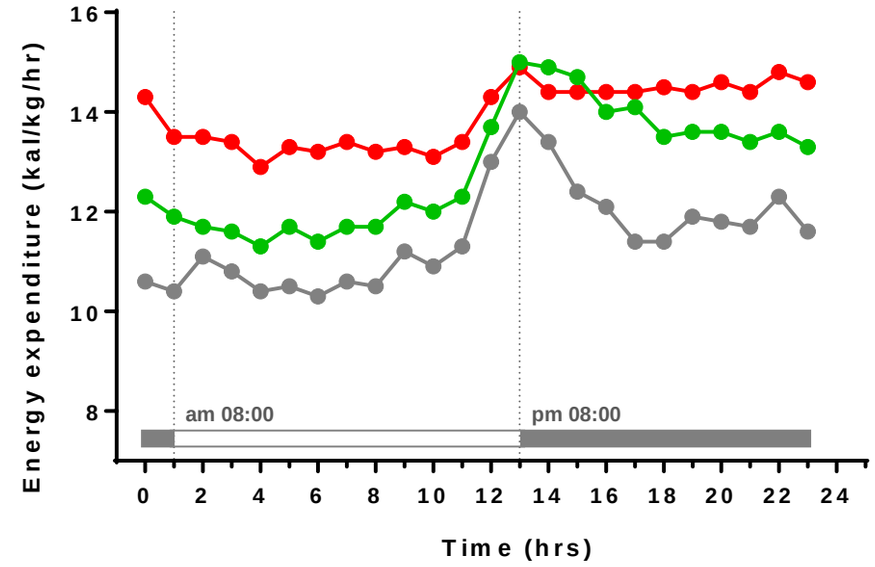


- Vehicle
- Liraglutide 50 nmol/kg, BID (3 mg/day in human)
- HM15211 2.87 nmol/kg, BID (4 mg/wk in human)

❖ **HM15211 enhances energy expenditure by beige adipocyte induction**

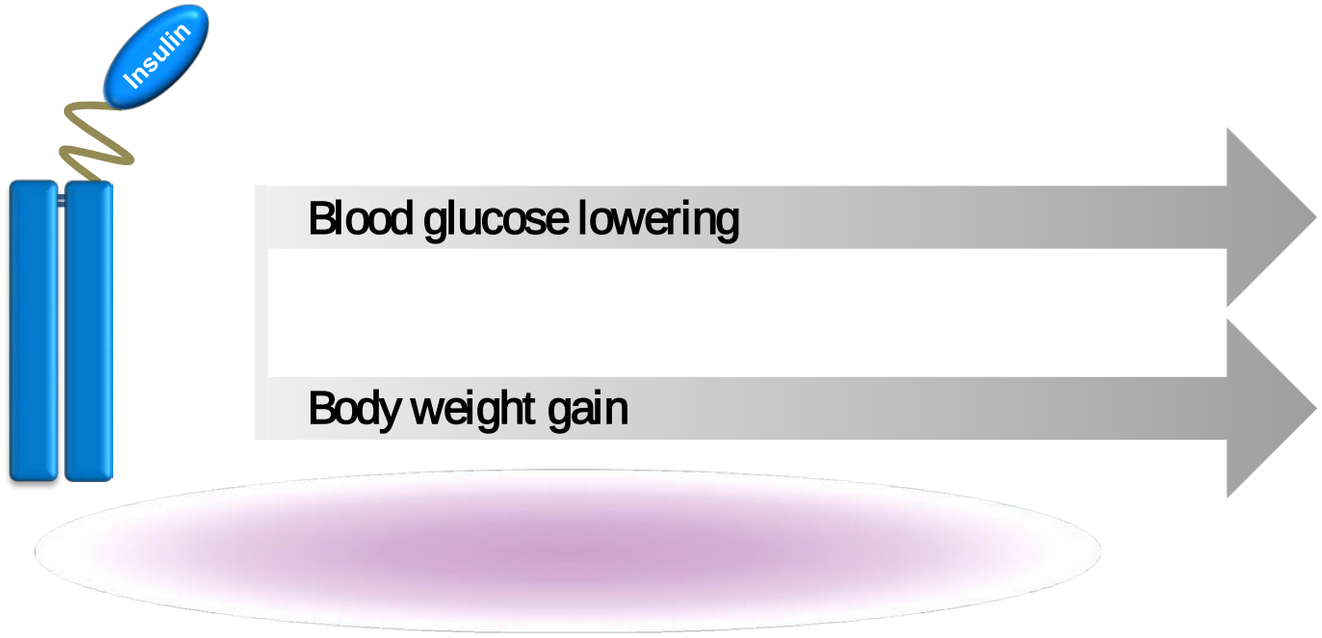


Energy expenditure in DIO mice (n=10)



