ABSTRACT

Background and Aims: LAPS-CA Exendin-4 (HM1202C) is a glucagon-like peptide-1 (GLP-1) receptor agonist being developed for treatment of type 2 diabetes mellitus (T2DM). In this 1b phase study the effects of different HM1202C regimens on insulin secretion rate (ISR), β-cell responsiveness, and gastric emptying (GE) compared to placebo and to liraglutide were investigated.

Materials and Methods: Adults with T2DM received 6 mg HM1202C weekly (cohort A; age: 52±6 years, HbA1c: 8.4±1.3%, n=13), 16 mg HM1202C monthly (cohort B; age: 51±6 yr, HbA1c: 8.1±1.3%, 1.8 mg basal glucose (cohort C; age: 54±4 yr, HbA1c: 8.0±1.9%), or placebo (age: 54±1 yr, HbA1c: 8.6±0.6%). Subjects in cohorts A and C were evaluated at baseline and steady state, and cohort B was evaluated at trough (day8/28) and peak (day1/28) drug concentration. Ilet-cell function was assessed during standardised 75 g glucose infusion (GGI). Inclusion criteria: 2, 4, 6, 12, and 18 mg/m² of IV glucose for 30 min each. Insulin C-peptide levels, and plasma glucose response to each GGI step were measured. ISR was determined using a population-based C-peptide stimulation model. AUC (max/min) and AUC (C-peptide) as measures of ISRs were determined for each treatment. C-cell responsiveness was assessed as the ratio of ISR to blood glucose (BG) over the duration of the GGI, and the slope of the ISR/BG was compared between the treatments. The role of GE was determined for 1g of liquid antacids following a mixed meal with a meal tolerance test (MTT) was performed. For GE, non-intestinal to intestinal was tested using a margin of 0.3 for the lobe-scale (LS) mean ratio.

Results: Insulin secretion for all active treatments was increased compared to placebo and for HM1202C 6- and 16 mg was greater than for liraglutide (point estimates LS ratio: 1.785±0.03%, CI: 1.331-2.342±0.01, one-sided p<0.0008, and LS mean ratio: 1.440±0.040, 90% CI: 1.080-1.920±0.01, one-sided p<0.0196). Comparisons of the relationship between ISR and plasma glucose using mixed effects modelling showed an improvement in beta cell responses relative to placebo in baseline which was not different among the treatments in the month of treatment. GE was observed to be a determinant of effect (p<0.001). For postprandial biomarkers following the MMT the LS means of the Cmax, AUC0-120, and AUC0-300 parameters were significantly (one-sided p<0.05) reduced in subjects who received either 6 mg HM1202C or 16 mg HM1202C when compared to placebo. Cohort A demonstrated less diminution of GE and was non-inferior lower CI limit (dL) to liraglutide in terms of antacid omission Cmax, AUC120-240min and AUC180-210min. While for Cohort B the effect on gastric emptying appeared to be similar or even less when compared to liraglutide, formal non-inferiority could not be established for all parameters. GE was delayed in cohorts A and B compared to placebo.

RESULTS

Study Population: Demography

Mixed meal tolerance test - Compared to placebo, the least square (LS) means for glucose (mg/dL) were significantly higher in LG (p<0.05) compared to placebo, for both the 120 and 180 min post-prandial points. The LS mean ratio for the 120 min post-prandial points was 1.07 (90% CI: 1.06-1.08), which was reduced to 0.90 (90% CI: 0.88-0.91) compared to placebo, for both the 120 and 180 min post-prandial points. The LS mean ratio for the 120 min post-prandial points was 0.93 (90% CI: 0.91-0.95), which was reduced to 0.88 (90% CI: 0.86-0.90) compared to placebo, for both the 120 and 180 min post-prandial points.

Conclusion: HM1202C improved measures of β-cell function significantly compared to placebo, and for the weekly treatment regimen (cohort A), significantly compared to liraglutide. The results of this study suggest the efficacy of GLP-1 receptor agonist and that with regard to gastric emptying it differed less or similarly compared to other known GLP-1 receptor agonists.

STUDY DESIGN

Total patient numbers = 47

N=13 (16 mg once a month) N=13 (6 mg once a week)

LAPS-CA Exendin-4 (HM1202C) Enhances Insulin Secretion and Beta Cell Responsiveness in Subjects with Type 2 Diabetes

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CONCLUSIONS

HC and SH were supported by grants from the Swedish Research Council. HC and SH were supported by grants from the Swedish Research Council. The authors declare no potential conflicts of interest.

