AN ONGOING PHASE 2 STUDY OF HM15912, A NOVEL LONG-ACTING GLUCAGON-LIKE PEPTIDE 2(GLP-2) ANALOG FOR SHORT BOWEL SYNDROME-INTESTINAL FAILURE (SBS-IF) PATIENTS

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BACKGROUND

- Intestinal GLP-2 is secreted upon nutrient ingestion and is known to play critical role in intestinal growth by promoting crypt cell proliferation. Because of its intestinal proliferation property, GLP-2 analogue has long been used to treat people with SBS.[1]
- The only marketed drug for SBS, teduglutide, has an extended half-life compared to native GLP-2, but its relatively short half-life and instability in aqueous formulation necessitate daily administration through a complex reconstitution step.

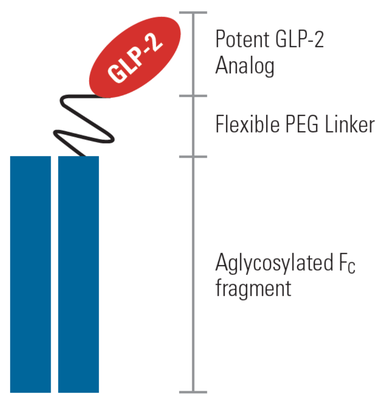


Figure 1. A monthly SC injection GLP-2 analogue

- HM15912 is a novel long-acting GLP-2 analogue chemically conjugated, via a bifunctional polyethylene glycol linker, to a recombinant human IgG4 Fc fragment.
- In first-in-human study, HM15912 showed improved pharmacokinetic profile with over 100 hours of half-life which can support the possibility of monthly dosing. Furthermore, the conjugation of GLP-2 analogue and IgG4 Fc fragment improves physicochemical stability in an aqueous formulation. This makes it possible to provide the patient with a pre-filled syringe.
- In this presentation, we present the ongoing proof-of-concept study of HM15912 in SBS-IF patients. (NCT 04775706 / EudraCT No.2021-000176-11)

STUDY DESIGN

Figure 2. Schematic of Study Design

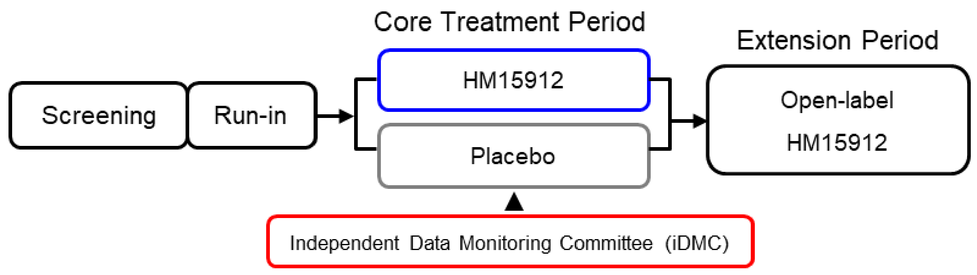
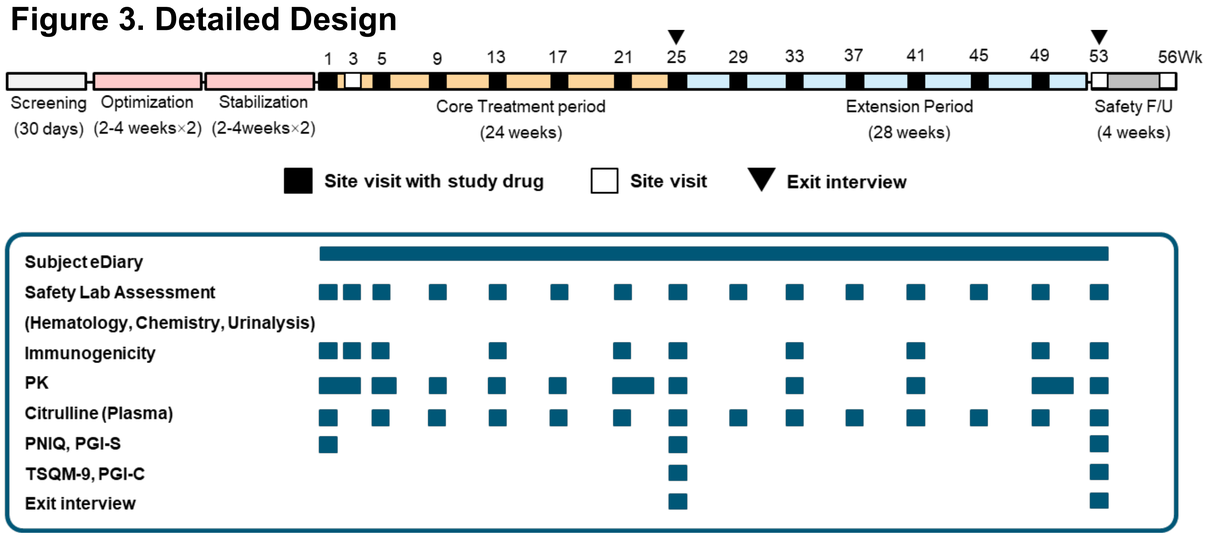