Hypothesis

Basal Insulin

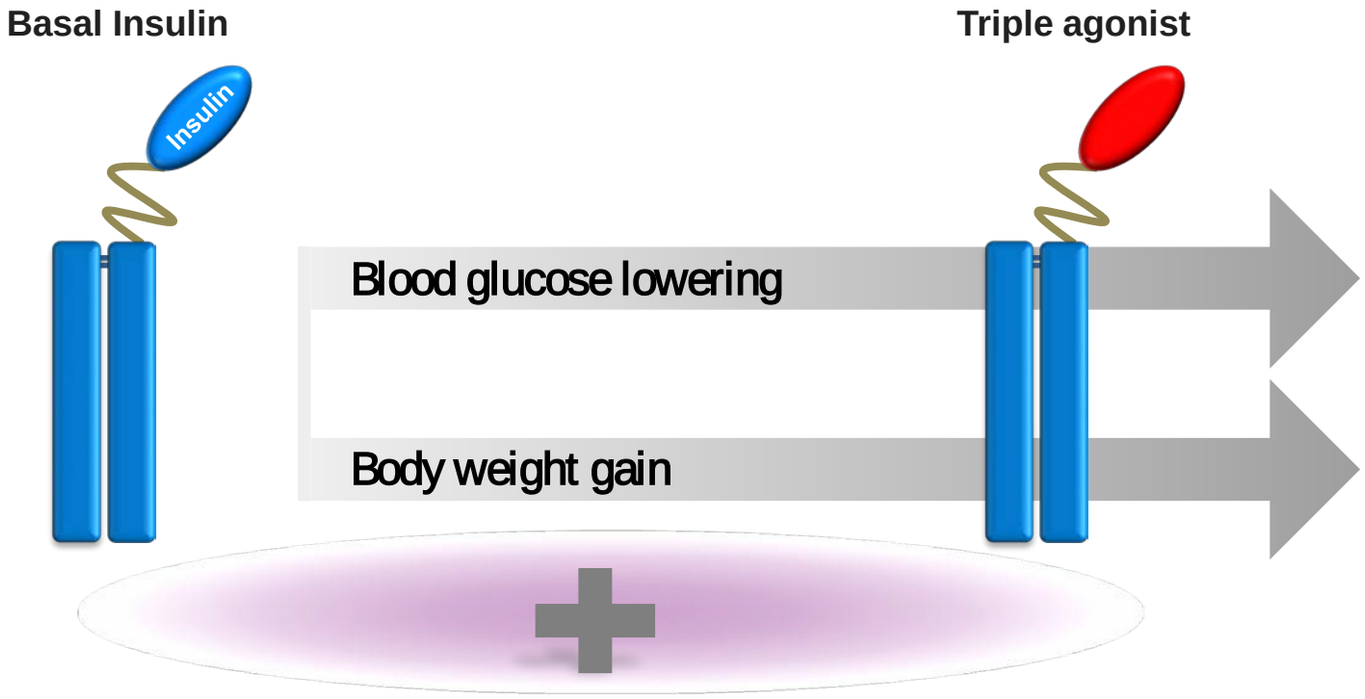


Long-acting basal Insulin

HM12460A [Ph1, US]

- ^{LAPS}Insulin
- Human insulin conjugated to human IgG Fc fragment
- Targeting once-weekly basal insulin
- Under efficacy evaluation in diabetic patients (P1b)

Hypothesis



- **Potential for enhanced glycemic control**
- **Efficient weight loss,**
  not weight gain neutralization

Long-acting basal Insulin

HM12460A [Ph1, US]

- ^{LAPS}Insulin
- Human insulin conjugated to human IgG Fc fragment
- Targeting once-weekly basal insulin
- Under efficacy evaluation in diabetic patients (P1b)

Long-acting triple agonist

HM15211 [Ph1, US]

- IgG Fc fragment conjugated for long duration of action
- Efficient weight loss add and NASH/fibrosis improvement in animal disease models
- Expected for once-weekly regimen
- Under safety and PK evaluation in healthy volunteers (P1)

