

LBA 41

Safety, tolerability, pharmacokinetics, and pharmacodynamics of HRS-4729, a novel GLP-1/GIP/glucagon triple-receptor agonist: a randomized, double-blind, placebo-controlled phase 1 study

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Background and Objective

- HRS-4729, a novel long-acting triple GLP-1/GIP/glucagon receptor agonist, has shown therapeutic potential for metabolic disorders in preclinical studies.
- We aimed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of HRS-4729 in healthy adults and people living with obesity without diabetes.

Methods

- This was a randomized, double-blind, placebo-controlled phase 1 (NCT06762600; **Figure 1**).
- In the single ascending dose (SAD) part, adults with a BMI of 19–35 kg/m² and without diabetes were randomized to receive subcutaneous (SC) injection of HRS-4729 (at doses from 0.04 to 9 mg) or placebo.
- In the multiple ascending dose (MAD) part, adults living with obesity (BMI 28–40 kg/m²) and without diabetes were randomized to receive weekly HRS-4729 (1mg fixed dose; 4, 8, or 12 mg with titration), placebo, or weekly ribupatide injection (4 mg titration) for 12 weeks.

Results

Participants

- 42 adults with mean BMI 29.0 kg/m² were enrolled in SAD part and 60 participants were enrolled in MAD part with mean BMI 31.4 kg/m² (**Table 1**).

Safety and Tolerability

- All treatment-emergent adverse events (TEAEs) were mild to moderate (**Table 2**).
- No serious TEAEs occurred, and no TEAEs led to treatment discontinuation.
- The most common gastrointestinal AEs following HRS-4729 were nausea, vomiting, and diarrhea.
- No hypoglycemic events were documented in participants receiving HRS-4729.

