46th ESPEN CONGRESS
46th ESPEN Congress
on Clinical Nutrition & Metabolism
Milan, Italy • 7-10 September 2024
CLINICAL NUTRITION : "THE" TRANSVERSAL SCIENCE

A PHASE 1, OPEN-LABEL, SINGLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF HM15912 IN SUBJECTS WITH SEVERE RENAL IMPAIRMENT AND NORMAL RENAL FUNCTION

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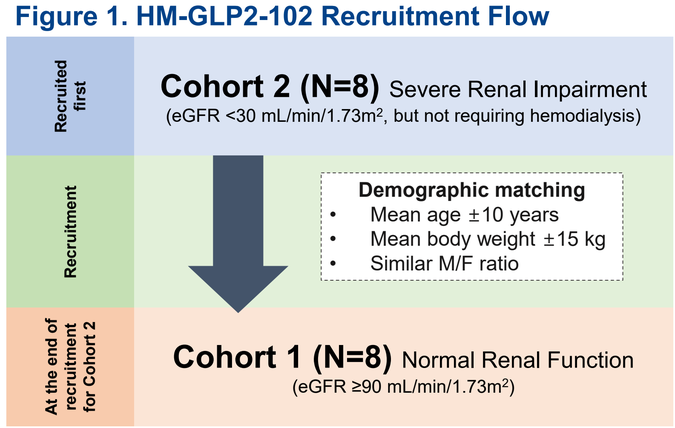
Rationale

HM15912 is a novel long-acting glucagon-like peptide-2 (GLP-2) analog being developed for the treatment of short bowel syndrome-associated intestinal failure (SBS-IF). SBS patients are at increased risk of renal impairment (RI) due to several factors, including dehydration, fluid and electrolyte imbalance, and infection associated with long-term parenteral nutrition. The purpose of this study was to compare the pharmacokinetics (PK) of HM15912 in subjects with severe RI and normal renal function.

Methods

This study was an open-label, single-dose, parallel-group study to investigate the effect of RI on the PK, safety and tolerability of HM15912 in subjects with severe RI and subjects with normal renal function as a control group.
A total of 16 subjects, 8 subjects with severe RI (Cohort 2) and 8 subjects with normal renal function (Cohort 1), were enrolled. Cohort 2 was recruited first. At the end of recruitment for Cohort 2, demographics were pooled to determine the mean age and weight, which were used as a reference to recruiting for Cohort 1, such that each subject in Cohort 1 had an age within ±10 years and a weight within ±15 kg of the mean of Cohort 2. Care was taken when recruiting subjects for Cohort 1 so that the group was not younger and of lower body weight than Cohort 2, and an attempt was made to maintain a similar male/female ratio between Cohort 1 and Cohort 2.

Figure 1. HM-GLP2-102 Recruitment Flow



Objectives

- **Primary**
  To evaluate the effect of severe renal impairment (RI) on the pharmacokinetics of HM15912 following single SC dose
- **Secondary**
  To evaluate the safety and tolerability of a single SC dose of HM15912 in subjects with severe RI and normal renal function

Results

Demographics

- A total of 16 subjects, 8 subjects in each cohort, were enrolled and completed the study.
- The two cohorts were well matched with the exception of eGFR, which was expected given the different inclusion criteria for the two cohorts.

Table 1. Demographic Characteristics

Characteristics	Cohort 1 a) (N=8)	Cohort 2 b) (N=8)
Age (years), Mean ± SD	59.6 ± 3.3	63.3 ± 8.4
Sex, n (%)		
Male	6 (75%)	6 (75%)
Female	2 (25%)	2 (25%)
Baseline body weight (kg), Mean ± SD	87.04 ± 7.44	89.64 ± 14.76
Baseline eGFR (mL/min/1.73m²), Mean ± SD	97.86 ± 4.22	17.15 ± 7.52

* SD=Standard Deviation.

Safety

- Of the 16 enrolled subjects, one subject from each cohort (2/16, 12.5%) reported any treatment-emergent adverse events (TEAEs) and all TEAEs were considered mild (Grade 1) or moderate (Grade 2).
- There were no treatment-related adverse events (TRAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interests (AESIs) and TEAEs leading to study discontinuation or death.