Objective & study strategies

Combination of HM15211 with long-acting basal insulin might provide benefits in [1] glycemic control and [2] body weight management in…

- **Genetic diabetic model**

***db/db* mice**
: Obesity and T2DM phenotype by leptin receptor deficient

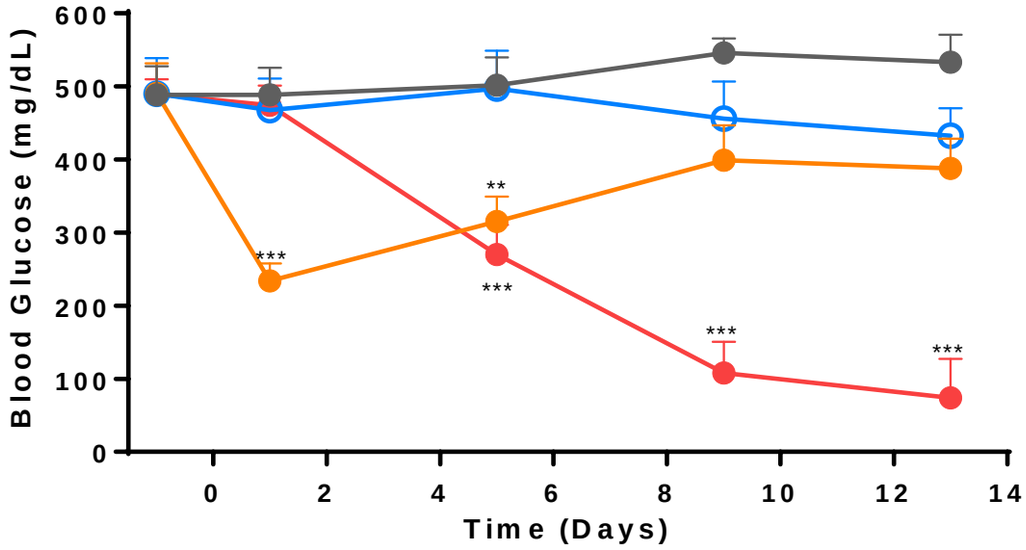
- **Acquired diabetic model**

DIO/STZ rats
: Obesity and insulin resistance by high fat diet
: Partial β-cell destruction by low dose STZ

Glycemic control by HM15211/HM12460A COMBO in *db/db* mice

Non-fasting blood glucose profile

(***db/db* mice**, n=7)



Vehicle

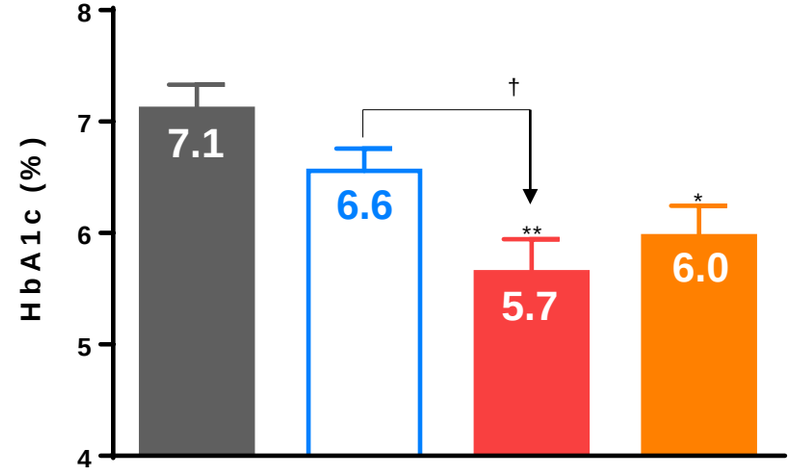
HM12460A 42.2 nmol/kg, Q2D (12 nmol/kg in human)

HM12460A 42.2 nmol/kg, Q2D + HM15211 2.6 nmol/kg, Q2D

IDeg 18.5 nmol/kg BID + Lirag 30 nmol/kg, BID (50 U + 1.8 mg in human)

HbA1c after 2 weeks treatment

(***db/db* mice**, n=7)



