Therapeutic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in NASH and fibrosis animal models

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Employee of Hanmi Pharm. Co., Ltd.
NASH progression

**Hepatocyte lipotoxicity**
- Obesity; Dyslipidemia; Insulin resistance and T2DM

→ Liver fat accumulation

**Inflammation**
- Lipid peroxidation ↑
- Oxidative stress ↑

→ Liver cell apoptosis

Resident / infiltrated macrophage activation

**Fibrosis**
- Inflammatory tissue injury
- HSC activation
- Fibrogenic component ↑

→ Scar replaces damaged liver cells
→ Liver function failure
NASH progression and potential drug candidates

**Normal**

**NAFL**

**NASH**

**Cirrhosis**

### Hepatocyte lipotoxicity
- Obesity; Dyslipidemia; Insulin resistance and T2DM
- Liver fat accumulation

### Inflammation
- Lipid peroxidation $\uparrow$
- Oxidative stress $\uparrow$
- Liver cell apoptosis
- Inflammatory cytokine
- Resident / infiltrated macrophage activation

### Fibrosis
- Inflammatory tissue injury
- HSC activation
- Fibrogenic component $\uparrow$
- Scar replaces damaged liver cells
- Liver function failure

#### Drug candidates (selected)
- GLP-1RA
  - Liraglutide; semaglutide (P2, Novo)
- ACC inhibitor
  - GS-0976 (P2, Gilead)
- PPAR agonist
  - Elafibranor (P2, GENFIT)
- ASK1 inhibitor
  - Selonsirtib (P3, Gilead)
- FXR agonist
  - Obeticholic acid (P3, Intercept.)
  - GS-9674 (P2, Gilead)

**Note.** ✓ Indicated compounds were used as active comparators in efficacy studies
What is long-acting GLP-1/GIP/Glucagon triple agonist?

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

[General profile]
- Extended half-life ($t_{1/2} = 42.7 \sim 55$ hrs in mice; $82.8 \sim 85.7$ hrs in rats)
- High glucagon (GCG) activity suitable for obesity treatment
- Balanced GLP-1 and GIP activity to neutralize hyperglycemic risk of high GCG
- Anti-inflammatory effect by GIP activity
- Recently completed FIH clinical study in healthy obese subjects

LAPSCOVERY: Long Acting Peptide/Protein DISCOVERY Technology
Efficient weight loss by HM15211 and related MoA

Weight change in pair-fed controlled DIO mice

- **White adipose tissue browning**
  - Vehicle
  - Liraglutide
  - HM15211

- **Enhanced energy expenditure**

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**~***p<0.001 ~ 0.001 vs. vehicle by One-way ANOVA , †††p<0.001 vs. pair-fed by One-way ANOVA**
Efficient hepatic fat reduction by HM15211 and related MoA

1) Liver preferential distribution

<table>
<thead>
<tr>
<th>HM15211 Conc. (ng/mL for Serum, ng/g for Tissue)</th>
<th>0</th>
<th>1000</th>
<th>2000</th>
<th>3000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
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<tr>
<td>Heart</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Large I.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small I.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

2) Hepatic lipid metabolism reprogramming

De novo lipogenesis

<table>
<thead>
<tr>
<th></th>
<th>Fold Increase</th>
<th>SREBP-1C</th>
<th>ACC1</th>
<th>ACC2</th>
<th>FAS</th>
<th>SCD1</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-oxidation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3) Enhanced hepatic fat reduction in DIO mice

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

H&E

100μm

Hepatic TG (mg/g)
**Hypothesis**

**Weekly triple agonist**

**Glucagon**
- Browning of WAT
- Energy expenditure ↑
- Liver targeting
  - Lipolysis ↑ & lipogenesis ↓

**GLP-1**
- Appetite ↓
- Inflammation ↓

- Body weight ↓
- Fat mass, blood lipid ↓
- Liver fat ↓

→ NASH improvement: Steatosis ↓, Inflammation ↓
→ Insufficient for fibrosis improvement

**HM15211 [Ph1, US]**
- Expected for once-weekly regimen
- Completed for P1 SAD study in healthy obese subjects
Hypothesis

Weekly triple agonist

- Glucagon
  - Browning of WAT
  - Energy expenditure ↑
  - Liver targeting
    - Lipolysis ↑ & lipogenesis ↓

- GLP-1
  - Appetite ↓
  - Inflammation ↓

- GIP
  - Inflammation ↓

- Body weight ↓
- Fat mass, blood lipid ↓
- Liver fat ↓
- Liver inflammation ↓

→ NASH improvement: Steatosis ↓, inflammation ↓, ballooning ↓
→ Fibrosis improvement

