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

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Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.
Hanmi’s GLP-1/GIP/GCG triple 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 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**
• Obesity is one of the risk factors for neurological disorders

**Parkinson’s disease**
- Insulin resistance, T2DM ↑ PD
- ↑ Insulin levels, α-synuclein aggregation
- Leptin ↑ survival of DA cells

**Alzheimer’s disease**
- ↑ BMI, T2DM ↑ AD risk
- Leptin/insulin resistance ↑ AD
- Leptin ↓ Aβ, p-tau

**Multiple sclerosis**
- Obesity ↑ MS risk
- Caloric restriction ↑ EAE lifespan
- ↓ insulin sensitivity in MS

• Neuroprotective effects of GLP-1, glucagon and GIP

[Image of the diagram showing Peripheral contributions, Peripheral-CNS Crosstalk, and Neuroprotection with GLP-1, Glucagon, GIP, and their effects on neurite outgrowth, progenitor proliferation, glutamate neurotoxicity, inflammation, etc.]
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
Parkinson’s disease mouse model

- MPTP is a specific neurotoxin affecting the nigrostriatal system.

- Experimental scheme

**Subchronic PD model**

- Day 1 (D1): C57Bl/6
- Day 0 (D0): MPTP, HM15211
- Day 7 (D7): Sacrifice

**Chronic PD model**

- Day 2 (D2): C57Bl/6
- Day 0 (D0): MPTP (twice a week)
- 5 weeks: Behavior tests (Traction test, pole test, rotarod test)
- 6 weeks: Sacrifice

**Note:**
- Training for behavior test
- Behavior tests (Traction test, pole test, rotarod test)
Dopaminergic neuroprotection by HM15211

Subchronic PD model

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>MPTP 2.5 nmol/kg</th>
<th>+ HM15211 5.03 nmol/kg</th>
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<td>Striatum</td>
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Chronic PD model

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

**European Association for the Study of Diabetes (EASD) 54th Annual Meeting, Berlin, Germany; 01-05 Oct., 2018**
Motor function restoring by HM15211

Subchronic PD model

**Vehicle**

- Traction test (score)
  - **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**

Chronic PD model

**Vehicle**

- Traction test (score 0~3)
  - MPTP 25 mg/kg (sc, twice weekly)
  - MPTP/P + HM15211 5.03 nmol/kg (sc, QW)

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

\*~\*\*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

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
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

Alzheimer’s disease in diabetic mouse model

**Experimental scheme**
- D0 (6w) db/db 6 wks old
- HM15211 (Q2D for 12 weeks)
- 12w Sacrifice

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

![Graph showing inhibition of Aβ1-42 and AGE accumulation](graph)

- Am yloid beta 1-42 (% vs. vehicle)
- AGE (μg/ml)

**Results:**
- **Aβ1-42 (% vs. vehicle):**
  - ***p<0.001 vs. db/db (18w) vehicle by One-way ANOVA

- **AGE (μg/ml):**
  - ***p<0.001 vs. db/db (18w) vehicle & db/m (18w) vehicle by One-way ANOVA

European Association for the Study of Diabetes (EASD) 54th Annual Meeting, Berlin, German; 01-05 Oct., 2018
Reduction of inflammation and oxidative stress by HM15211

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

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