Safety, Pharmacokinetics and Pharmacodynamics of a Novel dual GIP and GLP-1 receptor agonist (HS-20094) in Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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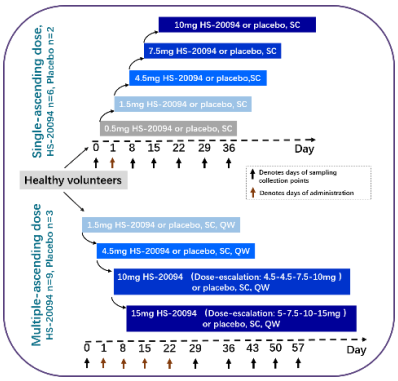
Background And Aims

HS-20094 is a novel dual agonist of glucagon-like peptide-1 and glucagon receptor, being developed for the treatment of type 2 diabetes mellitus and obesity. This study was conducted to assess the safety, pharmacokinetics and pharmacodynamics of HS-20094 in healthy Chinese subjects.

Methods

This phase 1, randomized, double-blind, placebo-controlled study was comprised of two parts: a single-ascending dose (SAD; doses 0.5-10 mg) and 4-week multiple-ascending dose (MAD; doses 1.5-15 mg). Eligible subjects were randomly assigned in a 3:1 ratio to receive HS-20094 or placebo subcutaneously once weekly. Doses above 4.5 mg were reached by titration in MAD part. The primary objective was to investigate the safety and tolerability of HS-20094.

Study Design



Results

A total of 88 subjects received at least 1 dose of HS-20094 or placebo. Baseline demographics and clinical characteristics was shown in **Table 1**.

➢ **Table 1. Baseline demographics and clinical characteristics**

Baseline characteristics	SAD		MAD	
	Placebo	HS-20094	Placebo	HS-20094
	N=10	N=30	N=12	N=36
Age (years)	29.4±3.7	28.5±5.1	32.0±6.4	32.6±5.6
Sex, Male (n, %)	8 (80.0)	22 (73.3)	9 (75.0)	26 (72.2)
Height (cm)	169.9±7.135	167.16±8.759	166.1±7.9	166.9±8.3
Weight (kg)	65.7±7.0	65.2±9.7	65.9±8.6	66.5±8.0
BMI (kg/cm^2)	22.8±2.6	23.3±2.3	23.8±1.7	23.8±1.6

Note: Data are presented as mean (SD), or n (%); BMI= body mass index.

Overall, HS-20094 was well tolerated (**Table 2**). The most frequent side effects reported with HS-20094 were gastrointestinal (decreased appetite, nausea), all of which were considered to be mild to moderate in severity. No severe hypoglycemic events were reported.

Following a single dose of HS-20094, the median T_{max} ranged from 8 to 48h. The mean $t_{1/2}$ was estimated to be approximately 6-7days (160-166h), thus supporting a once-weekly dosing regimen. After 4 weeks of doses or dose-titrations（up to 15mg）, the median T_{max} was 12-24h. The geometric mean of $T_{1/2}$ was estimated to be 155.8-169.9 h. The total exposure of HS-20094 increased in an approximately dose-proportional manner. The mean accumulation ratios of C_{max} and AUC were in a range of 1.924 and 2.032, indicating a mild accumulationThe pharmacokinetics of HS-20094 was summarized in **Table 3.**

HS-20094 demonstrated a decreasing trend in glucose AUC (**Figure 1a**). A dose-dependent weight loss was observed in the MAD part (**Figure 1b**). The