HM15211 [Ph1, US]

- Expected for once-weekly regimen
- Completed for P1 SAD study in healthy obese subjects
Weekly triple agonist

**Glucagon**
- Browning of WAT: Energy expenditure ↑
- Liver targeting: Lipolysis ↑ & lipogenesis ↓
- BG increasing risk ↑

**GLP-1**
- Appetite ↓
- Inflammation ↓
- INS secretion ↑

**GIP**
- Inflammation ↓
- INS secretion ↑

**HM15211** [Ph1, US]
- Expected for once-weekly regimen
- Completed for P1 SAD study in healthy obese subjects

⇒ NASH improvement: Steatosis ↓, inflammation↓, ballooning↓
⇒ Fibrosis improvement
⇒ Hyperglycemic risk of glucagon use ↓
HM15211, long-acting GLP-1/GIP/Glucagon triple agonist, might have therapeutic potential in NASH and fibrosis as well as obesity

- The efficacy was evaluated in rodent disease models

<table>
<thead>
<tr>
<th>AMLN-diet</th>
<th>Induction periods</th>
<th>Disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6 mice (8 weeks old)</td>
<td>28 weeks</td>
<td>Obese; Fatty liver</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>MCD-diet</th>
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<th>Disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCD-diet</td>
<td>6 ~ 12 weeks</td>
<td>Lean; NASH w/ mild to advanced fibrosis</td>
</tr>
</tbody>
</table>
Change of weight and steatosis score in AMLN-diet mice

Experimental scheme

AMLN-diet mice
(8 weeks old)

C57BL/6 mice

Model induction

Drug treatment

Analysis

Body weight

Hepatic TG

Steatosis score

Weight change (AMLN mice, n=7)

Normal, Vehicle

AMLN-mice, Vehicle

Body weight change (% vs. D0)

Time (Days)

Selonsertib 30 mg/kg, QD

(250 mg/day in human)

Obeticholic acid 30 mg/kg, QD

(250 mg/day in human)

HM15211 2.87 nmol/kg, Q2D

(4 mg/week in human)

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

†††p<0.001 vs. selonsertib or OCA One-way ANOVA
Change of weight and steatosis score in AMLN-diet mice

Experimental scheme

- AMLN-diet: C57BL/6 mice (8 weeks old)
- Model induction: 28 weeks
- Drug treatment: 4 weeks
- Analysis:
  - Body weight
  - Hepatic TG
  - Steatosis score

Weight change (AMLN mice, n=7)

- Normal, Vehicle
- AMLN-mice, Vehicle
- Selonsertib 30 mg/kg, QD (250 mg/day in human)
- Obeticholic acid 30 mg/kg, QD (250 mg/day in human)
- HM15211 2.87 nmol/kg, Q2D (4 mg/week in human)

Steatosis score (AMLN mice, n=7)

- Normal, Vehicle
- AMLN, Vehicle
- Selonsertib
- Obeticholic acid
- HM15211

H&E staining (AMLN mice, representative image)

- Normal, Veh
- AMLN, Veh
- Selonsertib
- Obeticholic acid
- HM15211

*p < 0.05
***p < 0.001 vs. AMLN mice, vehicle by One-way ANOVA
†††p < 0.001 vs. selonsertib or OCA One-way ANOVA
Change of hepatic fat content in MCD-diet mice

Hepatic TG (MCD mice, n=7)

Real-time liver MRI (MCD mice, representative image)

European Association for the Study of Diabetes (EASD) 54th Annual Meeting, Berlin, Germany; 1-5 Oct., 2018
Change of NASH prognosis markers in MCD-diet mice

**Hepatic TBARS**
(MCD mice, n=7)

**Blood ALT and bilirubin level**
(MCD mice, n=7)

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

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*~**p<0.05 ~ 0.001 vs. MCD mice, vehicle by One-way ANOVA
††~††p<0.01 ~ 0.001 vs. Liraglutide by One-way ANOVA
Change of hepatic marker expression in MCD-diet mice

**F4/80 staining** (MCD mice, representative image)

<table>
<thead>
<tr>
<th>Normal, vehicle</th>
<th>MCD, vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCD, Liraglutide</td>
<td>MCD, HM15211</td>
</tr>
</tbody>
</table>

**Inflammation & HSC activation marker gene expression** (MCD mice, n=7, qPCR)

![Graph showing relative expression (Fold increase) for TNF-α]

