Potent body weight loss, and therapeutic efficacy in a NASH animal model by a novel long-acting GLP-1/GIP/Glucagon tri-agonist (HM15211)

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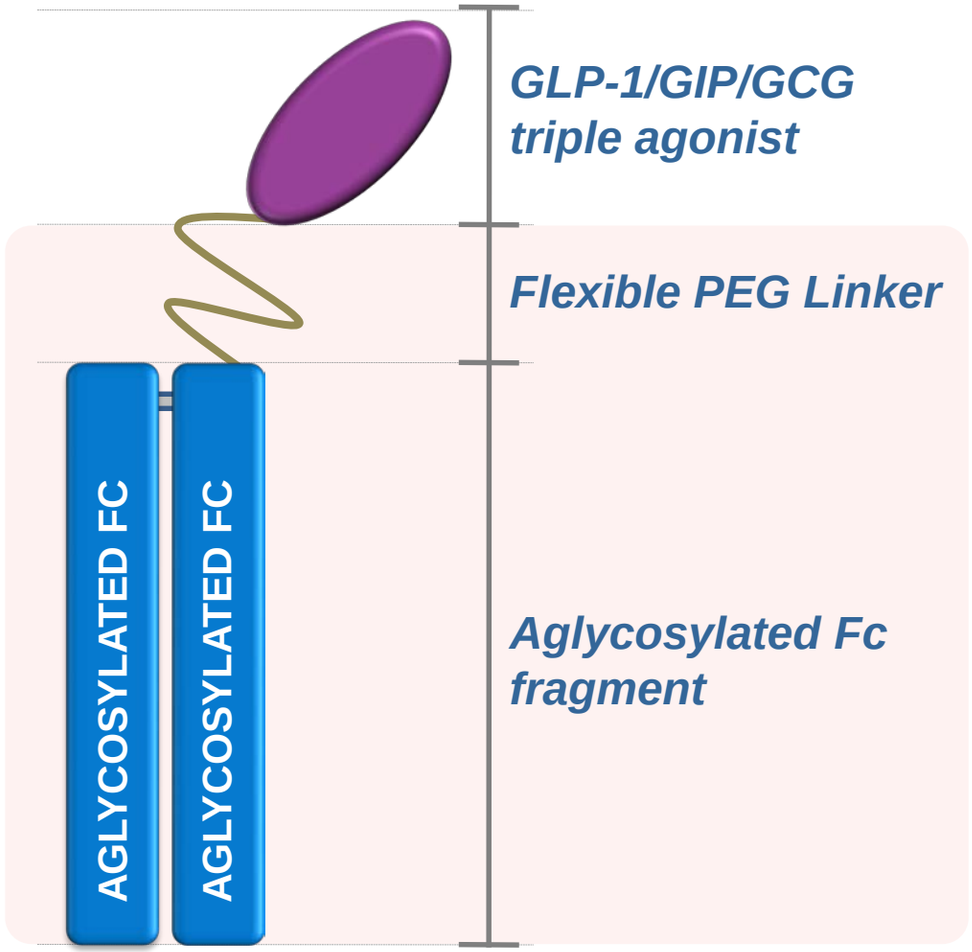
Presenter Disclosure

An employee of Hanmi Pharm. Co., Ltd.

General properties of incretins single- and co-agonist

	Single agonist	Dual agonist		Triple agonist
	GLP-1RA	GLP-1/GCG	GLP-1/GIP	GLP-1/GIP/GCG
Body weight	↓	↓↓	↓	~ ↓↓↓
Lipid profile	↓	↓↓	↓	~ ↓↓↓
NASH	↓	↓↓	↓	~ ↓↓↓
Blood glucose	↓	↓	↓↓	~ ↓↓
	Suitable for glycemic control Not enough for potent BWL	Improved BWL efficacy Balanced activity ratio required for glycemic control	Enhanced glycemic control Still not suitable for potent BWL	Target indications depend on activity ratio **Specialized for NASH & obesity when high GCG applied**
Competition Landscape	Liraglutide (Launched, Novo) Semaglutide (Filed, Novo) Dulaglutide (Launched, Lilly) Efpeglenatide (P2, Sanofi/Hanmi)	SAR425899 (Sanofi) NN9277 (Novo) LY3305677 (Lilly) JNJ-64565111 (Janssen/Hanmi)	SAR438335 (Sanofi) LY3298176 (Lilly)	NN9423 (Novo) LY3298176 + long-actingGCG (Lilly) HM15211 (Hanmi)

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



LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

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

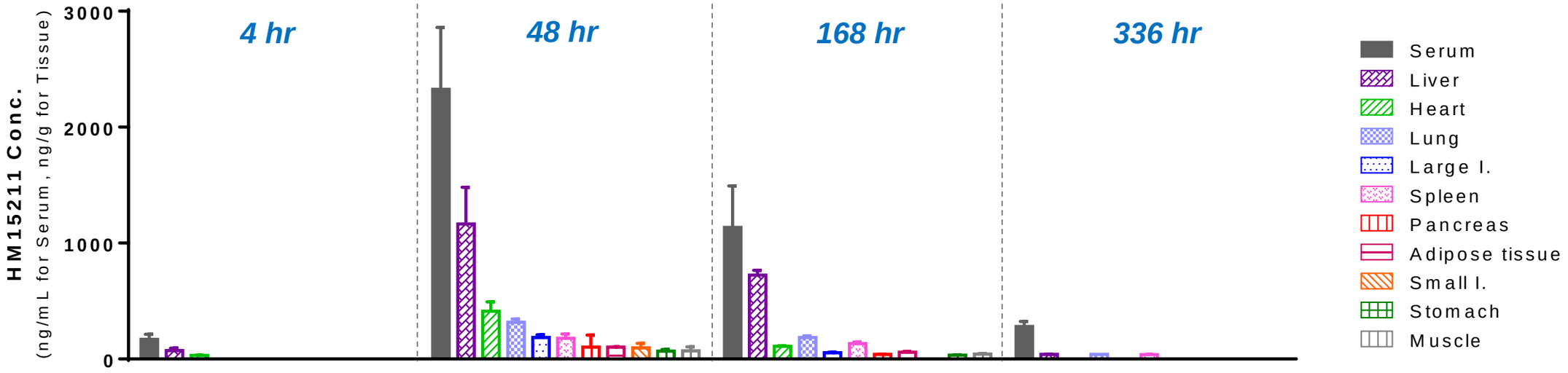
[General profiles]

- High glucagon activity, suitable for liver preferential distribution and NASH treatment
- Balanced GLP-1 and GIP action to neutralize hyperglycemic risk of high GCG
- Improved lipid profile, and anti-inflammatory effect by new born GIP
- Similar intrinsic activity profile between human and rodent receptor
- Extended half life ($t_{1/2}$ = 42.7 ~ 55 hr in mice; 82.8 ~ 85.7 hr in rats)
- Good Solubility (≥ 150 mg/mL) & bioavailability (≥ 95 %)

Time-dependent tissue distribution of HM15211

Tissue distribution in SD rats

(n=3/group, single administration)



Target organs	T_{max} (48h)		Elimination (336h)	
	Conc. (ng/mL or ng/g)	T/S ratio (%)	Conc. (ng/mL or ng/g)	T/S ratio (%)
Serum	2325.8	-	280.6	-
Liver	1165.5	**50.6**	39.7	**14.4**
Heart	441.5	**17.8**	<LLOQ	-
Lung	317.7	**14.1**	40.8	**14.8**
Large intestine	185.6	**8.1**	<LLOQ	-
Spleen	179.8	**7.8**	37.3	**13.4**
Pancreas	102.4	**5.4**	<LLOQ	-
Adipose tissue	103.2	**4.6**	<LLOQ	-
Small intestine	96.6	**4.0**	<LLOQ	-
Stomach	69.0	**3.2**	<LLOQ	-
Muscle	69.7	**3.0**	<LLOQ	-

* Brain, kidney were not detectable.

Objective

HM15211, long-acting GLP-1/GIP/Glucagon tri-agonist, might have therapeutic potential in NASH and obesity

- **To assess the**
  a. Efficacy and related MoAs in NASH animal models
  b. Efficacy and related MoAs in obesity animal models

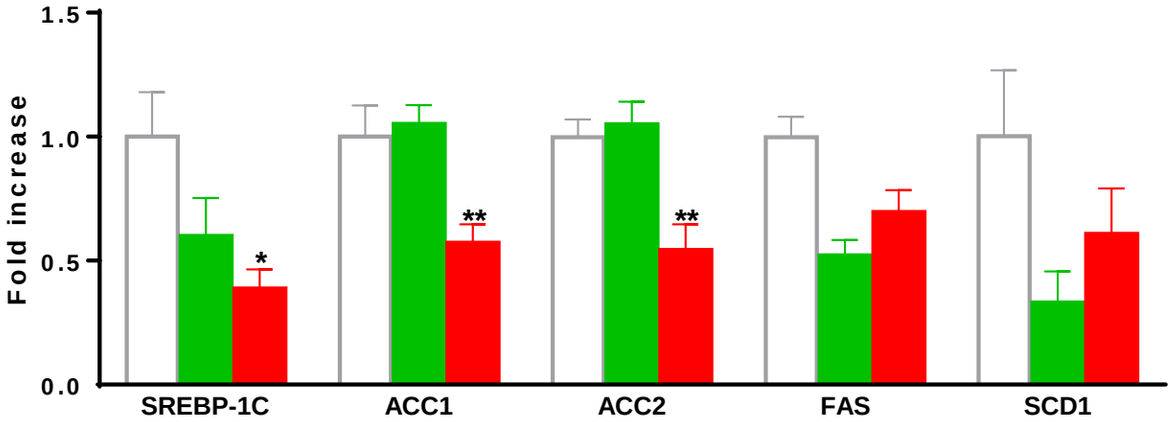
Efficacy and related MoAs in NASH animal models