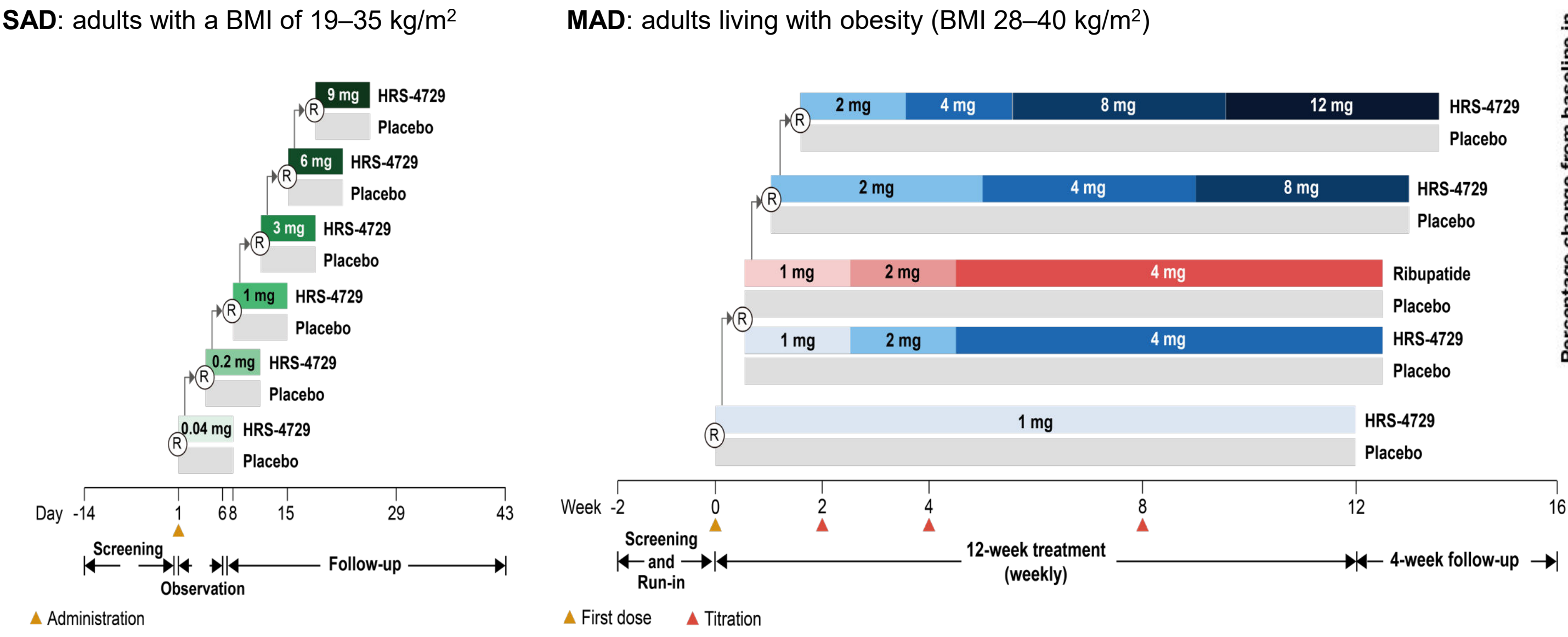
PK Profile

- Following single doses of 0.2 to 9 mg, HRS-4729 exposure increased in an approximately dose-proportional manner (**Figure 2**).
- Minimal accumulation was observed following repeated once-weekly dosing, with an accumulation ratio (AUC_{tau}) of 1.7.

Table 1. Baseline characteristics									
	SAD								All (N=42)
	Placebo (N=11)	HRS-4729							
		0.04 mg (N=2)	0.2 mg (N=6)	1 mg (N=6)	3 mg (N=6)	6 mg (N=6)	9 mg (N=5)	Total (N=31)	
Male, n (%)	7 (63.6)	2 (100.0)	1 (16.7)	3 (50.0)	3 (50.0)	5 (83.3)	5 (100.0)	19 (61.3)	26 (61.9)
Age (years)	37.9 (10.6)	30.5 (7.8)	43.0 (11.4)	37.2 (11.2)	36.8 (14.3)	30.7 (5.5)	27.8 (8.1)	35.0 (11.0)	35.8 (10.8)
Weight (kg)	82.8 (16.5)	75.0 (5.9)	72.3 (8.6)	74.8 (13.1)	86.7 (10.5)	93.7 (12.8)	89.0 (12.1)	82.6 (13.4)	82.6 (14.0)
BMI (kg/m ²)	29.3 (4.3)	25.1 (1.7)	27.2 (3.0)	26.3 (3.1)	30.3 (2.6)	31.3 (1.6)	31.1 (2.7)	28.9 (3.3)	29.0 (3.5)

	MAD							All (N=60)
	Placebo (N=9)	HRS-4729					Ribupatide 4 mg (N=10)	
		1 mg (N=10)	4 mg (N=10)	8 mg (N=11)	12 mg (N=10)	Total (N=41)		
Male, n (%)	6 (66.7)	6 (60.0)	6 (60.0)	5 (45.5)	6 (60.0)	23 (56.1)	5 (50.0)	34 (56.7)
Age (years)	33.7 (6.0)	39.4 (10.8)	35.8 (8.4)	32.9 (5.8)	34.5 (6.8)	35.6 (8.2)	38.3 (10.5)	35.8 (8.3)
Weight (kg)	88.1 (10.3)	83.2 (6.1)	87.9 (6.3)	92.2 (11.4)	86.5 (8.1)	87.5 (8.7)	85.5 (9.7)	87.3 (9.0)
BMI (kg/m ²)	30.3 (1.3)	31.2 (1.8)	31.7 (2.1)	32.8 (2.0)	30.9 (1.2)	31.7 (1.9)	30.9 (2.2)	31.4 (1.9)

BMI: body-mass index



SAD R: 2:1 for HRS-4729:placebo in the 0.04 mg dose cohort; 6:2 in the 0.2 to 9 mg dose cohorts. MAD R: 10:2 for HRS-4729:placebo in the 1, 8, and 12 mg dose cohorts; 10:2:10:2 for ribupatide:placebo:HRS-4729:placebo in the 4 mg dose cohort.