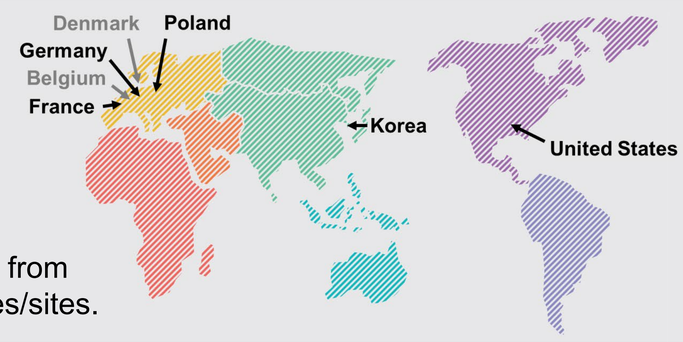
Figure 3. Detailed Design



Subjects will receive HM15912 or placebo subcutaneously every 4 weeks during 6-month core treatment period. After the core treatment period, an open label extension period will follow for another 6-months. During this periods, all subjects will receive IP.**(Fig. 2, Fig. 3)**

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	• Men or women, aged 18 years of age or older with intestinal failure resulting in SBS • The latest intestinal resection being ant least 6 months prior to screening • Have a stoma and able to separate stool and urine • Require PN/IV at least 3 days per week for at least 12 months
Key Exclusion Criteria	• Any history of colon cancer • Have a hospital admission within 1 month prior to Screening visit • eGFR<60mL/min/1.73m^2 by CKD-EPI 2021 • Have cardiac disease defined as decompensated heart failure (New York Heart Association Class IV) • Have any use of GLP-2, dipeptidyl peptidase 4 (DPP-4) inhibitor, growth hormone, glutamine, or analogs thereof within 3 months prior to Screening



Active recruiting from multiple countries/sites.

SBS-IF patients with stoma who require PN/IV support at least 3 days per week for least 12 months will be enrolled in this study (Table 1). Effect of HM15912 in SBS-IF with Colon in continuity will be assessed in a separate clinical trial near future, because stoma and colon in continuity patients showed different responses in terms of PN/IV volume reduction based on the previous studies with other GLP-2 analogues.[2]

Safety and PK profile will be collected and serve as primary endpoints. To assess pharmacodynamic profile of HM15912, change from baseline weekly PN/IV volume at week 25 will be measured.

Table 2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess safety and tolerability of HM15912 after multiple SC doses for 24 weeks	• Incidence of AEs • Incidence of injection site reactions • Incidence of Clinical laboratory abnormalities • Clinically significant findings on physical examination • Changes from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters
To assess the PK profile of HM15912	• Maximum serum concentration (C_{max}) • Time to maximum serum concentration (t_{max}) • Elimination half-life ($t_{1/2}$) • Volume of distribution (Vd/F) • Clearance (CL/F) • Area under the concentration-time curve from time zero to the last observable concentration (AUC_{0-t}) and AUC extrapolated to infinity ($AUC_{0-\infty}$)
Secondary	
To assess the PD profile of HM15912	• Change in weekly PN/IV volume from baseline to Week 25 • Note: The baseline PN/IV volume (L/week) is the average of actual PN/IV volume received during the last 2 weeks of the Stabilization period

Independent Data Monitoring Committee (iDMC)
An independent data monitoring committee (iDMC) will be established to monitor safety data periodically during the study.

Patient Reported Outcome
Questionnaire
There are 4 kinds of questionnaires will be used for this study. These include the **PNIQ** to asses health-related quality of life, the **TSQM-9** to assess treatment satisfaction, the **PGI-C** to assess subject-perceived change in PN/IV requirement and the **PGI-S** to assess subject-perceived change in severity of SBS-IF symptoms and in PN/IV interference in daily activities.

Exit Interview
A semi-structured Exit Interview will be conducted by videoconference within 10 days from Week 25 and Week 53 respectively to provide an in-depth, qualitative assessment of the subject's experience and the subject-perceived change due to treatment/placebo.

CONCLUSION

This study will provide the rationale as well as data on the threshold of efficacy and safety for future pivotal studies. Moreover, long-term extension period will provide more robust safety and efficacy data on HM15912. (NCT 04775706 / EudraCT No.2021-000176-11)

REFERENCE

1. ROWLAND, Katherine J.; BRUBAKER, Patricia L. Life in the crypt: a role for glucagon-like peptide-2?. *Molecular and cellular endocrinology*, 2008, 288.1-2: 63-70.
2. JEPPESEN, Palle B., et al. Factors associated with response to teduglutide in patients with short-bowel syndrome and intestinal failure. *Gastroenterology*, 2018, 154.4: 874-885.

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