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Once Weekly HM11260C (epeglenatide) Significantly Improves Glycemic Control and Reduced Body Weight in Patients with Type 2 Diabetes: A Phase II Dose Finding Study

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ABSTRACT

BACKGROUND

Objectives

To assess the efficacy and tolerability of HM11260C in type 2 diabetes mellitus (T2DM) patients over the 12 weeks from baseline in comparison with placebo (once weekly subcutaneous [SC] administration) on glycemic control, as assessed by HbA1c in subjects with T2DM.

Background and aims: HM11260C (epeglenatide) is a novel long acting GLP-1R agonist with a 1-Tyr-120 glycosylation resulting in a flat PK profile. This 12-week, randomized, placebo controlled, double-blind parallel group study with an open-label active control (liraglutide) arm, was designed to investigate the dose ranging efficacy, safety, and tolerability of once weekly (QW) dose of HM11260C in subjects with Type 2 Diabetes (T2DM).

RESULTS

Table 3. Significance change of study parameters in T2DM patients

Table 2. Mean HbA1c change at Week 13

Table 4. Mean Fasting Plasma Glucose at Week 13

Table 5. Mean Body Weight Change at Week 13

Table 6. Adverse Events

Table 7. Percent of Patients Achieving HbA1c Targets

Table 8. Safety Parameters

SUMMARY & CONCLUSIONS

Epeglenatide demonstrated dose-dependent Glucose-Lowering effects

1 mg dose similar to the reference Liraglutide

4 mg dose perhaps better than Liraglutide to be further tested

Body weight loss with Epeglenatide 3 and 4 mg was fairly similar to the reference Liraglutide group

Nausea and Vomiting AEs were consistent with GLP-1 receptor agonist class and rapidly subsided after the initial 2 weeks

GI AEs profiles can be improved by applying thioridazine based on simulation data

Heart rate increases seemed less than the reference Liraglutide

No neutralizing antibodies were detected with Epeglenatide

REFERENCES


HM11260C. A New Generation Long Acting GLP-1R Agonists with a unique Pharmacodynamic Profile Improves Glucose Control and Reduces Body Weight in type 2 Diabetes Mellitus (HM11260C-008), 2nd IPRAD, B1-A01, 2015

This study is supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (200903010400).
Significant Effects of HM1260C (efpeglenatide) on Body Weight over 20 weeks in Obese Subjects without Diabetes: a Randomized, Double-blind, Placebo Controlled study

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ABSTRACT

Background and aims: HM1260C (efpeglenatide) is a novel long acting GLP-1R agonist with a TI:2:1 – 10x more affinity than a full PK profile. The 20-week, randomized, double-blind, placebo (PBO)-controlled, parallel group study, was designed to evaluate the efficacy, safety, and tolerability of once a week (QW) or every other week (Q2W) doses of HM in obese subjects without diabetes.

Materials and methods: 207 subjects (mean age 43.4 yrs and BMI 35.5 kg/m²) were randomized to one of four HM doses (0.5 mg DN, 5 mg DN, 5 mg QW, or 8 mg QW) or PBO. HM was administered subcutaneously for 20 weeks. The database was truncated on week 20 for the study.

RESULTS: The body weight loss with 5 mg QW, 5 mg Q2W and 8 mg QW was 0.6 kg, 7.4 kg and 7.1 kg (P=0.0011) vs PBO treatment groups, whereas body weight gain was observed with PBO 3.6 kg. More subjects in the HM treatment groups achieved significant body weight loss of ≥5% or ≥10%, and the mean reductions in BMI from baseline were greater, compared with PBO. Changes in waist circumference were -6.3 cm, -4.4 cm, -7.1 cm, 0.0 cm and -0.2 cm on QW, 6 mg QW, 5 mg QW, 5 mg Q2W and PBO. The most frequent adverse events were gastrointestinal events which were observed relatively frequently and increased injection site reactions which were observed relatively rarely.

Conclusion: All doses of HM meaningfully reduced body weight and were well tolerated. These results warrant further studies to assess treatment schemes as well as the long term efficacy and safety of HM in obesity.