Change in hepatic lipid metabolic gene expression

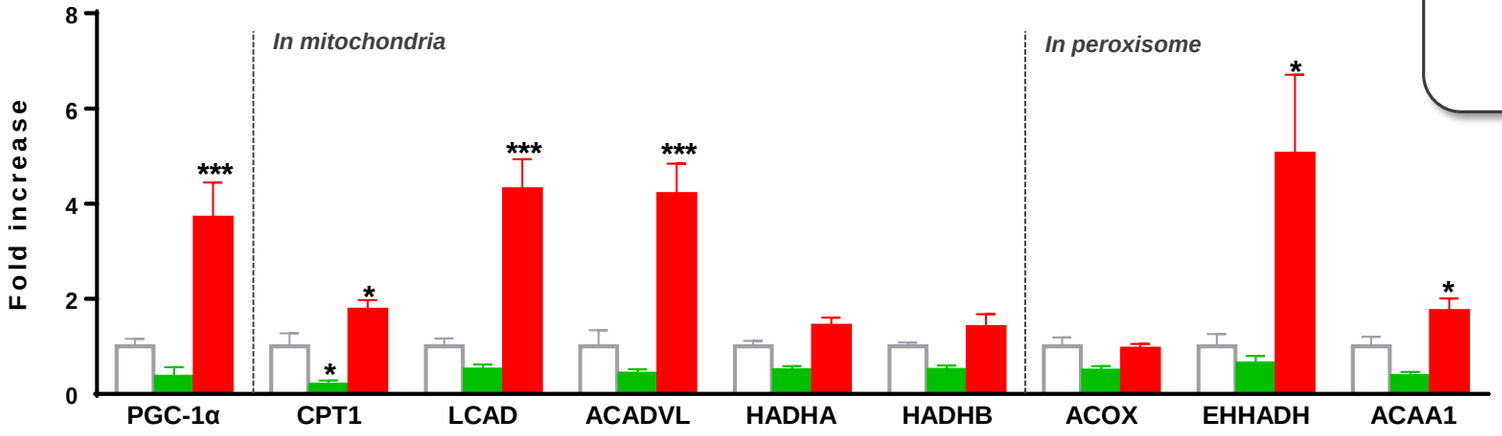
Lipid metabolism gene expression in DIO mice
(n=7/group, 4 wks treatment, qPCR)

Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 1.44 nmol/kg, Q2D (2 mg/wk in human)

De novo lipogenesis



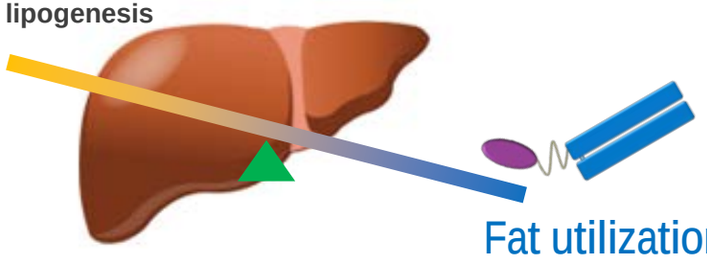
β-oxidation



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

❖ Favorable lipid metabolic gene regulation by HM15211

Fat accumulation
: inhibiting de novo lipogenesis



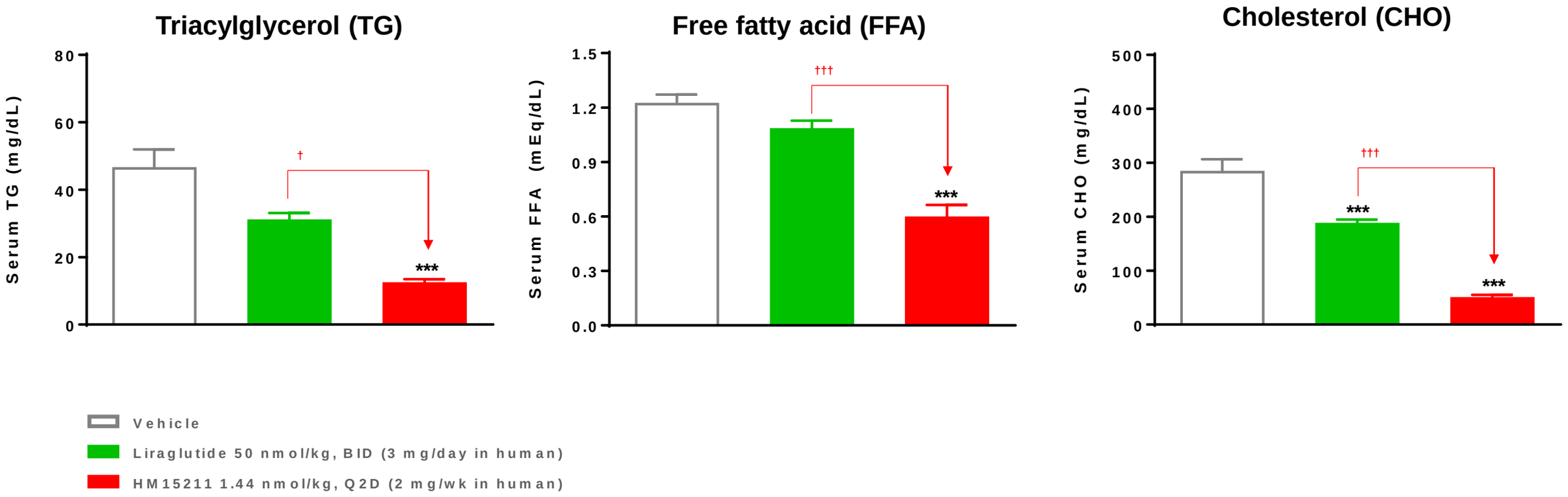
Fat utilization
: enhancing β-oxidation

Improvement of lipid profile, the main risk factor of NASH

†Abbreviation
SREBP-1C : Sterol regulatory element-binding protein
ACC : Acetyl-CoA carboxylase
FAS : Fatty acid synthase
SCD1 : Steroyl-CoA desaturase1
PGC-1α : Peroxisome proliferator-activated receptor gamma coactivator 1α
CPT1 : Carnitine palmitoyltransferase1
LCAD : Long chain acyl-CoA dehydrogenase
ACADVL : Acryl-CoA dehydrogenase, very long chain
HADHA or B : Hydroxy Acyl-CoA dehydrogenase α or β subunit
ACOX : Acetyl-CoA oxidase
EHHADH : Enoyl-CoA hydratase & 3-hydroxyacyl CoA dehydrogenase
ACAA1 : Acetyl-CoA acyltransferase1

Change in blood lipid profile

Serum lipid profiles in DIO mice
(n=7/group, 4 wks treatment)



***p<0.001 *vs.* vehicle by One-way ANOVA
†~†††p<0.05 ~ 0.001 *vs.* Liraglutide by One-way ANOVA

Change in NASH prognosis markers

Experimental scheme

C57BL/6 mice

Week 0 — 6 — 10

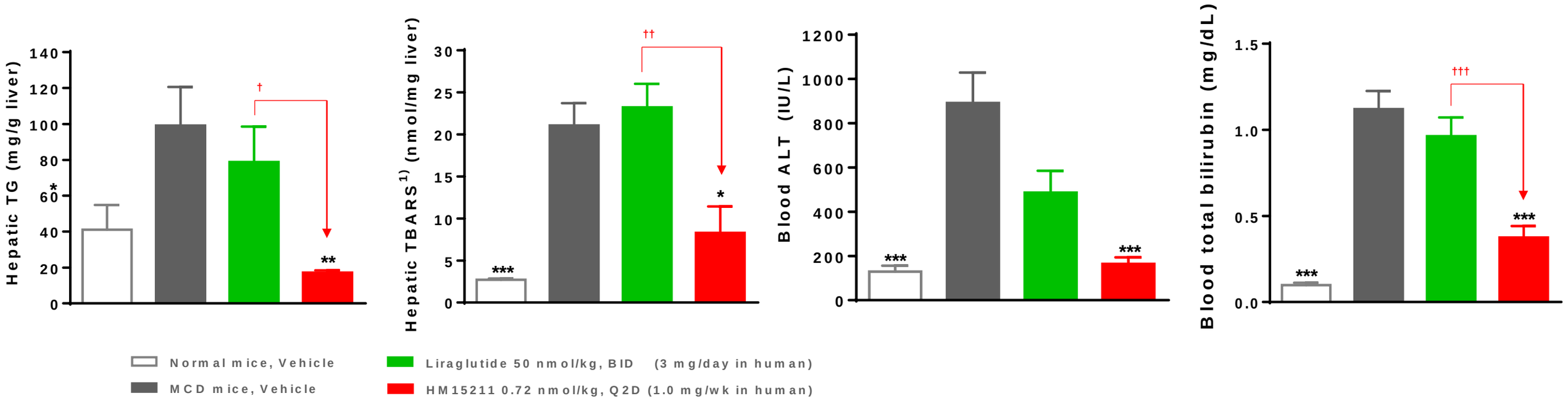
Drug treatment

MCD diet

Hepatic TG, TBARS
NASH markers

Hepatic lipid metabolism & liver function markers in MCD diet mice

(n=7/group, 4 wks treatment)



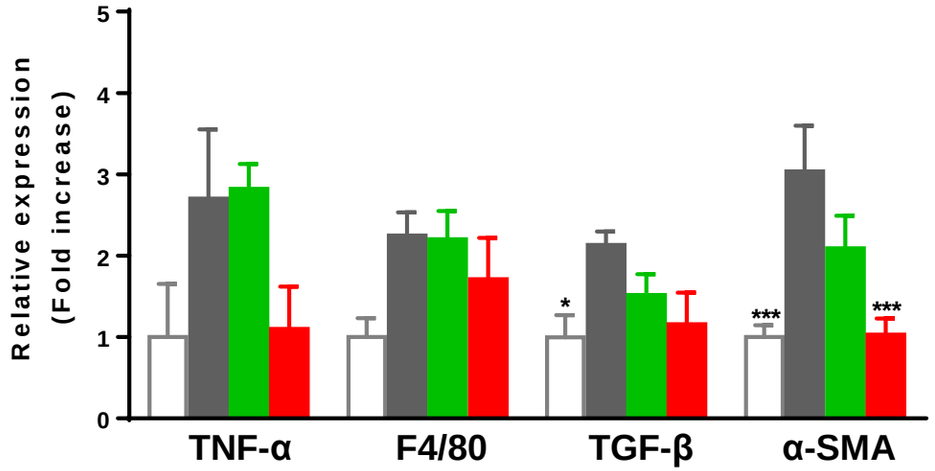
***p<0.001 *vs.* MCD mice, vehicle by One-way ANOVA