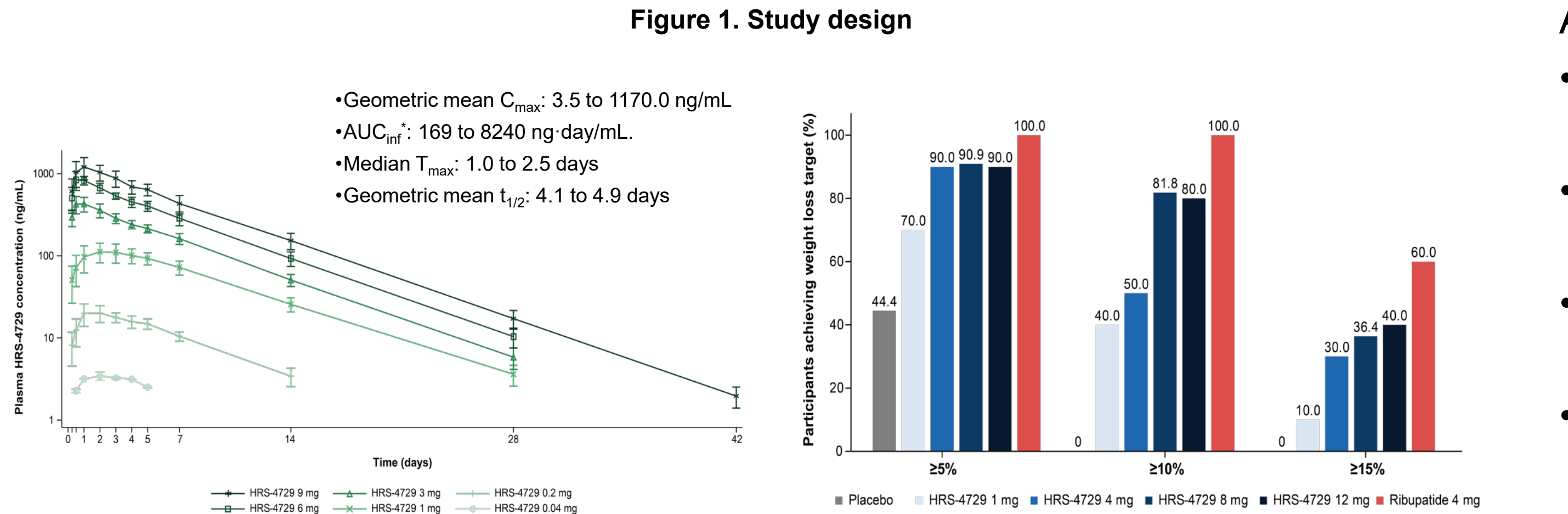


Figure 2. PK profile of HRS-4729 after single-dose administration. Data are mean (SD). Figure is presented on a semi-logarithmic scale. *As per the statistical analysis plan, the AUC_{0-∞} analysis did not include the 0.04 mg dose group.

	SAD			MAD		
	Placebo (N=11)	HRS-4729 (N=31)		Placebo (N=9)	HRS-4729 (N=41)	Ribupatide (N=10)
Any TEAEs	2 (18.2)	21 (67.7)		6 (66.7)	32 (78.0)	9 (90.0)
Mild	2 (18.2)	19 (61.3)		6 (66.7)	27 (65.9)	5 (50.0)
Moderate	0	2 (6.5)		0	5 (12.2)	4 (40.0)
Severe	0	0		0	0	0
Serious	0	0		0	0	0
Leading to treatment discontinuation	0	0		0	0	0
Gastrointestinal	1 (9.1)	16 (51.6)		1 (11.1)	16 (39.0)	6 (60.0)
Nausea	0	12 (38.7)		0	15 (36.6)	4 (40.0)
Vomiting	0	15 (48.4)		0	11 (26.8)	4 (40.0)
Diarrhea	0	2 (6.5)		1 (11.1)	3 (7.3)	3 (30.0)
Abdominal distension	1 (9.1)	1 (3.2)		0	3 (7.3)	0
Constipation	0	1 (3.2)		0	1 (2.4)	0
Abdominal pain	0	1 (3.2)		0	1 (2.4)	0
GERD	0	0		0	1 (2.4)	0
Eructation	1 (9.1)	0		0	0	0

TEAE: treatment-emergent adverse event; GERD: gastroesophageal reflux disease.