- Normal, Vehicle
- Liraglutide 50 nmol/kg, BID (3 mg/day in human)
- MCD mice, Vehicle
- HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

*~***p<0.05 ~ 0.001 vs. MCD mice, vehicle by One-way ANOVA
Change of hepatic marker expression in MCD-diet mice

F4/80 staining (MCD mice, representative image)

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<td>MCD, Liraglutide</td>
<td>MCD, HM15211</td>
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Inflammation & HSC activation marker gene expression (MCD mice, n=7, qPCR)

![Graph showing relative expression (Fold increase) for TNF-α, TGF-β, and α-SMA]

- Normal, Vehicle
- Liraglutide 50 nmol/kg, BID (3 mg/day in human)
- HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

*~***p<0.05 ~ 0.001 vs. MCD mice, vehicle by One-way ANOVA
Change of NAFLD activity score in MCD-diet mice

**Experimental scheme**

**Model induction**
- MCD-diet
- C57BL/6 mice (8 weeks old)

**Drug treatment**
- 6 weeks
- 4 weeks

**Expected disease status**
- Study #1
  - Liver fat ↑
  - Inflammation onset

**NAFLD activity score** (MCD mice, n=7)

- Normal, Vehicle
- MCD mice, Vehicle
- Liraglutide 50 nmol/kg, BID (3 mg/day in human)
- HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

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

---

European Association for the Study of Diabetes (EASD) 54th Annual Meeting, Berlin, Germany; 1-5 Oct., 2018
Change of NAFLD activity score in MCD-diet mice

**Experimental scheme**

- **Model induction**: MCD-diet
  - C57BL/6 mice (8 weeks old)
- **Drug treatment**
  - Study #1: 6 weeks (MCD), 4 weeks (MCD, Vehicle)
  - Study #2: 10 weeks (MCD), 5 weeks (MCD, Vehicle)

**Expected disease status**

- Liver fat ↑
- Inflammation onset
- Inflammatory liver damage ↑
  - → liver fat ↓, ballooning ↑

**NAFLD activity score** (MCD mice, n=7)

**Study #1**

- **Normal, Vehicle**: 1
- **Liraglutide 50 nmol/kg, BID** (3 mg/day in human): 3
- **Triple**: 4

**Study #2**

- **Normal, Vehicle**: 1
- **GLP-1**: 3
- **HM15211 0.72 nmol/kg, Q2D** (1 mg/wk in human): 4
- **Selonsertib 30 mg/kg, QD** (250 mg/day in human): 5
- **Obeticholic acid 30 mg/kg, QD** (250 mg/day in human): 4

*~**p<0.05 ~ 0.01 vs. MCD mice, vehicle by One-way ANOVA, †††p<0.01 vs. Liraglutide by One-way ANOVA
Change of NAFLD activity score in MCD-diet mice

**Study #1**
- Model induction: 6 weeks MCD-diet
- Drug treatment: 4 weeks

**Study #2**
- Model induction: 10 weeks MCD-diet
- Drug treatment: 5 weeks

**Expected disease status**
- Study #1: Liver fat ↑, Inflammation onset
- Study #2: Inflammatory liver damage ↑ → liver fat ↓, ballooning ↑

**NAFLD activity score** (MCD mice, n=7)

- Study #1: Normal, Vehicle, MCD mice, Vehicle, Liraglutide 50 nmol/kg, BID (3 mg/day in human), ASK1i, FXR, Triple
- Study #2: Normal, Vehicle, MCD mice, Vehicle, Selonsertib 30 mg/kg, QD (250 mg/day in human)

*~**p<0.05 ~ 0.01 vs. MCD mice, vehicle by One-way ANOVA, †††p<0.01 vs. Liraglutide by One-way ANOVA
Change of hepatic collagen and fibrosis score in MCD-diet mice

**Experimental scheme**

<table>
<thead>
<tr>
<th>MCD-diet</th>
<th>Model induction</th>
<th>Drug treatment</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6 mice (8 weeks old)</td>
<td>6 weeks</td>
<td>4 weeks</td>
<td>Study #1</td>
</tr>
<tr>
<td></td>
<td>10 weeks</td>
<td>5 weeks</td>
<td>Study #2</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>4 weeks</td>
<td>Study #3</td>
</tr>
</tbody>
</table>

**Hepatic hydroxyproline & fibrosis score**

(MCD mice, n=7)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hydroxyproline (nmol/g liver)</th>
<th>Fibrosis score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study #1</td>
<td>0.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Study #2</td>
<td>0.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Study #3</td>
<td>0.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

- Normal, Vehicle
- HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

**Sirius red staining**

(MCD mice, representative image from study #1)