BACKGROUND

The abstract included results of an interim analysis available at the time of submission. Since then, the final analysis has been completed and is reported in the paper. Obesity is highly associated with a majority of metabolic diseases (WHO Obesity and Overweight Fact sheet, updated March 2013). For diabetes, drugs are currently available for the treatment and that can lower the risks associated with obesity are needed.

OBJECTIVES

Primary objective: To assess the efficacy of efpeglenatide on body weight over the 20 weeks from baseline in obese subjects

Secondary objectives:
- To assess the safety, tolerability, and immunogenicity of efpeglenatide over the 20 weeks from baseline in obese subjects.
- To assess the efficacy of efpeglenatide on body weight over the 20 weeks from baseline in obese subjects.

STUDY DESIGN

- Study Duration: 20 weeks
- Total subjects: 207
- Randomization: Subject was randomized to one of four groups
- Treatment groups:
  - Placebo
  - 4 mg QW
  - 6 mg QW
  - 6 mg Q2W
  - 8 mg Q2W

RESULTS

- Figure 1: Disposition
- Figure 2: Body Weight Change over 20 weeks
- Figure 3: BMI Change at Week 21
- Figure 4: Waist Circumference Change at Week 21

Table 1: Baseline Characteristics

Table 2: Subjects Who Lost at Least 5% and 10% Body Weight at Week 21

Table 3: Heart Rate and Blood Pressure Change at Week 21

Table 4: Adverse Events

REFERENCES


AUTHOR DISCLOSURE

Richard E. Pratley, MD
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Table 5: Immunoegenicity

<table>
<thead>
<tr>
<th>Serum ADA (IU/mL)</th>
<th>Placebo</th>
<th>4 mg QW</th>
<th>6 mg QW</th>
<th>6 mg Q2W</th>
<th>8 mg Q2W</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Week 21</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

SUMMARY

- Statistically significant body weight reduction was observed over 20 weeks with once a week (QW) and every other week (Q2W) treatment of efpeglenatide in all groups.
- Statistically significant increases in heart rate were observed, however they were within the expected range for GLP-1 receptor agonists and were not associated with clinical adverse events. No new or worsening ADAs were detected, but was only significant at the 6 mg Q2W dose.
- Most of the heart rate changes occurred with the first few injections and subsided over the course.
- Overall, treatment with efpeglenatide in this weight loss study was safe, well-tolerated, and well-tolerated.

CONCLUSION

- All doses of efpeglenatide meaningfully reduced body weight and exceeded regulatory requirements for anti-obsesity drugs. These results warrant further studies to assess treatment schemes as well as the long-term efficacy and safety of efpeglenatide in obesity.

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Supergagonalistic mechanism of increased gludcdynamic and weight loss effects of LAPS-CA-Exendin-4 (efpeglenatide)

RESULTS

Figure 1. GLP-1R internalization by CA-Exendin-4 and Exendin-4

Figure 2. Insulin release in vivo and in vitro potencies

Figure 3. GLP-1 receptor internalization by GLP-1RA

Figure 4. Comparison of DPP-IV susceptibility in long-term digestion

Figure 5. Glucose lowering and body weight loss efficacy at human drug fluctuation mimicking condition in diabetic and obese animal models

Figure 6. Glucose lowering by human monthly fluctuation mimic condition in db/db mice (n=4, 4 weeks)

CONCLUSIONS

• Following conjugation to Fe the fast receptor dissociation kinetics of CA-Exendin-4 were maintained in efpeglenatide. (k, 4.2×10−5 s−1 vs. 1.6×10−4 s−1 for efpeglenatide).

• Efpeglenatide lead to significantly lower GLP-1R internalization than liraglutide and dulaglutide in human GLP-1R transformed cells. This translated into more potent glucose lowering in db/db mice and greater body weight loss in DIO mice in comparison to liraglutide and dulaglutide.

• Efpeglenatide maintained potent glucose lowering efficacy in db/db mice even at conditions mimicking human dosing.

• CA-Exendin-4 even after conjugation to the human Fe-fragment seems to achieve more pronounced GLP-1R activation due to reduced receptor internalization and consequently leads to more potent effects. These findings may explain the observed efficacy of efpeglenatide in clinical trials relative to liraglutide.

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FURTHER INFORMATION

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