††p<0.01 *vs.* Liraglutide by One-way ANOVA

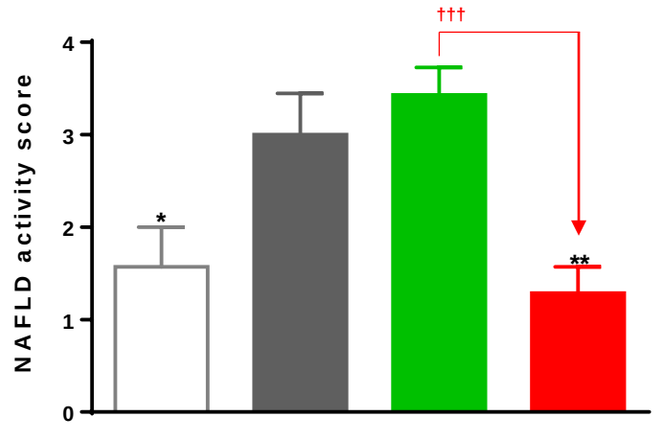
1) TBARS is surrogate of malondialdehyde, the lipid peroxidation product; oxidative stress marker

Change in hepatic inflammatory markers and NAS

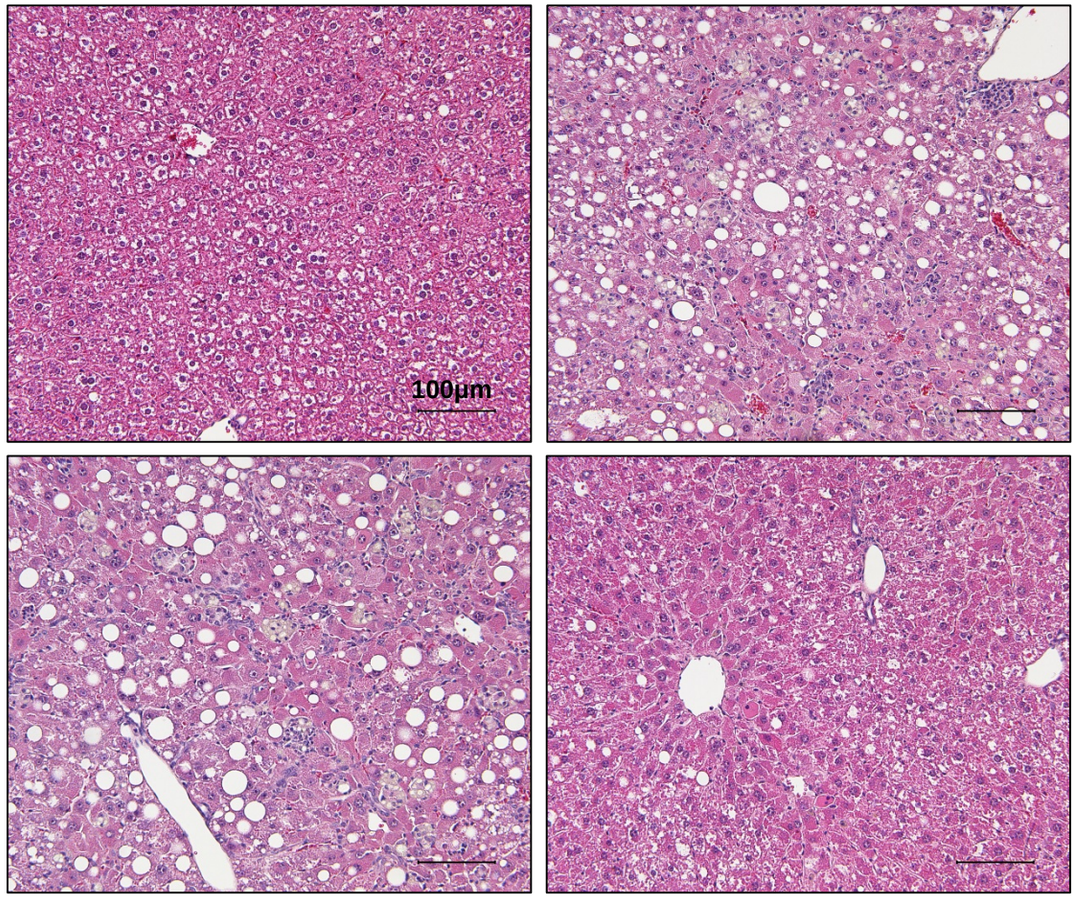
Inflammation & HSC activation marker gene expression in MCD diet mice (n=7/group, 4 wks treatment, qPCR)



NAFLD activity score in MCD diet mice
(n=7/group, 4 wks treatment)



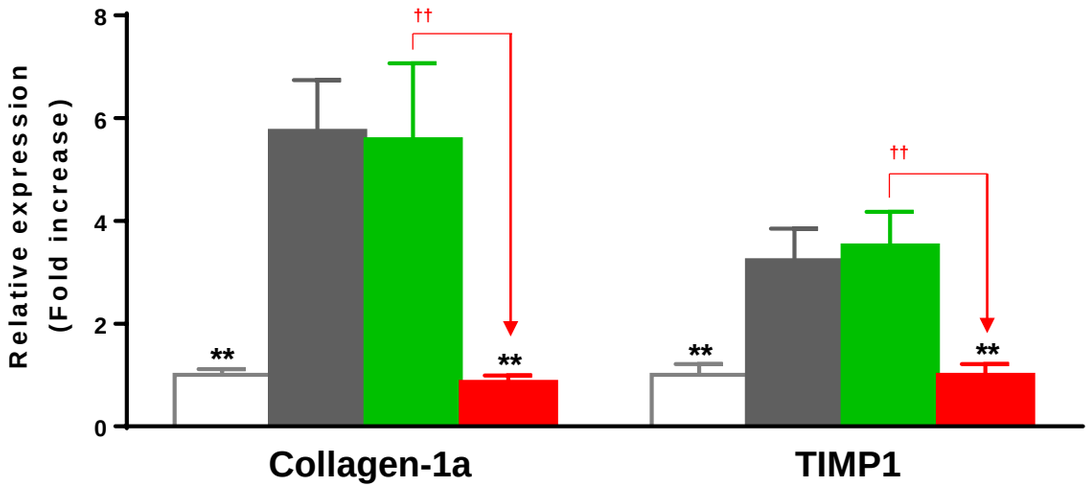
H&E staining in MCD diet mice
(representative image, 4 wks treatment)



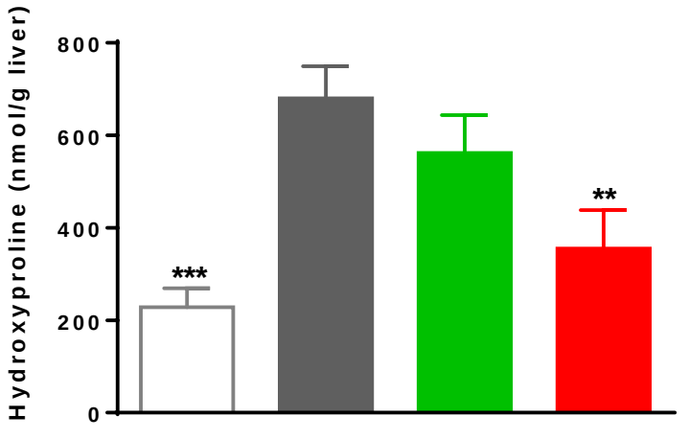
Normal mice, Vehicle
MCD mice, Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 0.72 nmol/kg, Q2D (1.0 mg/wk in human)

Change in hepatic fibrosis marker

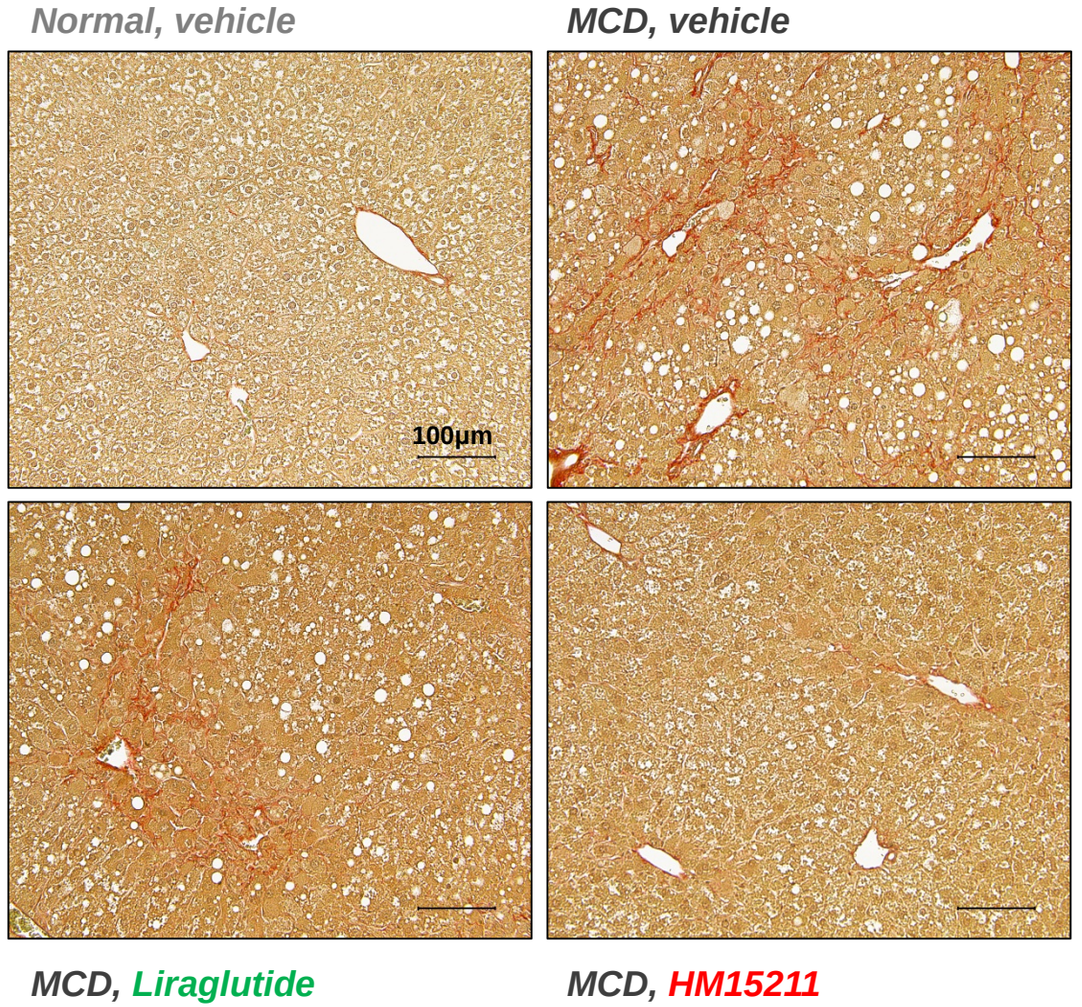
Fibrosis marker gene expression in MCD diet mice
(n=7/group, 4 wks treatment, qPCR)