- Normal, Vehicle
- MCD, vehicle
- MCD, HM15211

*~***p<0.05 ~ 0.001 vs. MCD mice, vehicle by One-way ANOVA
Change of hepatic fibrosis marker expression in MCD-diet mice

**Experimental scheme**

- **Model induction**
  - C57BL/6 mice (8 weeks old)
  - MCD-diet

- **Drug treatment**
  - 6 weeks: 4 weeks
  - 10 weeks: 5 weeks
  - 12 weeks: 4 weeks

- **Analysis**
  - Study #1: Marker expression (qPCR)
    - Hydroxyproline
    - Sirius red staining
  - Study #2: Hepatic TIMP-1
  - Study #3: Hepatic collagen-1α1

**Hepatic collagen-1α1 expression**
(MCD mice, n=7, qPCR)

**Hepatic TIMP-1**
(MCD mice, n=7, qPCR)

1) TIMP-1: Tissue Inhibitor of MetalloProtease-1
• Considering the progression of NAFLD from simple steatosis to NASH and fibrosis, recent drug candidates may have limited efficacy because they mainly target one step of disease progression

• In addition to efficient weight loss (energy expenditure ↑), the long-acting GLP-1/GIP/Glucagon triple agonist, HM15211, directly reduced liver fat (lipid metabolism reprogramming) and possibly inflammation, suggestive of therapeutic potential in NASH and fibrosis

• In AMLN-diet mice, HM15211, but not an ASK1 inhibitor and FXR agonist, provided efficient weight loss and completely reversed steatosis

• In MCD-diet mice, HM15211 reduced both 1) liver fat, 2) oxidative stress, and 3) marker gene expression including HSC activation (TGF-β and α-SMA), resulting in greater NAS reduction than GLP-1RA, ASK1 inhibitor, or a FXR agonist

• HM15211 could improve hepatic fibrosis regardless of induction period

  By directly affecting key steps (lipotoxicity and inflammation), HM15211 might provide improved therapeutic efficacy for the treatment of NASH and fibrosis; A Clinical study in NASH patients is planned for human efficacy translation

Please note posters or oral presentation reporting more information about HM15211:

165-OR: Neuroprotective effects of HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist in the neurodegenerative disease models

500-P: Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in an animal model

719-P: A novel combination of a long-acting GLP-1/GIP/Glucagon triple agonist and once weekly basal insulin offers improved glucose lowering and weight loss in diabetic animal model
Neuroprotective effects of HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist in the neurodegenerative disease models

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- Balanced GLP-1 and GIP to neutralize hyperglycemic risk of high GCG
- Anti-inflammatory effect by GIP activity
- Recently completed for FIH clinical study in healthy obese subjects

LAPSCOVERY: Long Acting Peptide/Protein DISCOVERY Technology
Incretin hormones in central nervous system

- Obesity is one of the risk factors for neurological disorders

**Parkinson’s disease**
- Insulin resistance, T2DM \(\uparrow\) PD
- \(\uparrow\) Insulin levels \(\uparrow\) \(\alpha\)-synuclein aggregation
- Leptin \(\uparrow\) survival of DA cells

**Alzheimer’s disease**
- \(\uparrow\) BMI, T2DM \(\uparrow\) AD risk
- Leptin/insulin resistance \(\uparrow\) AD
- Leptin \(\downarrow\) \(A\beta\), p-tau

**Multiple sclerosis**
- Obesity \(\uparrow\) MS risk
- Caloric restriction \(\uparrow\) EAE lifespan
- \(\downarrow\) insulin sensitivity in MS

**Neuroprotective effects of GLP-1, glucagon and GIP**
Objective

Evaluation of neuroprotective potential of HM15211…

• To assess the efficacy and related mode of actions
  a. in Parkinson’s disease mice model
  b. of Alzheimer’s disease in diabetic mice model
Efficacy and related MoAs in Parkinson’s disease mice model
MPTP is a specific neurotoxin affecting the nigrostriatal system.

