Lipolytic, Energy Expenditure, and Insulinotropic Effects of HM12525A: A Novel Long-Acting GLP-1/Glucagon Dual Agonist

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Background
Potential beneficial effects of GLP-1/Glucagon dual agonist
- Energy expenditure & Lipolysis
- Insulin secretion & Feed intake

HM12525A is a long acting GLP-1/Glucagon dual agonist with balanced dual agonism at GLP-1 and Glucagon receptors

Test materials Relative activity (cAMP assay) % of GLP-1 % of Glucagon GLP-1 100 Glucagon 100
HM12525A 50 37 1:1

Aims
1. To assess glycemic control of HM12525A
2. To assess body weight and fat mass changes by HM12525A
To assess liver function improvement by HM12525A

Methods
- 2B db/db (n=7) were treated (x:12 with HM12525A once a week, or, insulin-glucagon once daily, for 4 weeks respectively. Blood glucose levels were measured using a glucometer.

Liver
- For gTST, overnight fasted C57BL/6 mice were administrated with either HM12525A or insulin. After 15 min, blood was collected and the glucose and the serum insulin level was determined at 5, 30, 60, 120 min using commercially available kits.

Stomach
- 28 weeks HFD induced C57BL/6 mice (n=7) were treated (x:12 with HM12525A once a week, or, insulin-glucagon once daily, for 4 weeks respectively. The body weight and food intake was monitored daily.

Figure 1. HbA1c and body weight reduction in db/db mice (n=7, 4 weeks)

Figure 2. gTST in normal mice (n=7)

Figure 3. Body weight loss in DIO mice (n=2, 2 weeks)

Figure 4. Energy expenditure in DIO mice (n=10, 4 weeks)

Figure 5. Changes in energy expenditure mediator expression by HM12525A in white adipocytes (3T3-L1 cells)

Figure 6. Body composition change in normal and DIO mice (n=8, 4 weeks)

Figure 7. Reduction of lipid droplet formation in 3T3-L1 adipocytes

Figure 8. Liver function improvement in MCD diet db/db mice (12 days)

Figure 9. Ex vivo T cell activation of HM12525A

Immunogenic Potential
- Both non-conjugated active moiety and HM12525A showed negligible T cell activation, which is below the immunogenic threshold among 50 healthy human donors.

Figure 10. Clinical development milestone

References

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