Hepatic hydroxyproline in MCD diet mice
(n=7/group, 4 wks treatment)

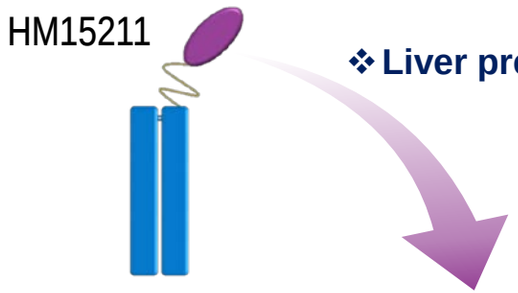


Sirus red staining in MCD diet mice
(representative image, 4 wks treatment)



Normal mice, Vehicle
MCD mice, Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 0.72 nmol/kg, Q2D (1.0 mg/wk in human)

Proposed MoAs of HM15211 for NASH treatment



❖ Liver preferential distribution

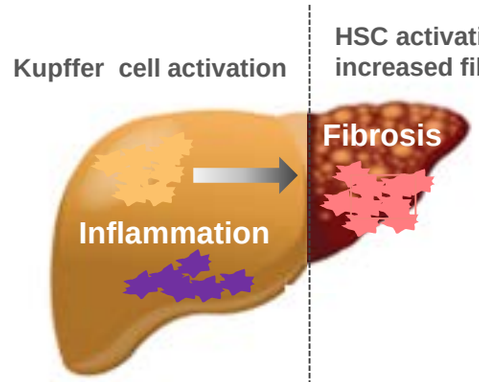
Progression of NASH

Normal

Dyslipidemia
Excess dietary lipid

NAFLD

Oxidative stress



NASH *Cirrhosis*

❖ Favorable reprogramming of lipid metabolism
❖ Improved lipid profile
❖ Reduced oxidative stress

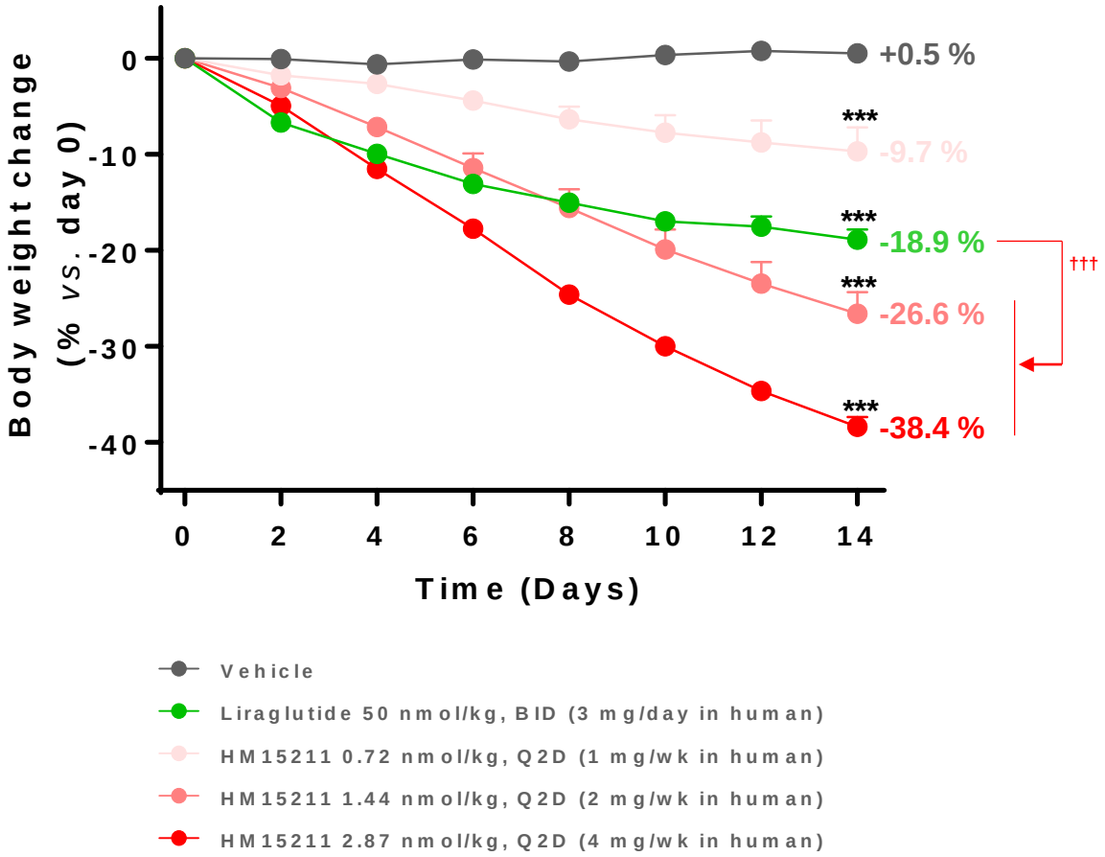
❖ Anti-inflammation
❖ Liver function protection

❖ Improved fibrosis

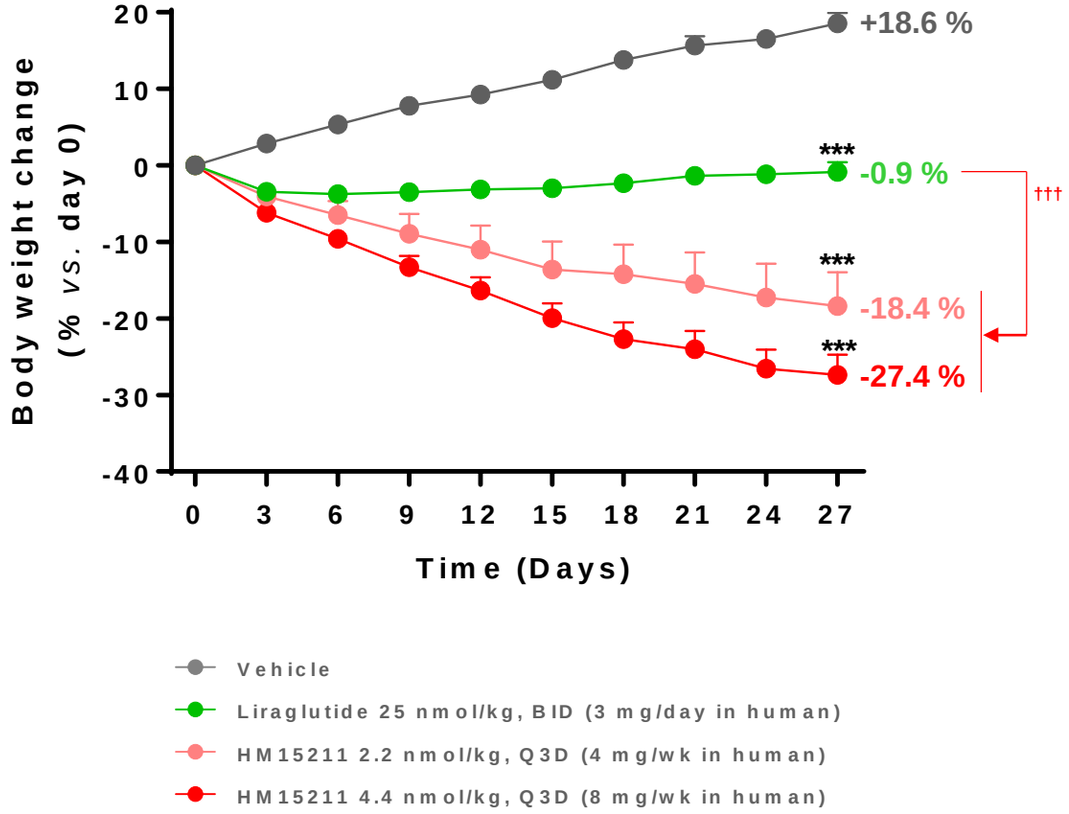
Efficacy and related MoAs in obesity animal models

Body weight change in obese animal models

DIO mice (n=7/group, 2 wks treatment)



DIO rats (n=6/group, 4 wks treatment)