Results

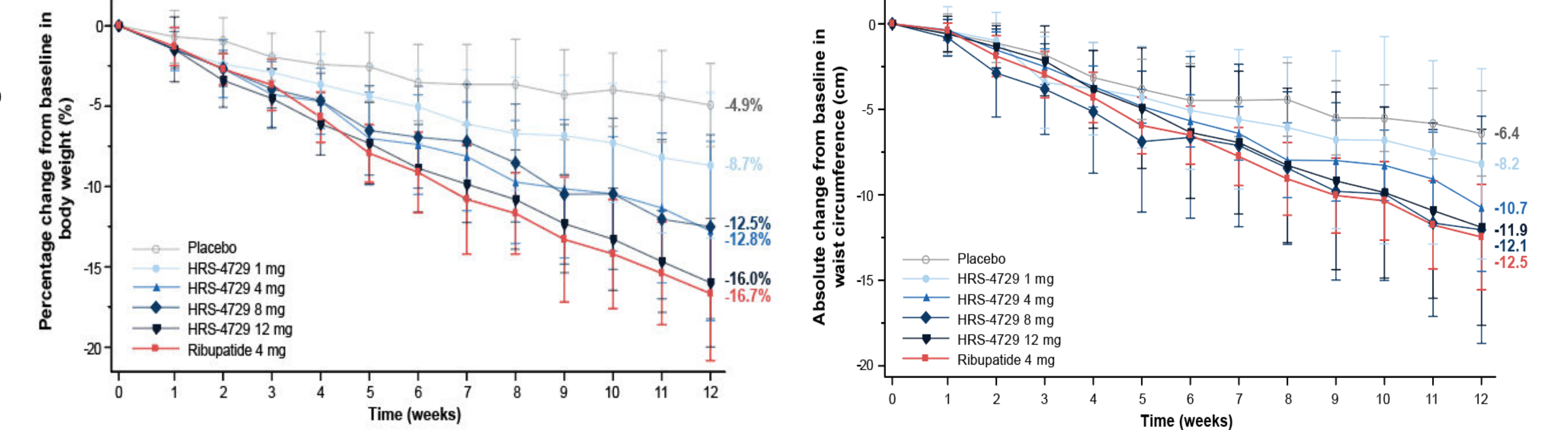


Figure 3. Percentage change in body weight. Data are mean (SD). Figure 5. Change in waist circumference (cm). Data are mean (SD).

PD Profile in MAD Study

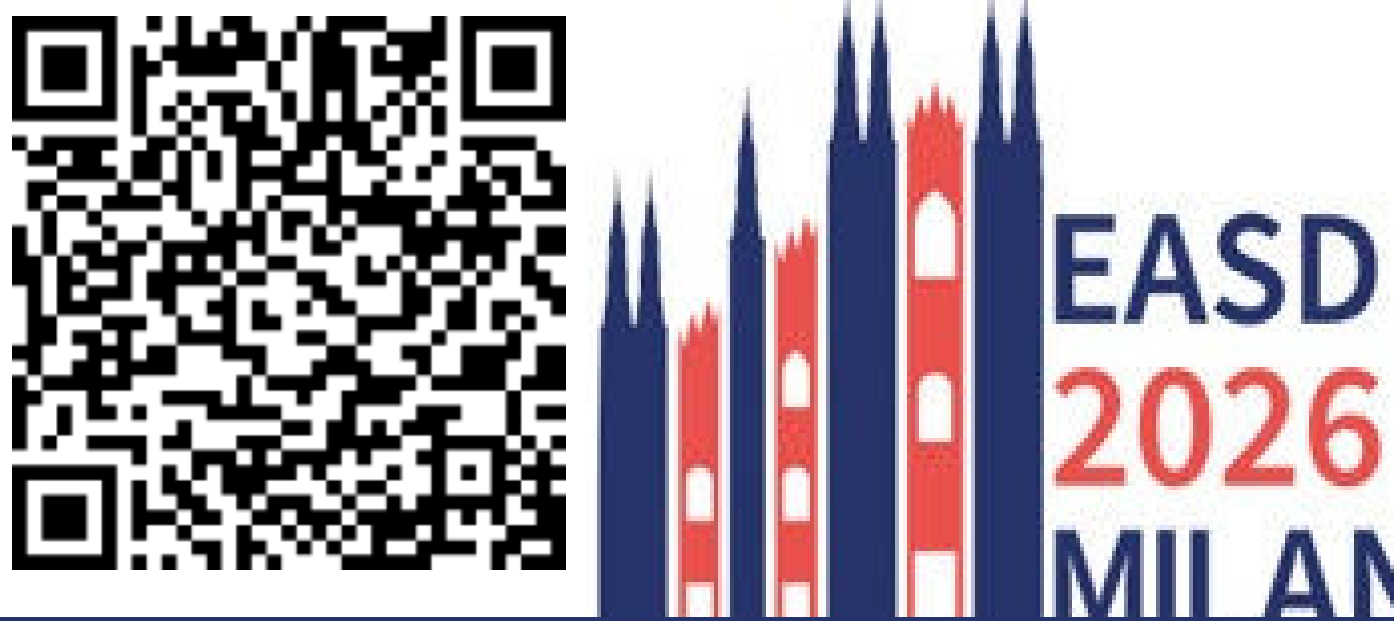
- At week 12:
- Mean percentage CFB in body weight with HRS-4729 was -8.7% to -16.0%, compared with -4.9% with placebo (**Figure 3**; **Table 3**).
 - 70.0% to 90.9% of participants treated with HRS-4729 achieved weight loss ≥5%, compared with 44.4% with placebo (**Figure 4**).
 - The proportion of participants achieving weight loss ≥10% was 40.0% to 81.8% with HRS-4729 versus 0% with placebo (**Figure 4**).
 - Mean CFB in waist circumference with HRS-4729 was -8.2 to -12.1 cm, compared with -6.4 cm with placebo (**Figure 5**; **Table 3**).
 - Greatest mean percentage CFB in liver fat content was -67.3% with HRS-4729 versus -17.2% with placebo (**Table 3**).
 - Ribupatide also showed robust changes in the above PD parameters, with mean CFB of -16.7% in body weight, -12.5 cm in waist circumference, and -38.4% in liver fat content (**Table 3**).
 - HRS-4729 also demonstrated reductions in lipids (such as LDL-C, triglycerides, and cholesterol), as well as blood pressure (**Table 3**).