➢ **Table 2. Treatment-emergent adverse events**

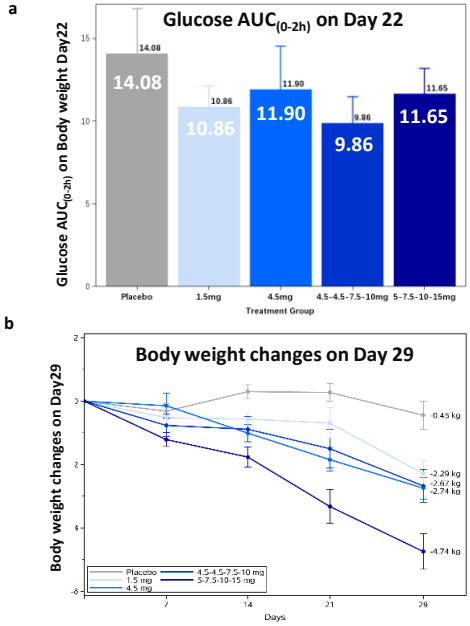
	SAD					MAD			
	0.5mg	1.5mg	4.5mg	7.5mg	10mg	1.5 mg	4.5 mg	10 mg	15 mg
	N=6	N=6	N=6	N=6	N=6	N=9	N=9	N=9	N=9
Any TEAE	2/6	2/6	2/6	6/6	6/6	5/9	9/9	8/9	9/9
Nauseous	0	0	2/6	2/6	1/6	0	4/9	2/9	3/9
Vomiting	0	0	1/6	0	0	0	0	0	2/9
Constipation	0	0	0	0	0	0	0	0	0
Abdominal Pain	0	0	0	0	0	0	1/9	0	0
Decreased Appetite	0	0	2/6	5/6	5/6	2/9	8/9	8/9	7/9
Increased ALT	2/6	1/6	0	1/6	0	0	3/9	0	3/9
Increased AST	0	1/6	0	1/6	0	0	2/9	0	2/9
Increased Lipase	0	0	0	2/6	2/6	0	2/9	0	2/9
Increased Amylase	0	0	0	1/6	0	0	1/9	0	1/9
Injection Site Reactions	0	0	0	0	0	0	3/9	0	1/9
Hypoglycemic Episode									
Total （< 3.9mmol/L)	0	0	0	0	2/6	4/9	4/9	7/9	7/9
Severe Hypoglycemia	0	0	0	0	0	0	0	0	0

➢ **Table 3. Pharmacokinetics of HS-20094**

	Group	1.5 mg	4.5 mg	10 mg	15 mg
Week 1	Number	9	9	9	9
	C_{max} (ng/mL)	165.4 (10.47)	533.7 (17.24)	513.3 (16.44)	645.8 (16.57)
	T_{max} (h)[a]	48 (12, 60)	36 (24, 84)	24 (24, 72)	24 (8, 60)
	AUC_{0-t} (h*ng/mL)	22552 (5.600)	72136 (16.17)	68892 (16.80)	82023 (16.03)
Week 4	Number	8	9	7	9
	C_{max} (ng/mL)	319.1 (6.942)	1085 (15.61)	2138 (18.30)	3653 (17.34)
	T_{max} (h)[a]	24 (12, 36)	24 (8, 48)	24 (12, 48)	12 (8, 48)
	AUC_{0-t} (h*ng/mL)	43101 (6.947)	145718 (17.33)	273519 (18.97)	433545 (16.41)
	$T_{1/2}$ (h)	155.8 (4.952)	156.2 (6.647)	161.8 (7.172)	169.9 (4.625)
	CL/F (L/h)	0.01742 (8.150)	0.01532 (21.12)	0.01756 (21.75)	0.01666 (18.55)
	V_d/F (L)	3.915 (6.272)	3.454 (17.66)	4.098 (15.27)	4.084 (17.64)

Note: Data were shown as Geometric Mean (coefficient of variability CV %), unless otherwise noted. [a]Median (minimum, maximum). C_{max}: maximum observed plasma concentration; T_{max}: time of C_{max}; AUC_{0-t} : area under the concentration time curve during dosing interval; $T_{1/2}$=terminal half-life, CL/F=apparent clearance of drug, V_d/F=apparent volume of distribution.

mean (SD) reduction of body weight from baseline was 4.74 (1.687)kg on day 29 in 15mg dose cohort compared to 0.45 (1.460)kg in the placebo cohort. The efficacy of weight loss maintained for at least 4 weeks after stopping the drug.



➢ **Figure 1. Efficacy of treatment with HS-20094**

Conclusions

HS-20094 was well tolerated and showed a glucose and body weight-lowering effect in Chinese healthy adults. The data of clinical safety, efficacy and PK support further evaluation of HS-20094 for the treatment of T2DM and potentially obesity.

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