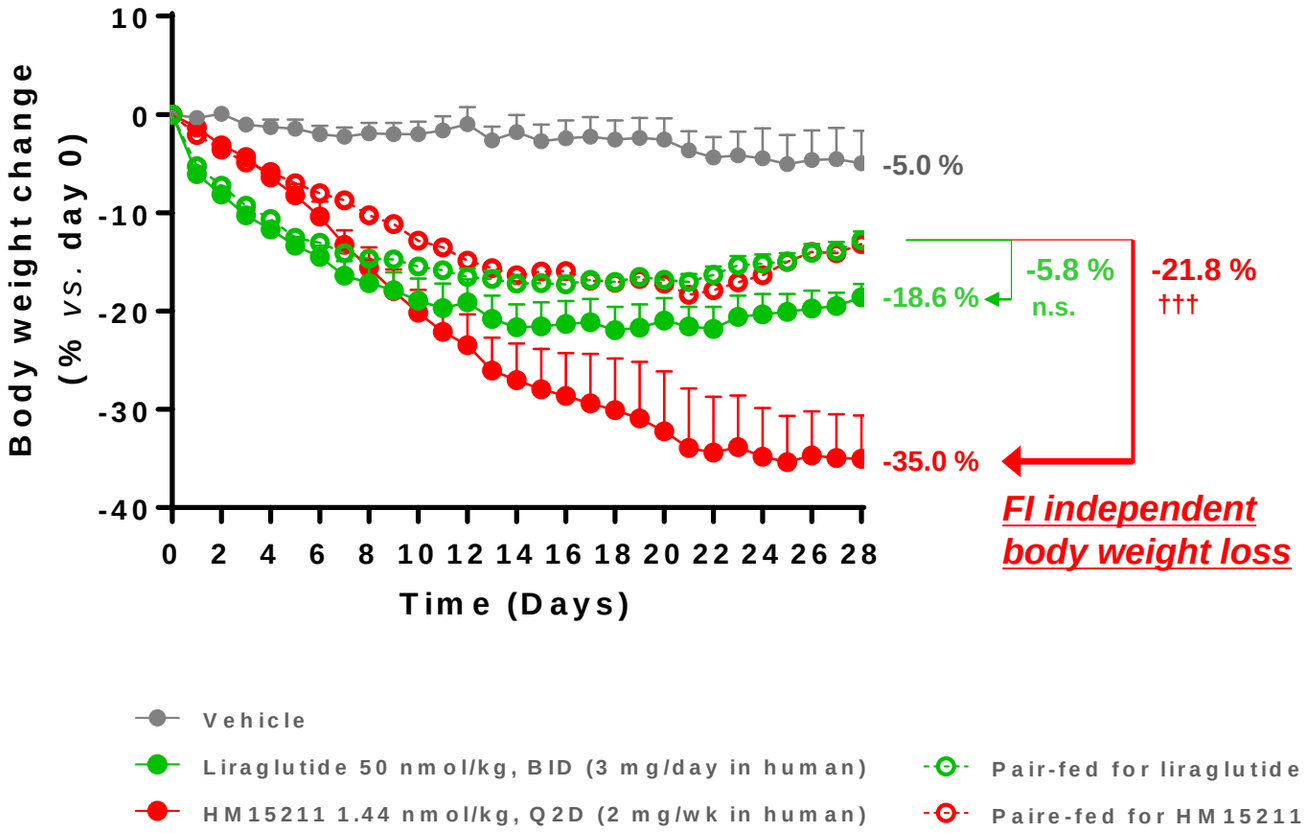


***p<0.001 *vs.* vehicle by Two-way ANOVA
†††p<0.001 *vs.* Liraglutide by Two-way ANOVA

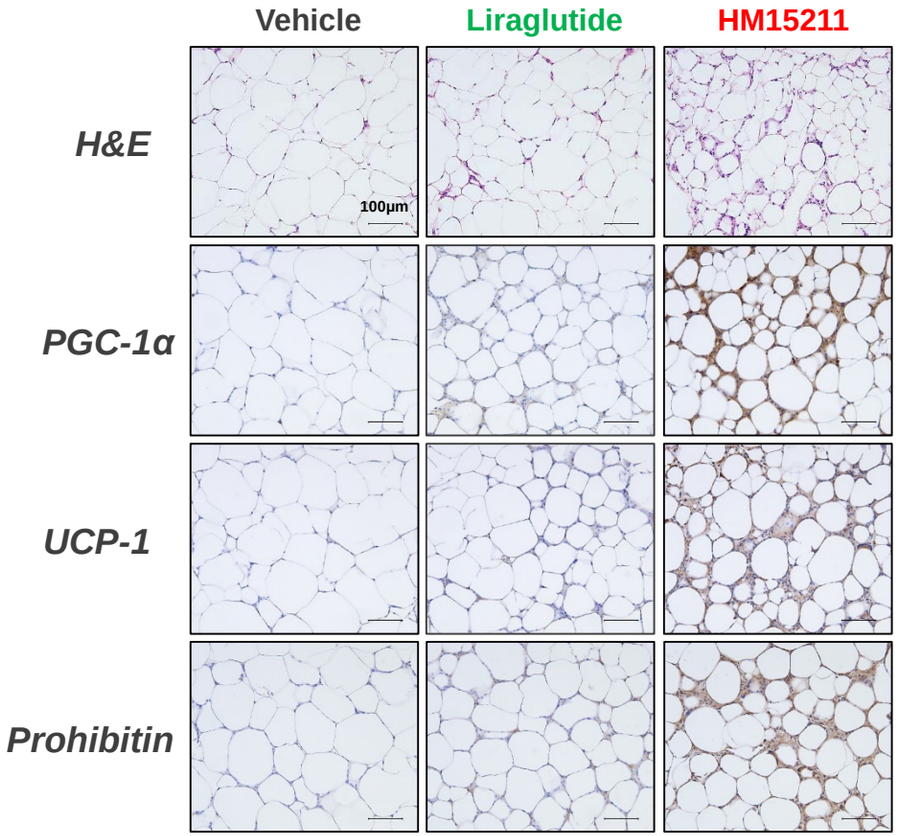
Anorexia-independent body weight change, and underlying MoAs

Body weight change in pair-fed controlled DIO mice

(n=6/group, 4 wks treatment)

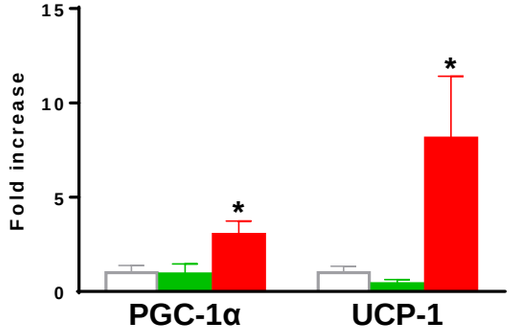


FI independent body weight loss



Thermogenic gene expression in WAT

(DIO mice, n=7/group, 4 wks treatment, qPCR)



†††p<0.001 *vs.* pair-fed by Two-way ANOVA, *p<0.01 ~ 0.001 *vs.* vehicle by One-way ANOVA

Summary & Conclusion

- **HM15211 is a novel long-acting triple agonist possessing high GCG and balanced GLP-1 and GIP activity**
- **High GCG activity makes HM15211 be preferentially distributed to liver**

In NASH animal models

- **HM15211 favorably reprograms hepatic lipid metabolic gene expression**
- **HM15211 improves lipid profiles, and NASH prognosis-related markers including hepatic TG, and oxidative stress**
- **HM15211 ameliorates hepatic inflammation, followed by NAS reduction**
- **In addition, HM15211 could reduces hepatic fibrogenic markers**

In obese animal models

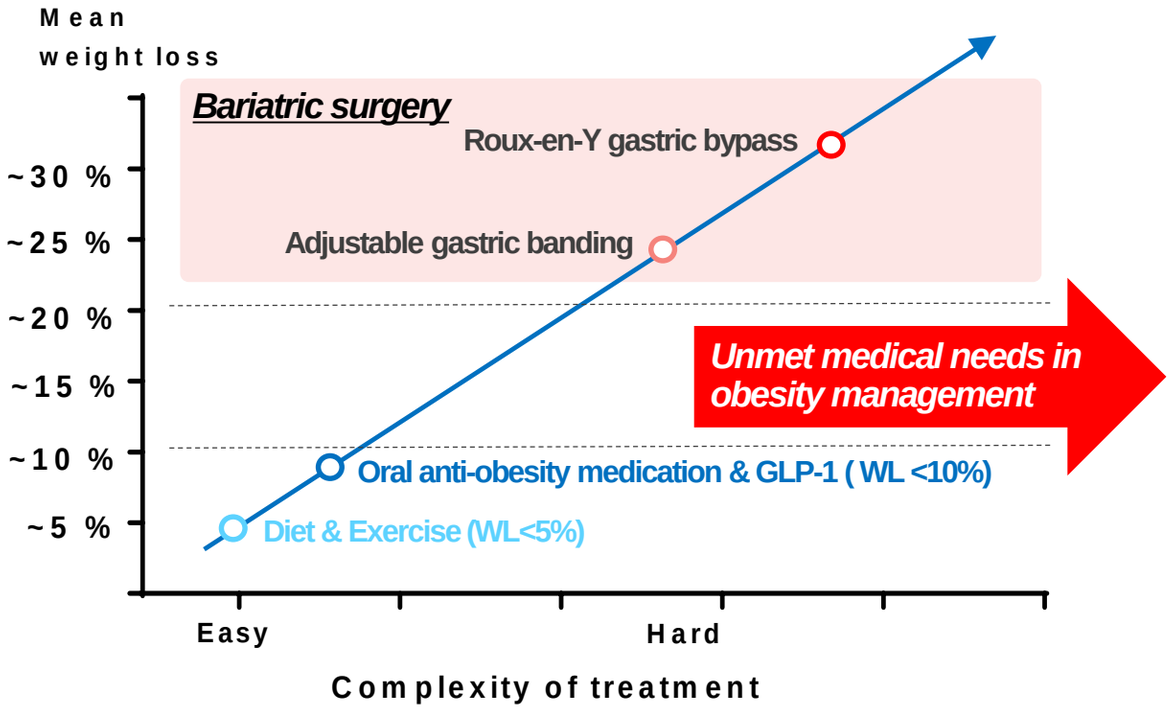
- **HM15211 provides superior efficacy in body weight loss than daily GLP-1RA**
- **Together with food intake regulation, enhanced energy expenditure *via* browning of WAT explains potent body weight loss efficacy of HM15211**
- **Consistently, HM15211 reduces hepatic TG contents**

With unique GLP-1/GIP/GCG activity, HM15211 might provide favorable therapeutic efficacy than existing therapeutics for the treatment of NASH as well as obesity

Back-up

Unmet needs in obesity, and rationale of triple agonist development

Insufficient weight loss by current anti-obesity medication



❖ **Therapeutic benefits of GCG in obesity and related disorders could be appeared under tight glycemic control by balanced GLP-1/GIP action**

Glucagon
- Energy expenditure ↑
- Lipolysis ↑ & lipogenesis ↓
- LDL clearance ↑
- HDL biogenesis ↑
- Blood glucose ↑

