American Diabetes Association. 83RD SCIENTIFIC SESSIONS
SAN DIEGO | JUNE 23–26, 2023

95-LB

# Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of a Novel Oral Small Molecule GLP-1 Receptor Agonist (HRS-7535) in Healthy Subjects: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single- and Multiple-Ascending Dose (SAD and MAD) Study

Jingying Wu[1], Wei Hu[1], Yijun Du[1], Qian Zhang[1], Renpeng Zhou[1], Qin Zhang[1], Huiling Qin[1], Zi Ye[2], Yimei Xu[2], Sheng Feng[2], Chang Shu[2], Yu Shen[2], Yang Fan[2]

[1]Phase I Clinical Trial Center, The Second Affiliated Hospital of Anhui Medical University, Hefei, China; [2]Clinical Research and Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

安徽医科大学第二附属医院 THE SECOND HOSPITAL OF ANHUI MEDICAL UNIVERSITY

## Introduction

- HRS-7535 is a novel oral small molecule glucagon-like peptide-1 receptor (GLP-1R) agonist that activates the GLP-1R receptor widely distributed on pancreatic and other tissues.
- This activation stimulates insulin release, suppress glucagon secretion. Moreover, GLP-1R activation reduces appetite and food intake, indicating its potential as a treatment for obesity and metabolic disorders.[1-3]
- One of the crucial advantages of HRS-7535 is its oral administration, which makes it more convenient and accessible than other injectable GLP-1R agonist.
- HRS-7535 has shown promising results in preclinical studies, exhibiting significant improvements in glucose tolerance, insulin secretion, and food consumption reduction (data on file).

## Methods

- This was a randomized, double-blind, multi-part, phase 1 trial (NCT05347758, **Figure 1**).
- Overtly healthy adults 18-55 years were eligible, with the body mass index of 19.0-28.0 kg/m$^2$ and the HbA1c of <6.2%.
- In the SAD phase, healthy subjects were randomized (6:2) to receive HRS-7535 (15, 60, and 120 mg) or placebo.
- Ten healthy adults were recruited for the food effect and were randomized (8:2) to receive HRS-7535 90 mg or placebo.
- In the MAD phase, healthy subjects were randomized (18:6) to receive HRS-7535 (120 mg [30/60/90/120 mg titration scheme]) or matching placebo once daily for 4 weeks.
- The primary endpoints of SAD and MAD phases were safety and tolerability.
- We reported the safety, tolerability, PKs, and PDs of HRS-7535 during the SAD and MAD phases in healthy adults.

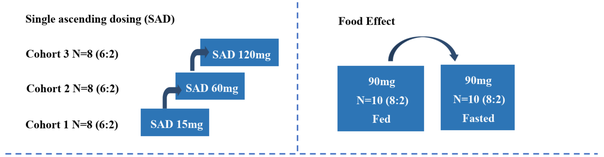


**Figure 1. Trial design**

## Results

### Participants

- 24 subjects participated in SAD and 24 participated in MAD **(Table 1)**.

**Table 1. Baseline characteristics**

| | SAD phase | | | | | MAD phase | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N=6) | HRS-7535 15mg (N=6) | HRS-7535 60mg (N=6) | HRS-7535 120mg (N=6) | SAD total (N=24) | Placebo (N=6) | HRS-7535 (N=18) | MAD total (N=24) |
| **Age, years** | 37.2 (11.4) | 26.2 (4.5) | 25.0 (4.6) | 47.3 (12.8) | 33.9 (12.6) | 29.3 (4.2) | 31.7 (8.9) | 31.1 (8.0) |
| **Male** | 5 (83.3) | 6 (100.0) | 6 (100.0) | 2 (33.3) | 19 (79.2) | 6 (100.0) | 16 (88.9) | 22 (91.7) |
| **Body weight, kg** | 71.2 (6.7) | 62.2 (8.6) | 65.9 (7.9) | 66.1 (10.7) | 66.3 (8.7) | 68.0 (8.9) | 67.6 (10.2) | 67.7 (9.7) |
| **BMI, kg/m$^2$** | 23.3 (1.0) | 23.1 (1.6) | 23.5 (2.3) | 24.3 (1.8) | 23.5 (1.7) | 22.9 (1.5) | 23.3 (2.5) | 23.2 (2.2) |

Data are mean (SD) or n (%).

### Safety

- The most frequently occurring treatment-emergent adverse events (TEAEs) during both the SAD and MAD phases were nausea and vomiting, with a noticeable increase in incidence as the dose was escalated or titrated. There was no clear dose-dependent trend observed for other TEAEs **(Table 2)**.
- All TEAEs reported in this study were mild and mainly gastrointestinal-related, and no moderate or severe TEAEs were documented.
- There were no reported AESIs, SAEs, deaths, or subjects withdrawing from the trial due to TEAEs.