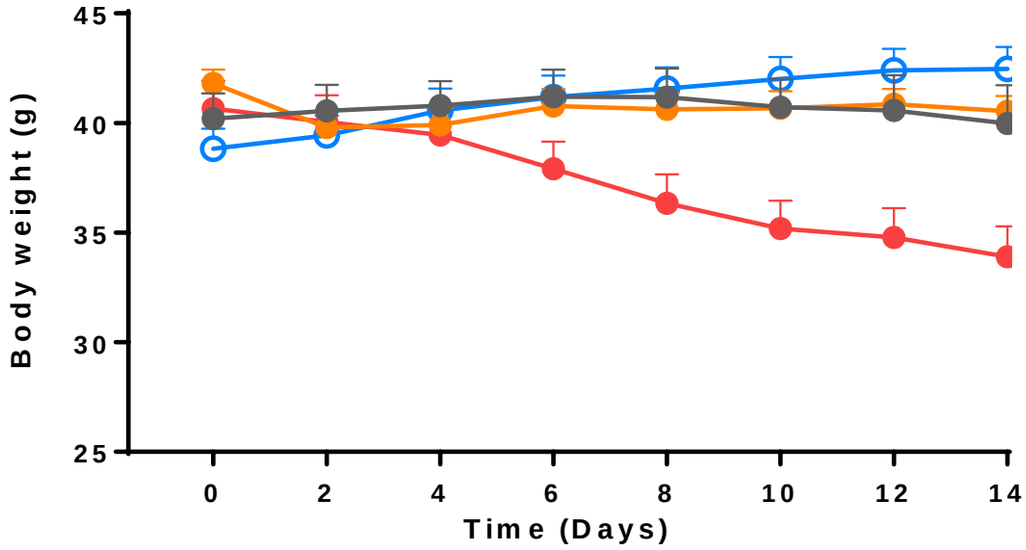
*~***p<0.05~0.001 *vs.* vehicle by one-way ANOVA

†p<0.05 *vs.* HM12460A mono by unpaired t-test

Body weight control by HM15211/HM12460A COMBO in *db/db* mice

Body weight profile

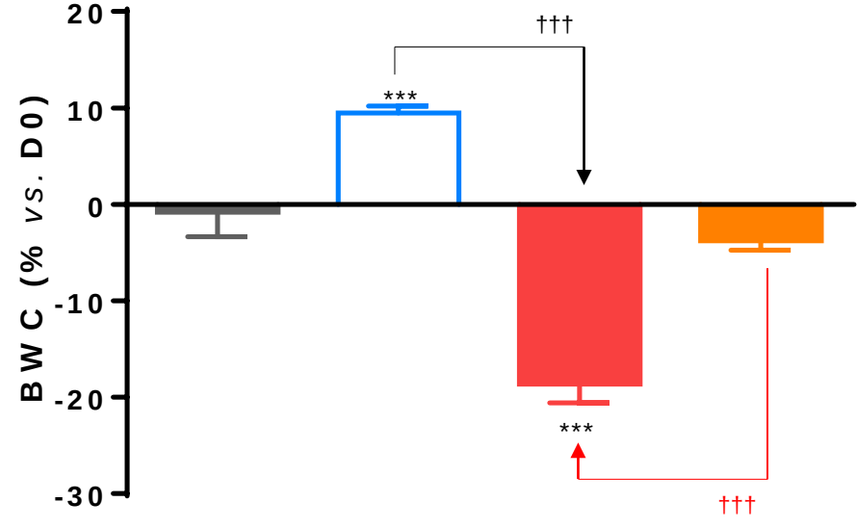
(***db/db* mice**, n=7)



- **Vehicle**
- **HM12460A 42.2 nmol/kg, Q2D (12 nmol/kg in human)**
- **HM12460A 42.2 nmol/kg, Q2D + HM15211 2.6 nmol/kg, Q2D**
- **IDeg 18.5 nmol/kg BID + Lirag 30 nmol/kg, BID (50 U + 1.8 mg in human)**

Body weight change after 2 weeks treatment

(***db/db* mice**, n=7)