GLP-1
- Insulin secretion ↑
- Appetite ↓

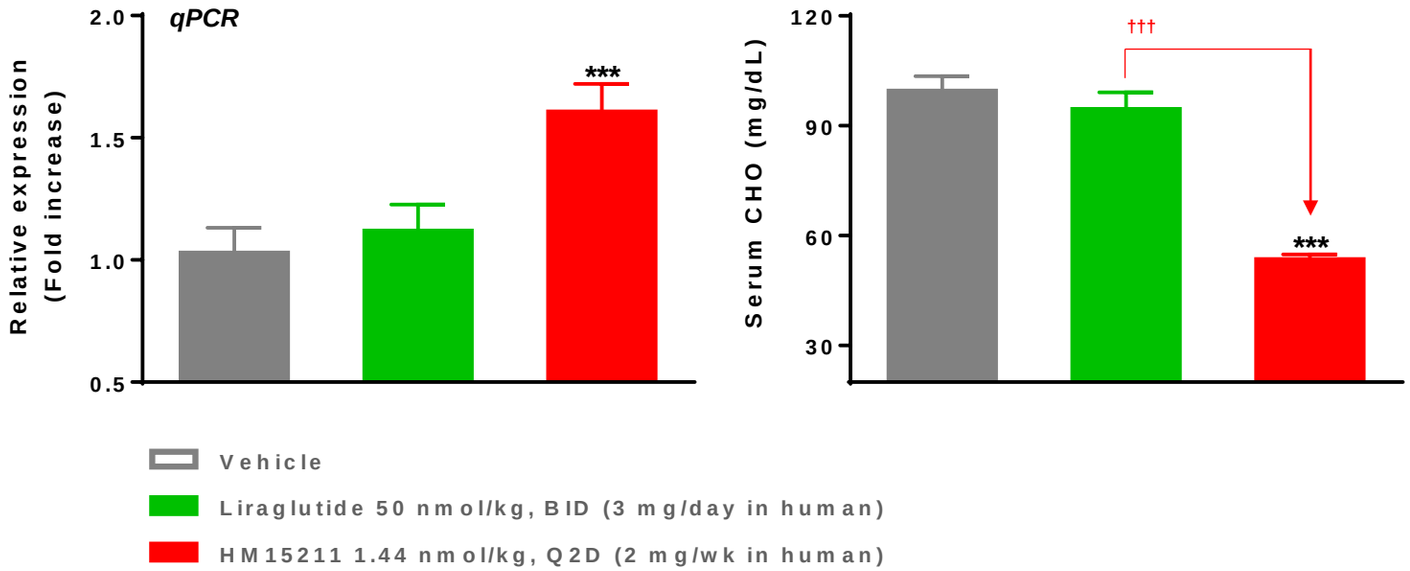
GIP
- Insulin secretion ↑
- Liver inflammation ↓

Obesity & NASH treatment w/ no hypoglycemia risk

Improved lipid profile by new-born GIP action of HM15211

LPL expression in WAT & serum cholesterol

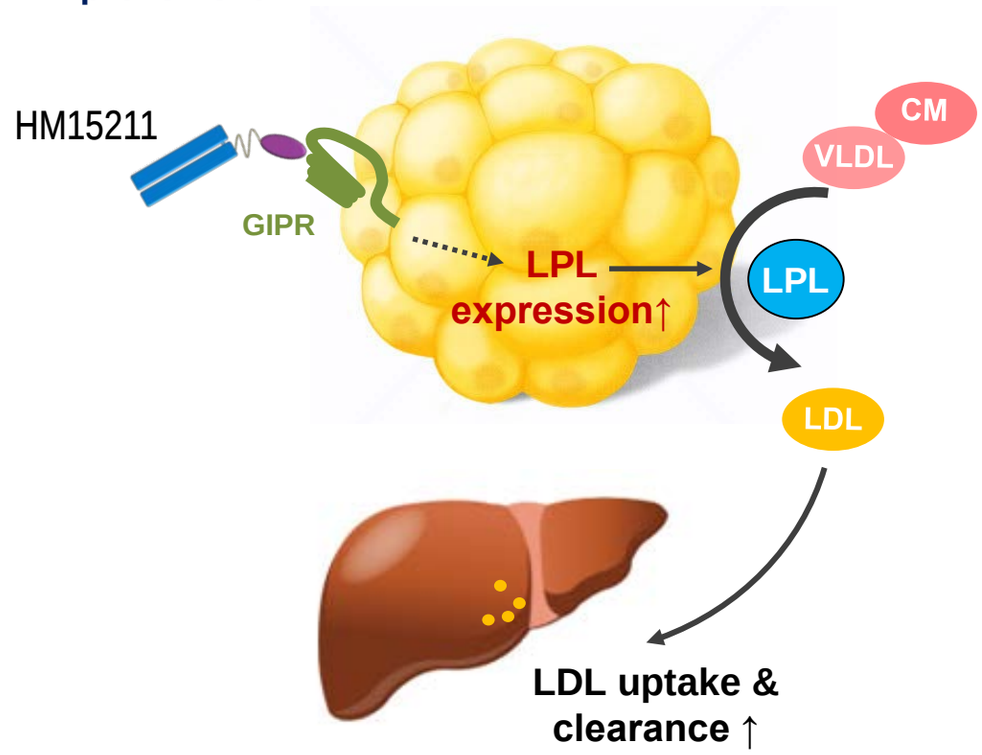
(n=5/group, normal mice, day 1 result after single administration)



***p<0.0.001 *vs.* vehicle by One-way ANOVA

†††p<0.001 *vs.* Liraglutide by One-way ANOVA

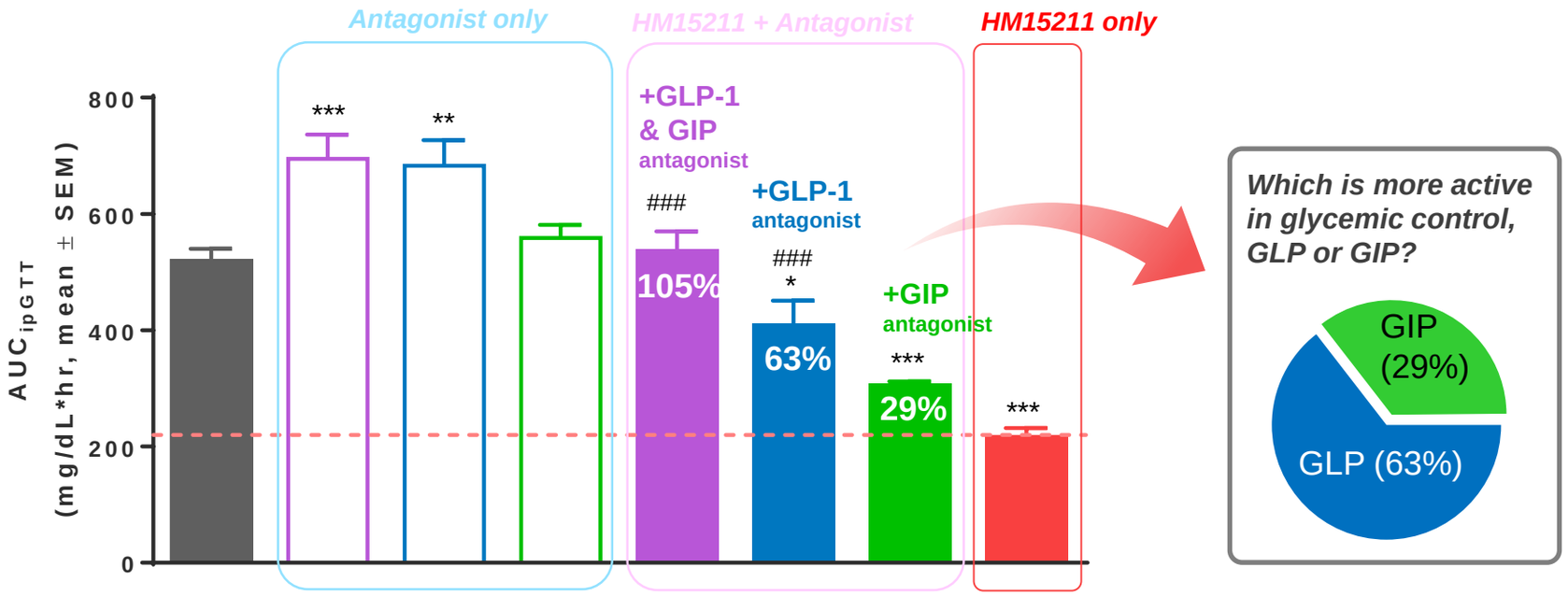
❖ Proposed GIP role of HM15211 in lipid profile improvement



LPL : Lipoprotein lipase
CM : chylomicron
VLDL : Very-low-density lipoprotein

No hyperglycemic risk of HM15211 by harmonized GLP-1 & GIP action

AUC_{ipGTT} in normal mice
(n=5, single administration)

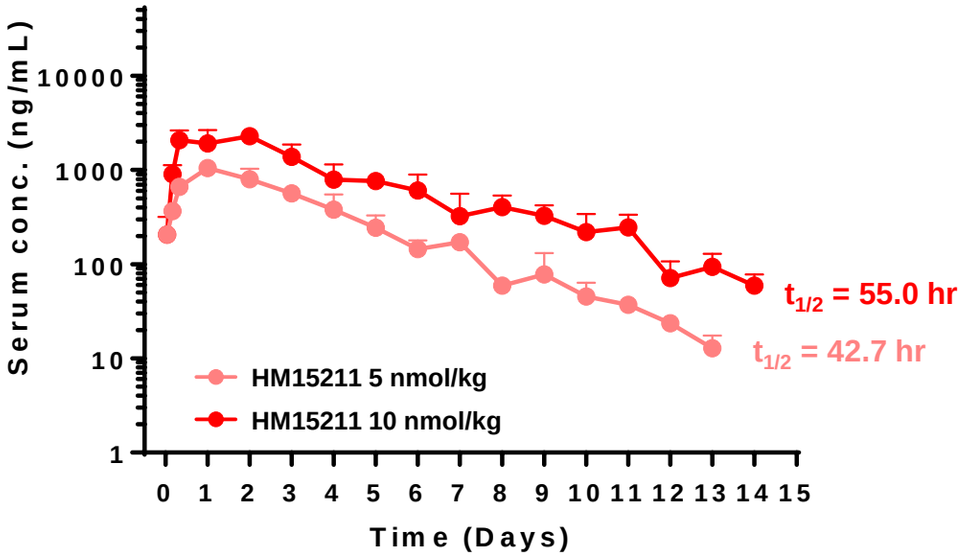


- Vehicle
- GLP-1 antagonist 600 nmol/kg + GIP antagonist 50 nmol/kg
- GLP-1 antagonist 600 nmol/kg
- GIP antagonist 50 nmol/kg
- HM15211 10nmol/kg + GLP-1 antagonist 600 nmol/kg + GIP antagonist 50 nmol/kg
- HM15211 10nmol/kg + GLP-1 antagonist 600 nmol/kg
- HM15211 10nmol/kg + GIP antagonist 50 nmol/kg
- HM15211 10nmol/kg