**Table 2. TEAEs occurring ≥20% of patients who received HRS-7535 or placebo**

| | SAD phase | | | | MAD phase | |
|---|---|---|---|---|---|---|
| | Placebo (N=6) | HRS-7535 15mg (N=6) | HRS-7535 60mg (N=6) | HRS-7535 120mg (N=6) | Placebo (N=6) | HRS-7535 (N=18) |
| **Any TEAEs** | 2 (33.3) | 4 (66.7) | 3 (50.0) | 6 (100.0) | 4 (66.7) | 17 (94.4) |
| **Nausea** | 0 | 1 (16.7) | 2 (33.3) | 6 (100.0) | 1 (16.7) | 15 (83.3) |
| **Vomiting** | 0 | 0 | 0 | 6 (100.0) | 0 | 11 (61.1) |
| **Protein urine present** | 0 | 0 | 0 | 0 | 2 (33.3) | 10 (55.6) |
| **Dizziness** | 0 | 1 (16.7) | 0 | 2 (33.3) | 2 (33.3) | 9 (50.0) |
| **Abdominal distension** | 0 | 0 | 0 | 0 | 0 | 9 (50.0) |
| **Headache** | 0 | 0 | 1 (16.7) | 2 (33.3) | 0 | 7 (38.9) |
| **Abdominal pain** | 0 | 0 | 1 (16.7) | 0 | 1 (16.7) | 6 (33.3) |
| **Blood uric acid increased** | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 5 (27.8) |
| **Mouth ulceration** | 0 | 0 | 0 | 0 | 1 (16.7) | 5 (27.8) |
| **Palpitations** | 0 | 0 | 0 | 1 (16.7) | 0 | 4 (22.2) |
| **Chest discomfort** | 0 | 0 | 0 | 0 | 0 | 4 (22.2) |
| **Upper respiratory tract infection** | 0 | 0 | 0 | 0 | 2 (33.3) | 3 (16.7) |
| **Blood triglycerides increased** | 2 (33.3) | 2 (33.3) | 1 (16.7) | 0 | 2 (33.3) | 0 |
| **Alanine aminotransferase increased** | 0 | 2 (33.3) | 0 | 0 | 0 | 0 |

### PK

- PKs were approximately proportional **(Figure 2)**.

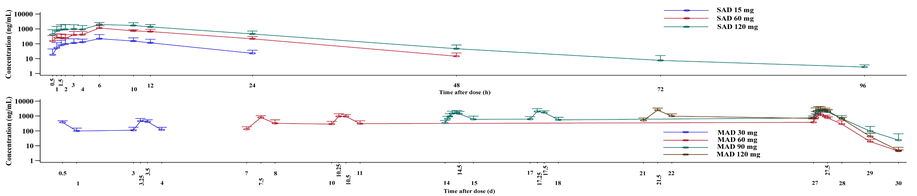


**Figure 2. Mean PK concentration-time curve**

- In the SAD phase, the median $T_{max}$ was 5.98-5.99 h and geometric mean $t_{1/2}$ was 5.28-9.08 h across the HRS-7535 dosing range.
- In the MAD phase, the median $T_{max}$ was 5.98-10.98 h and geometric mean $t_{1/2}$ was 6.48-8.42 h on Day 28 across the HRS-7535 dosing range.

### PD

- In the SAD phase, HRS-7535 exhibited a dose-dependent reduction in plasma glucose (PG) levels within 24 hours of the first dose of study treatment, resulting in lower peak PG levels compared to the placebo group. In the MAD phase, HRS-7535 resulted in an obvious reduction in changes in PG levels from baseline on Day 15 and Day 28, with more stable PG fluctuations compare to the placebo group **(Figure 3)** .
- In MAD phase, the mean reduction in body weight from baseline on Day 29 was 4.38 kg in subjects with HRS-7535 (**Figure 4**).

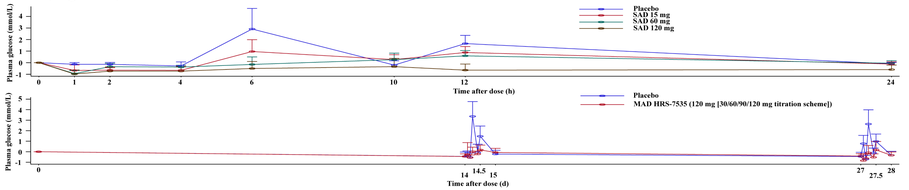


**Figure 3. Mean plasma glucose concentration change from baseline over time**

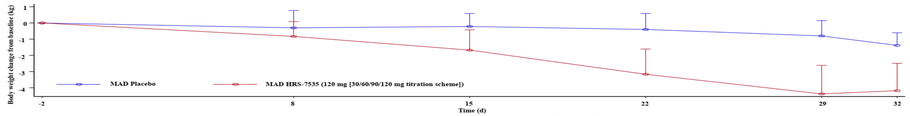


**Figure 4. Mean body weight change from baseline over time**

## Conclusions:

- **Both SAD and MAD of HRS-7535 showed acceptable safety profile and favorable PKs/PDs.**
- **The obvious reductions in body weight could be observed in healthy subjects.**
- **These finding support further clinical exploration of HRS-7535 in patients with metabolic syndromes.**

References: 1. Drucker, et al. Lancet 2006; 368: 1696–705; 2. Nauck, et al. Lancet Diabetes Endocrinol 2016; 4: 525–36; 3. Müller, et al. Mol Metab. 2019; 30:72-130.

*Contact: Jingying Wu, MD (angnewjy@sina.com)*