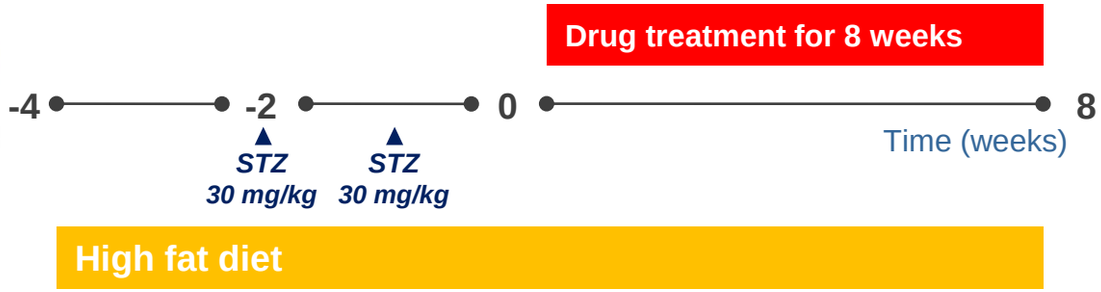


***p<0.001 *vs.* vehicle by one-way ANOVA
††† p<0.001 *vs.* HM12460A mono or IDegLira by unpaired t-test

Blood glucose lowering by HM15211/HM12460A COMBO in DIO/STZ rats

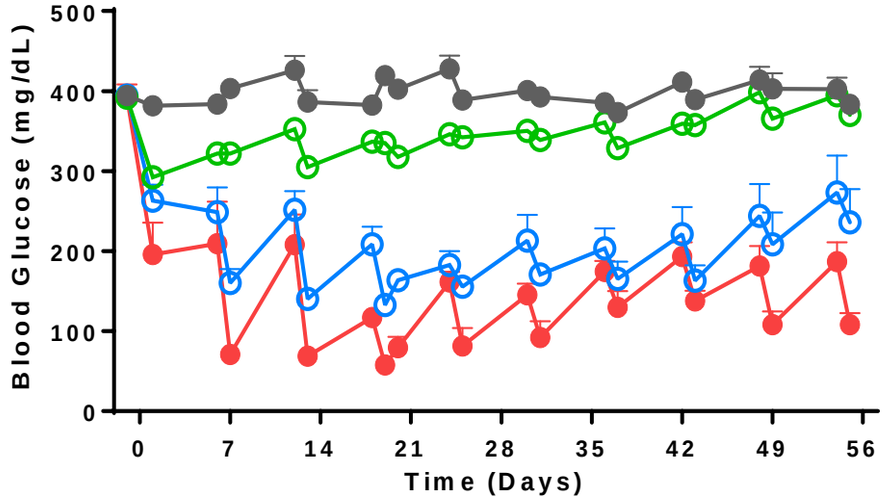
Study Design

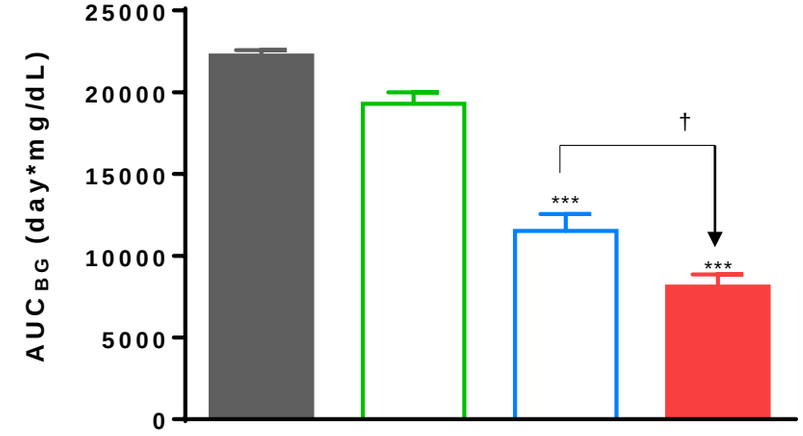
DIO/STZ rats



- Vehicle
- Liraglutide 15 nmol/kg, BID (1.8 mg in human)
- HM12460A 16.2 nmol/kg, Q3D (6 nmol/kg in human)
- HM12460A 16.2 nmol/kg, Q3D + HM15211 5.9 nmol/kg, Q3D

Non-fasting blood glucose profile and AUC_{BG} (DIO/STZ rats, n=6)