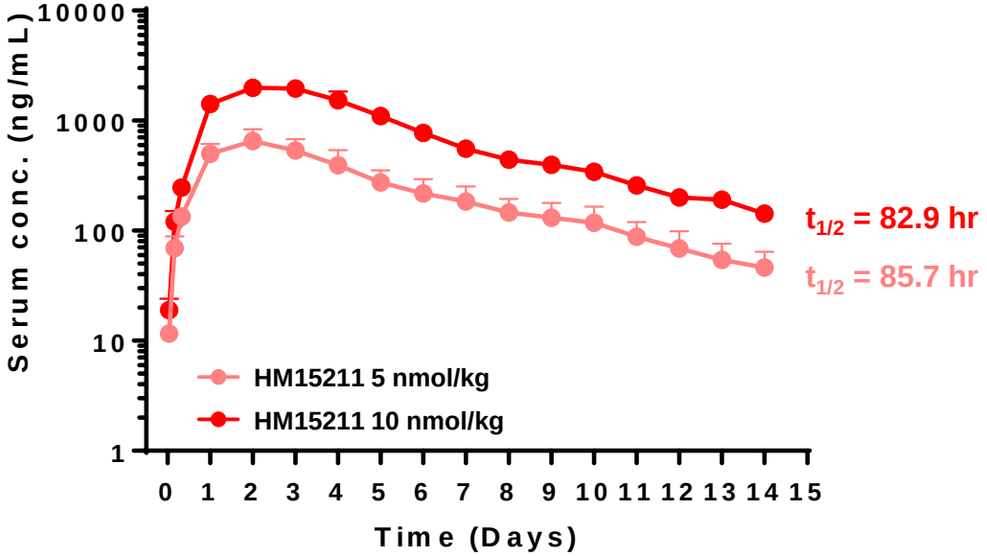
*~***p<0.05 ~ 0.001, ns (not significant) *vs.* vehicle,
###p<0.001 *vs.* HMT211 by One-way ANOVA
†p<0.001 by unpaired t-test

PK profiles of HM15211

PK in ICR mice
(n=3/time point, single administration)



PK in SD rats
(n=3/group, single administration)



Animal model	ICR mice		SD rats	
HM15211 dose	5 nmol/kg	10 nmol/kg	5 nmol/kg	10 nmol/kg
$AUC_{0\text{-}168h}$ (ng/mL*hr)	89201.6	240287.1	82150.9 ± 24404.6	265409.3 ± 21480.7
C_{max} (ng/mL)	1047.7	2285.7	653.5 ± 181.2	2033.9 ±122.3
T_{max} (hr)	24.0	48.0	48.0 ± 0.0	56.0 ± 13.9
$t_{1/2}$ (hr)	42.7	55.0	85.7 ± 8.3	82.8 ± 3.1
MRT_{last} (hr)	73.6	88.1	108.5 ±3.6	109.6 ± 1.7

Change in energy expenditure and respiratory exchange ratio

Experimental scheme

DIO mice

Vehicle

Liraglutide 50 nmol/kg, BID

HM15211 2.87 nmol/kg, Q2D

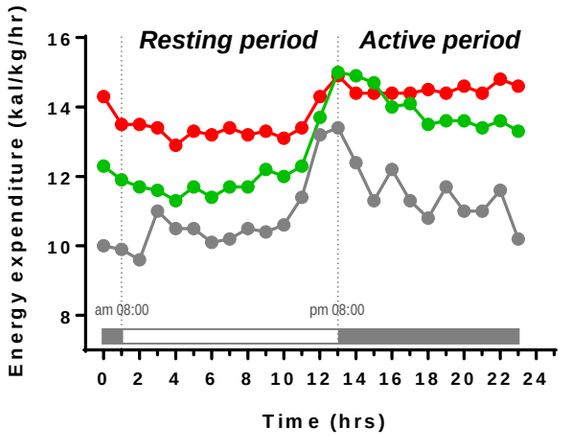
Week 0 — 1 — 2~4

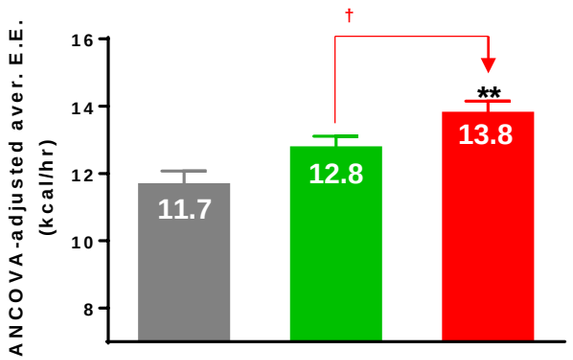
D6 D8

Indirect calorimetry

Lipid profile, IHC, marker expression

Energy expenditure in DIO mice
(n=10/group)



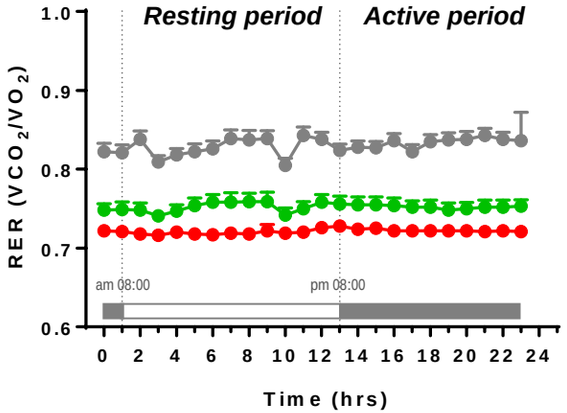


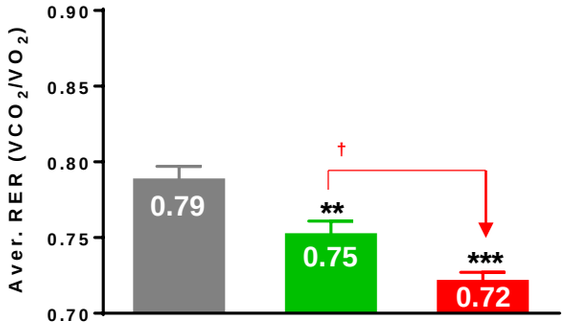
Vehicle

Liraglutide 50 nmol/kg, BID (3 mg/day in human)

HM15211 2.87 nmol/kg, Q2D (4 mg/wk in human)

RER [Respiratory Exchange Ratio] in DIO mice
(n=10/group)