Table 2. Overall Summary of TEAEs

Adverse Event Category, n (%)	Cohort 1 a) (N=8)	Cohort 2 b) (N=8)	Total (N=16)
Subjects with Treatment-Emergent Adverse Events (TEAEs)	1 (12.5%)	1 (12.5%)	2 (12.5%)
TEAEs by Maximum Severity			
Grade 1	1 (12.5%)	1 (12.5%)	2 (12.5%)
Grade 2	0	1 (12.5%)	1 (6.3%)

- TEAEs by system organ class and preferred term included blood and lymphatic system disorders (anaemia), metabolism and nutrition disorders (hyperkalaemia), and musculoskeletal and connective tissue disorders (back pain and pain in extremity).

Pharmacokinetics

- The mean (SD) HM15912 serum concentration increased similarly over time for both Cohort 1 (normal renal function) and Cohort 2 (severe renal impairment) until the Day 6 (120 hours) timepoint, after which time the mean (SD) HM15912 serum concentration decreased for both cohorts.
- The exposure in both cohorts was compared by PK parameters ($AUC_{0-\infty}$ and C_{max}). Compared to the normal renal function group, the geometric mean ratio (GMR) of $AUC_{0-\infty}$ for the severe renal impairment group was 1.25, with a 90% confidence interval (CI) of 0.93-1.68. The GMR of C_{max} was 0.91 (90% CI: 0.59-1.41).

Figure 2. HM15912 Serum Concentration by Cohorts

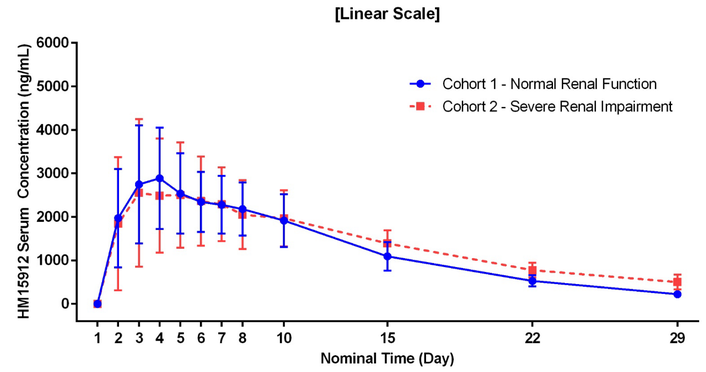


Table 3. Estimates of GMR of PK Parameters

PK Parameter Statistics	Cohort 1 a) (N=8)	Cohort 2 b) (N=8)
$AUC_{0-\infty}$ (h·ng/mL)		
Geo LS Mean (90% CI)	853049.68 (678440.62, 1072597.58)	1068108.48 (857049.65, 1331143.11)
Geo Mean Ratio (90% CI)		1.25 (0.93, 1.68)
C_{max} (ng/mL)		
Geo LS Mean (90% CI)	2746.45 (1983.06, 3803.71)	2497.85 (1772.46, 3520.10)
Geo Mean Ratio (90% CI)		0.91 (0.59, 1.41)

* Geo=Geometric; LS=Least squares; CI=Confidence interval.

a) Cohort 1: Normal Renal Function
b) Cohort 2: Severe Renal Impairment

Conclusions

HM15912 was well tolerated and safe in subjects with normal renal function and subjects with severe RI. PK profiles of HM15912 were similar in both groups. These results suggest that dose adjustment of HM15912 may not be necessary for SBS-IF patients with RI and support lowering of the eGFR limit in the eligibility criteria of **the ongoing phase 2 SBS-IF trial** (NCT04775706, EudraCT No. 2021-000176-11).

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References

- Banerjee, A., & Warwicker, P. (2002). Acute renal failure and metabolic disturbances in the short bowel syndrome. QJM, 95(1), 37-40.

THE ONGOING PHASE 2 SBS-IF TRIAL
For more information ➔