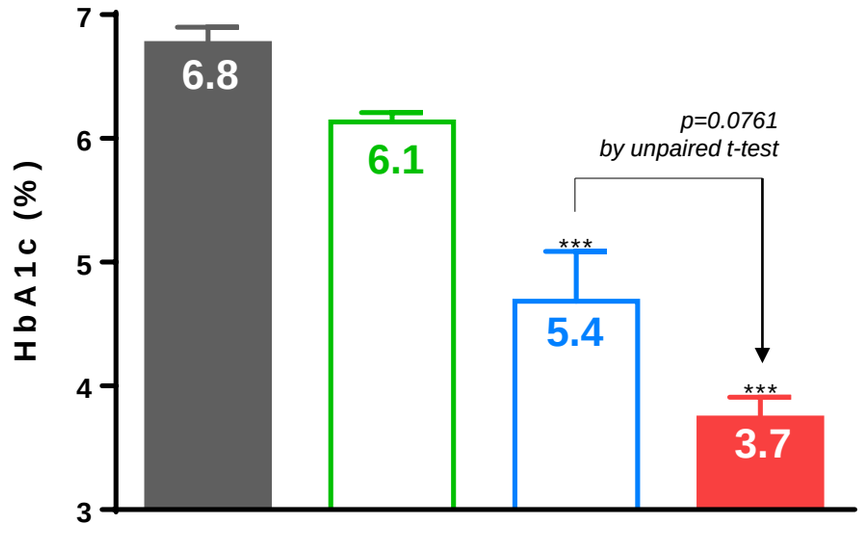


***p<0.001 *vs.* vehicle by one-way ANOVA
† p<0.05 *vs.* HM12460A mono by unpaired t-test

Glycemic and body weight control by HM15211/HM12460A COMBO in DIO/STZ rats

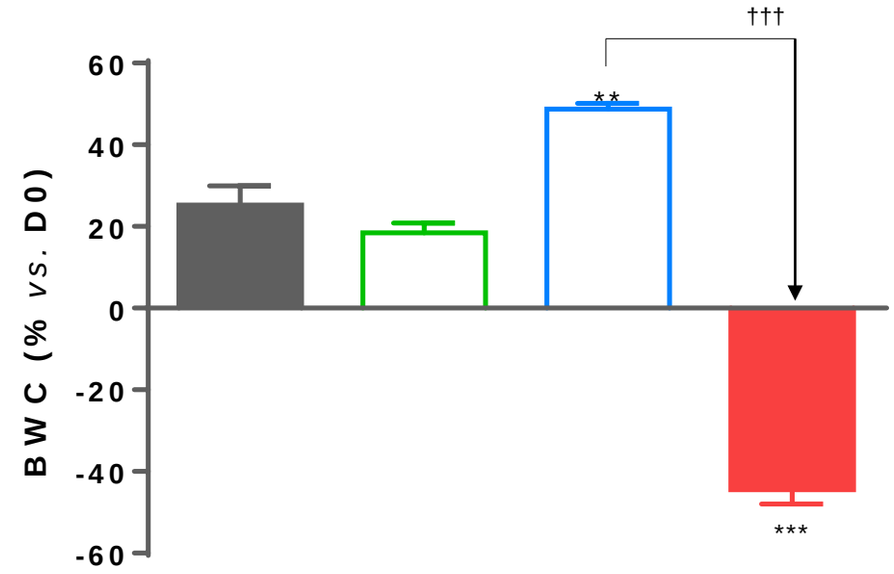
HbA1c after 8 weeks treatment

(**DIO/STZ rats**, n=6)



Body weight change after 8 weeks treatment

(**DIO/STZ rats**, n=6)



Vehicle
Liraglutide 15 nmol/kg, BID (1.8 mg in human)
HM12460A 16.2 nmol/kg, Q3D (6 nmol/kg in human)
HM12460A 16.2 nmol/kg, Q3D + HM15211 5.9 nmol/kg, Q3D

***p<0.001 *vs.* vehicle by one-way ANOVA
††† p<0.001 *vs.* HM12460A mono by unpaired t-test

Summary & Conclusion

- **Despite improved glycemic control efficacy, current insulin COMBO therapies (basal/bolus INS and INS/GLP-1RA combination) had relatively marginal effect on weight control**
- **HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist, could provide efficient weight loss via browning of WAT and subsequent enhanced energy expenditure, suggesting use as a novel COMBO partner of basal INS**
- **In *db/db* mice, the HM12460A and HM15211 COMBO provided better glycemic control (*vs.* insulin mono) and more weight loss than an INS/GLP-1RA COMBO**
- **In DIO/STZ rats, the HM15211 COMBO enhanced blood glucose lowering compared to HM12460A and provided more weight loss than GLP-1RA**

In addition to prandial insulin and GLP-1RA, a triple agonist could be an additional COMBO partner for basal insulin resulting in improved glycemic control and particularly effective body weight loss which can be hardly achieved by and INS/GLP-1RA COMBO

Please note posters reporting more information about HM15211:

1105-P: Neuroprotective effects of HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist in the neurodegenerative disease models
1106-P: Effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in a NASH and fibrosis animal model
1107-P: Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in the obese-osteoporosis rodent model