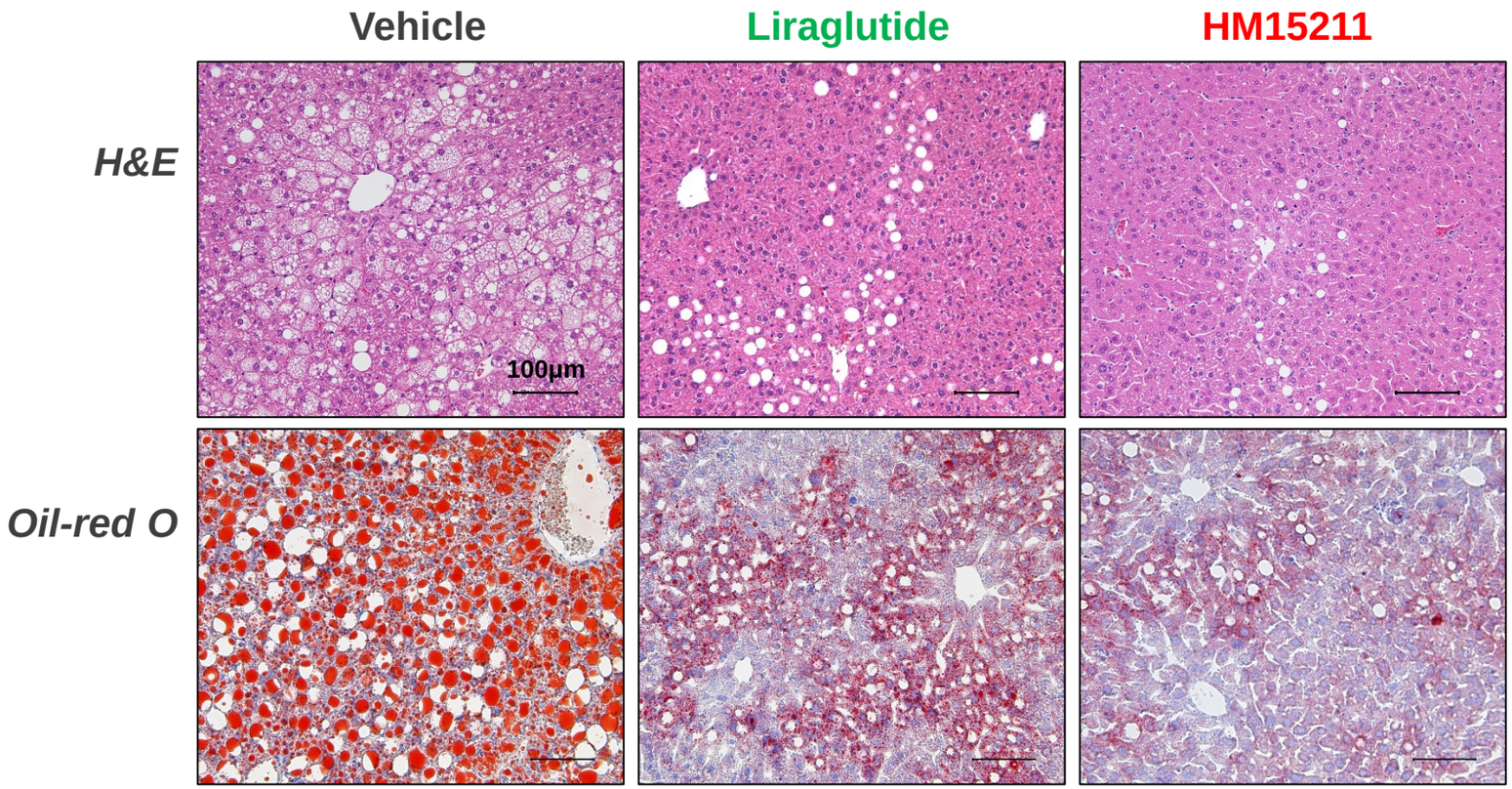


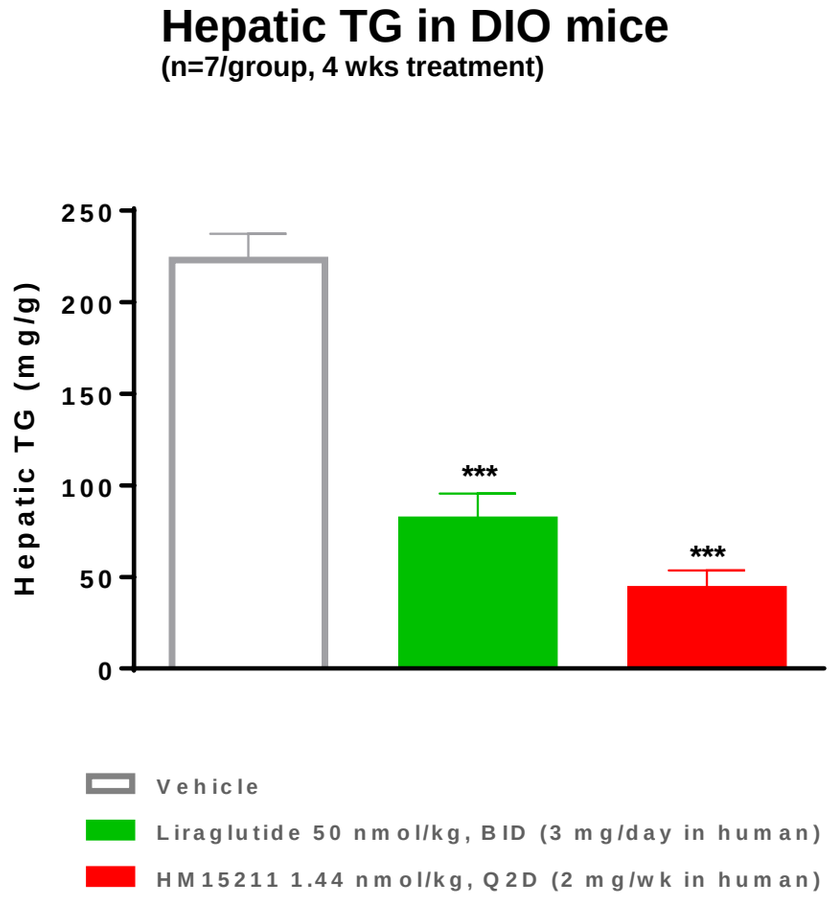


RER 1.0 = Sole carbohydrate burning
RER 0.7 = Sole fat burning

~*p<0.01 ~ 0.001 *vs.* vehicle by One-way ANOVA
†p<0.05 *vs.* Liraglutide by One-way ANOVA

Liver steatosis resolution in obese animal model



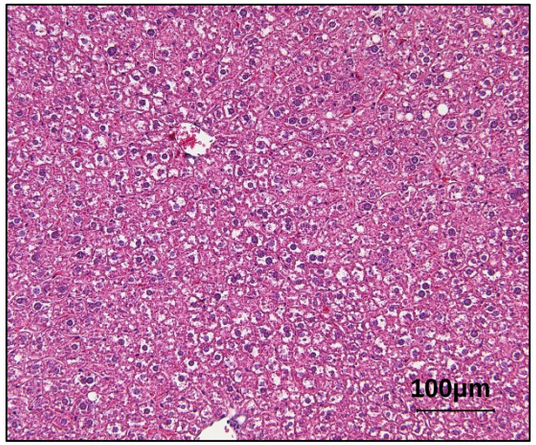


***p<0.001 *vs.* vehicle by One-way ANOVA

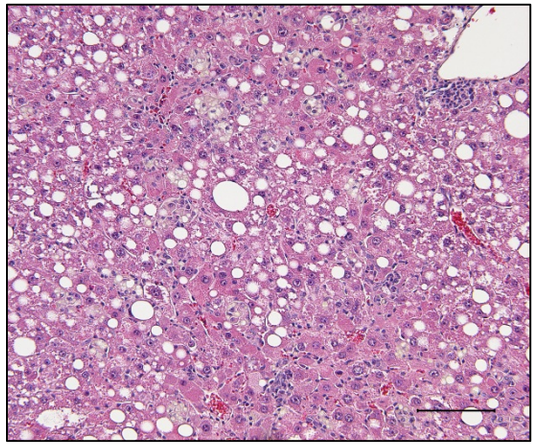
Hepatic inflammatory marker expression in liver tissue

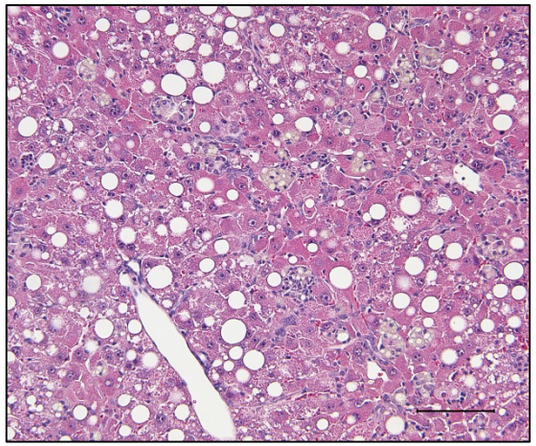
H&E staining in MCD diet mice
(representative image, 4 wks treatment)

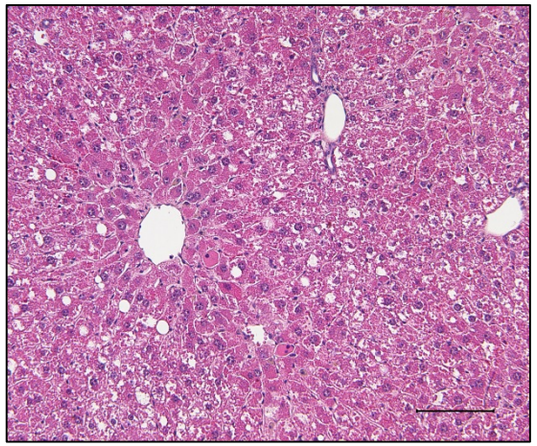
Normal, vehicle



MCD, vehicle





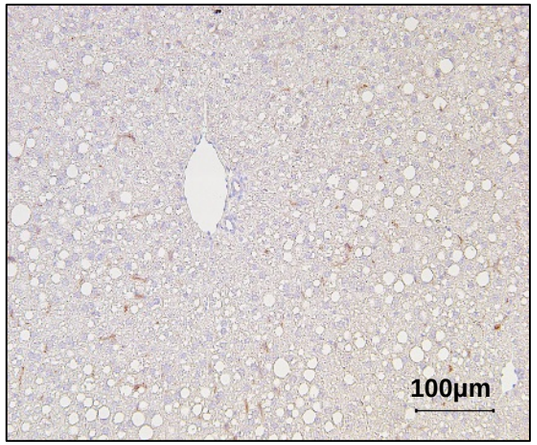


MCD, Liraglutide

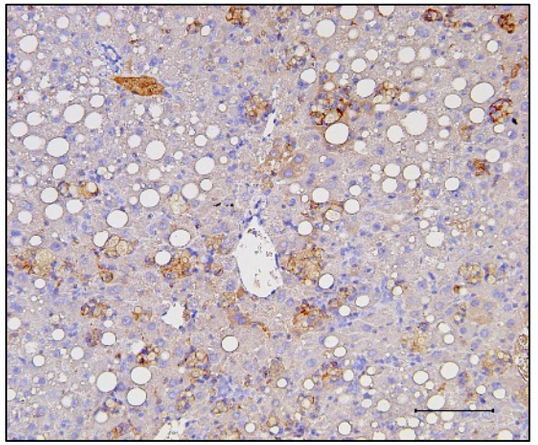
MCD, HM15211

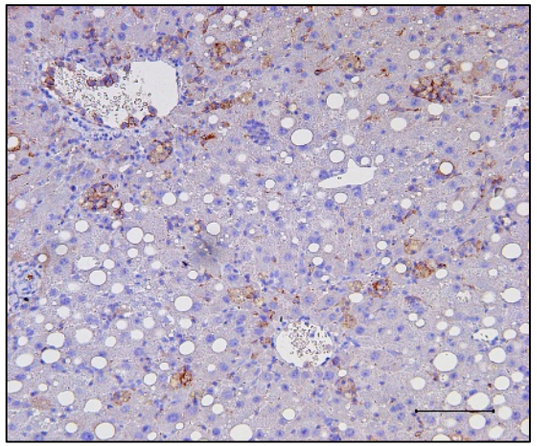
F4/80 staining in MCD diet mice
(representative image, 4 wks treatment)

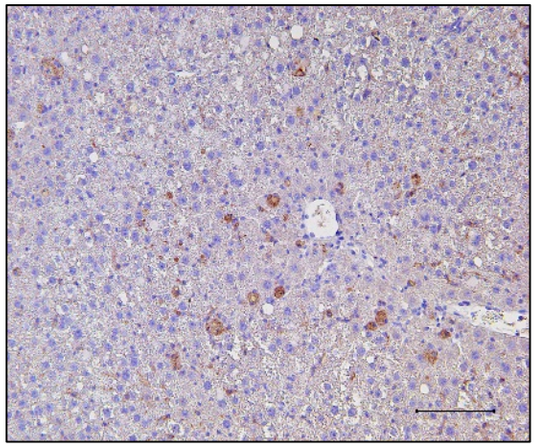
Normal, vehicle



MCD, vehicle







MCD, Liraglutide

MCD, HM15211