Table 3. Pharmacodynamics outcomes at Week 12						
	MAD					
	Placebo (N=9)	HRS-4729				Ribupatide 4 mg (N=10)
		1 mg (N=10)	4 mg (N=10)	8 mg (N=11)	12 mg (N=10)	
Percentage CFB in body weight, %	-4.9% (2.6)	-8.7% (4.5)	-12.8% (5.6)	-12.5% (5.7)	-16.0% (4.0)	-16.7% (4.2)
CFB in waist circumference, cm	-6.4 (2.5)	-8.2 (5.6)	-10.7 (3.7)	-12.1 (6.6)	-11.9 (5.7)	-12.5 (3.1)
Percentage CFB in liver fat content, %	-17.2%	-34.9%	-67.2%	-67.3%	-38.8%	-38.4%
CFB in LDL-C, mmol/L	0.04 (0.60)	-0.15 (0.20)	-0.25 (0.66)	-0.16 (0.54)	-0.54 (0.38)	0.16 (0.82)
CFB in triglycerides, mmol/L	-0.49 (0.56)	-0.42 (0.51)	-0.88 (0.67)	-1.04 (0.94)	-1.41 (0.62)	-0.74 (1.21)
CFB in cholesterol, mmol/L	0.03 (0.73)	-0.21 (0.24)	-0.30 (0.81)	-0.54 (0.69)	-1.05 (0.45)	0.43 (1.25)
CFB in DBP, mmHg	-3.0 (3.7)	-7.4 (4.5)	-8.2 (5.1)	-2.5 (4.2)	-10.8 (5.7)	-8.9 (5.7)
CFB in SBP, mmHg	-6.0 (7.4)	-8.2 (7.6)	-13.1 (12.4)	-5.8 (5.7)	-19.0 (8.2)	-15.6 (5.8)
Data are mean (SD). CFB: change from baseline; LDL-C: low-density lipoprotein cholesterol; DBP: diastolic blood pressure; SBP: systolic blood pressure.						

Data are mean (SD). CFB: change from baseline; LDL-C: low-density lipoprotein cholesterol; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Conclusions

- HRS-4729 demonstrated favorable safety and tolerability, with a safety profile similar to that of other incretin-based medications.
- HRS-4729 exposure increased in an approximately dose-proportional manner, with a half-life supporting once-weekly administration.
- HRS-4729 achieved robust weight loss, warranting further development in obesity.



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