- Experimental scheme

**Subchronic PD model**
- C57Bl/6
- D-1
- D0
- MPTP
- HM15211
- MPTP
- MPTP
- MPTP
- MPTP
- MPTP
- Sacrifice
- D7
- Behavior tests (Traction test, pole test, rotarod test)

**Chronic PD model**
- C57Bl/6♂ 10 wks old
- D-2
- D0
- MPTP (twice a week)
- HM15211 (QW)
- Training for behavior test
- Sacrifice
- 5w
- 6w
- Behavior tests (Traction test, pole test, rotarod test)
Dopaminergic neuroprotection by HM15211

Subchronic PD model

<table>
<thead>
<tr>
<th>Condition</th>
<th>Striatum</th>
<th>Substantia nigra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>MPTP</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>+ HM15211 2.5 nmol/kg</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>+ HM15211 5.03 nmol/kg</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
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</tbody>
</table>

Chronic PD model

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<tr>
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<tbody>
<tr>
<td>Vehicle</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
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<tr>
<td>MPTP/P</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
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<tr>
<td>+ HM15211 5.03 nmol/kg</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Tyrosine hydroxylase (TH): rate-limiting step for dopamine synthesis

***p<0.001 vs. Vehicle by One-way ANOVA
Motor function restoring by HM15211

Subchronic PD model

Chronic PD model

Vehicle  
MPTP 30 mg/kg, QD  
MPTP 30 mg/kg, QD + HM15211 2.5 nmol/kg, QW  
MPTP 30 mg/kg, QD + HM15211 5.03 nmol/kg, QW

Vehicle  
MPTP 25 mg/kg (sc, twice weekly)  
MPTP/P + Probenecid 250 mg/kg (ip, twice weekly)  
MPTP/P + HM15211 5.03 nmol/kg (sc, QW)

*~***p<0.05~0.001 vs. MPTP or MPTP/P by One-way ANOVA
Anti-inflammatory effect of HM15211

Subchronic PD model

Vehicle  MPTP  + HM15211 2.5 nmol/kg  + HM15211 5.03 nmol/kg

**Iba1 + area in striatum (% vs. vehicle)**

Chronic PD model

Vehicle  MPTP/P  + HM15211 5.03 nmol/kg

*~***p<0.05~0.001 vs. MPTP or MPTP/P by One-way ANOVA

European Association for the Study of Diabetes (EASD) 54th Annual Meeting, Berlin, German; 01-05 Oct., 2018
Efficacy and related MoAs of Alzheimer’s disease in diabetic mice model
Alzheimer’s disease in diabetic mouse model

**Diabetes / Obesity**
- Increased insulin resistance
- Accumulation of AGE: Vasculature
  
  **AGE**: Advanced Glycated Endproduct

**Impaired glucose metabolism** (Peripheral & brain)

**Hyperactivation of RAGE**

- **RAGE**: Receptor for AGE

**Release of proinflammatory factors**
- Reactive oxygen species
- Cytokines

**Worsening of diabetes**
- Increased risk of Alzheimer’s disease
  
  **Accumulation of Aβ, AGE**: Brain

**Experimental scheme**

- **db/db**: 6 wks old
- **HM15211** (Q2D for 12 weeks)

**Inhibition of Aβ1-42 and AGE accumulation by HM15211**

- **Aβ1-42** (% vs. vehicle)
- **AGE** (μg/ml)

---

*~***p<0.05~0.001 vs. db/db (18w) vehicle by One-way ANOVA
Reduction of inflammation and oxidative stress by HM15211

- IL-1β (pg/ml) and IFN-γ (pg/ml) levels in db/db_D0 (6w), db/m_vehical, db/db_Vehical, db/db_HM15211 1.08 nmol/kg.

- HNE protein adduct (μg/ml) levels in db/db_D0 (6w), db/m_vehical, db/db_Vehical, db/db_HM15211 1.08 nmol/kg, Q2D.

- Significance: *p<0.05, **p<0.01, ***p<0.001 vs. MPTP or MPTP/P by One-way ANOVA.

European Association for the Study of Diabetes (EASD) 54th Annual Meeting, Berlin, Germany; 01-05 Oct., 2018
Summary & Conclusion

- In MPTP/Probenecid induced chronic Parkinson’s disease model, HM15211 inhibited the increase of alpha synuclein, which is the most prominent pathological biomarker of Parkinson’s disease.

- In aged db/db mice, pathological characters of Alzheimer’s disease such as Aβ1-42 and AGE accumulations were shown. These were reversed by HM15211 treatment.

- These neuroprotective effects of HM15211 are derived from anti inflammatory effect through the altered cytokine expression and reduced lipid peroxidation.

Based on these results, the novel long-acting GLP-1 / GIP / Glucagon tri-agonist, HM15211 might have therapeutic potential for neurodegenerative diseases

Please note presentations reporting more information about HM15211:

119-OR : Therapeutic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in NASH and fibrosis animal models

500-P : Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in the obese-osteoporosis rodent model

719-P : A novel combination of a long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) and once weekly basal insulin offers improved glucose lowering and weight loss in a diabetic animal model