# Safety, tolerability, pharmacokinetics, and pharmacodynamics of DA-1726, an oxyntomodulin analogue, in a higher-dose phase 1 cohort with exploratory noninvasive liver assessment


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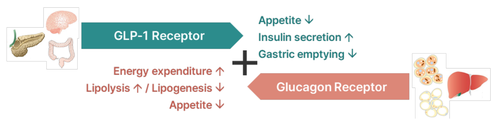
## Introduction

- **Obesity** is associated with metabolic complications, including **metabolic dysfunction–associated steatotic liver disease**.
- **DA-1726** is a novel **oxyntomodulin analogue** in **Phase 1** clinical development, acting as a **dual agonist of the GLP-1 and glucagon receptors** (NCT06252220).
- In this first-in-human Phase 1 study, results through Part 2 (up to 32 mg) demonstrated **favorable safety and tolerability**, along with **clinically meaningful body weight reduction**.
- Based on these findings, a **higher-dose cohort** was subsequently investigated to characterize DA-1726 at an **expanded dose range**.

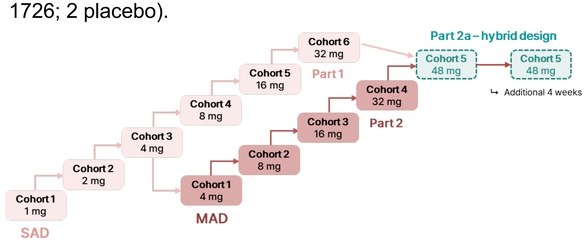



## Aim

To evaluate the **safety**, **tolerability**, **pharmacokinetics (PK)**, **pharmacodynamics**, and **exploratory noninvasive liver-related parameters** of DA-1726 in the higher-dose cohort of obese, otherwise healthy adults.

## Method

- Subjects were randomized to receive multiple ascending doses (MAD) of subcutaneous DA-1726 or placebo in a 2:1 ratio, once weekly for 4 weeks without titration.
- Of 9 subjects randomized in the 48 mg cohort, 6 entered an optional four-week extension phase at the same dose (4 DA-1726; 2 placebo).




## Results

### Demographics and baseline characteristics

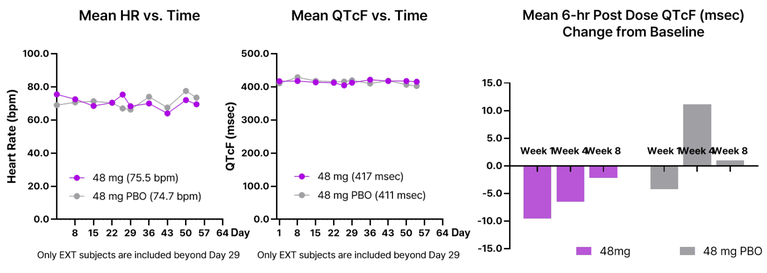
| Number of Subjects | 4 mg (N=6) | 8 mg (N=6) | 16 mg (N=6) | 32 mg (N=6) | 48 mg (N=6) | 48 mg Ext (N=4) | Pooled Placebo (N=15) |
|---|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | | |
| Mean (SD) | 46.8 (11.8) | 45.0 (8.7) | 45.8 (13.4) | 46.7 (5.9) | 48.0 (12.6) | 46.8 (16.0) | 40.6 (12.2) |
| **Male** | | | | | | | |
| n (%) | 2 (33.3) | 4 (66.7) | 4 (66.7) | 2 (33.3) | 4 (66.7) | 2 (50.0) | 9 (60.0) |
| **Weight (kg)** | | | | | | | |
| Mean (SD) | 84.4 (11.0) | 89.3 (11.8) | 96.0 (9.1) | 90.4 (14.4) | 110.4 (12.7) | 108.4 (15.3) | 99.1 (14.5) |
| **Body Mass Index (kg/m²)** | | | | | | | |
| Mean (SD) | 32.6 (2.4) | 31.2 (1.1) | 35.3 (3.9) | 34.0 (2.6) | 38.1 (3.3) | 37.9 (4.2) | 36.1 (4.6) |
| **Waist Circumference (cm)** | | | | | | | |
| Mean (SD) | 98.8 (8.4) | 102.2 (4.5) | 108.0 (7.8) | 104.8 (4.0) | 118.7 (10.1) | 115.0 (10.5) | 111.0 (12.8) |

### Favorable tolerability of DA-1726

- Gastrointestinal adverse events were mostly mild to moderate in severity and transient
- No serious adverse events or treatment-related discontinuations were observed

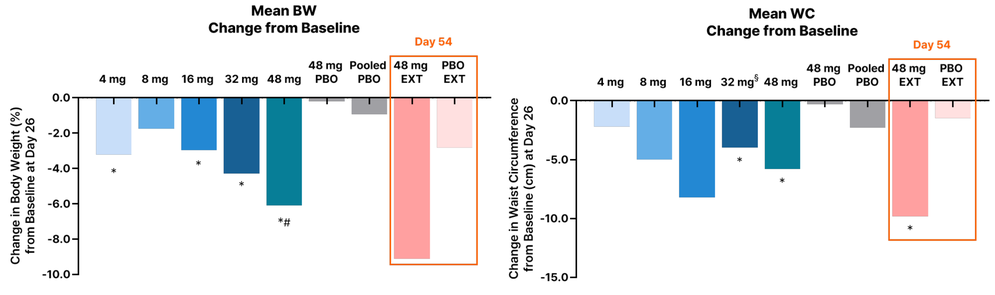
| System Organ Class<br>Preferred Term<br>Maximum Severity | Pooled DA-1726 (N=30), n (%) | Pooled Placebo (N=15), n (%) |
|---|---|---|
| **Subjects with Any TEAE** | 14 (46.7) | 5 (33.3) |
| Mild | 4 (13.3) | 2 (13.3) |
| Moderate | 8 (26.7) | 3 (20.0) |
| Severe | 2 (6.7) | 0 (0.0) |
| **Gastrointestinal Disorders** | 11 (36.7) | 2 (13.3) |
| Mild | 7 (23.3) | 1 (6.7) |
| Moderate | 4 (13.3) | 1 (6.7) |
| **Vomiting** | 10 (33.3) | 2 (13.3) |
| Mild | 6 (20.0) | 2 (13.3) |
| Moderate | 4 (13.3) | 0 (0.0) |
| **Nausea** | 6 (20.0) | 2 (13.3) |
| Mild | 5 (16.7) | 2 (13.3) |
| Moderate | 1 (3.3) | 0 (0.0) |
| **Constipation** | 3 (10.0) | 1 (6.7) |
| Mild | 3 (10.0) | 1 (6.7) |
| **Diarrhea** | 1 (3.3) | 1 (6.7) |
| Mild | 1 (3.3) | 0 (0.0) |
| Moderate | 0 (0.0) | 1 (6.7) |
| **Abdominal Distension** | 1 (3.3) | 0 (0.0) |
| Mild | 1 (3.3) | 0 (0.0) |

### No clinically meaningful changes in heart rate or QTcF were observed




### DA-1726 demonstrated substantial reductions in body weight and waist circumference

- **Body weight (48 mg)**: **−6.1%** at Day 26 and **−9.1%** at Day 54, with no plateau through Week 8
- **Waist circumference (48 mg)**: **−5.8 cm** at Day 26 and **−9.8 cm** at Day 54

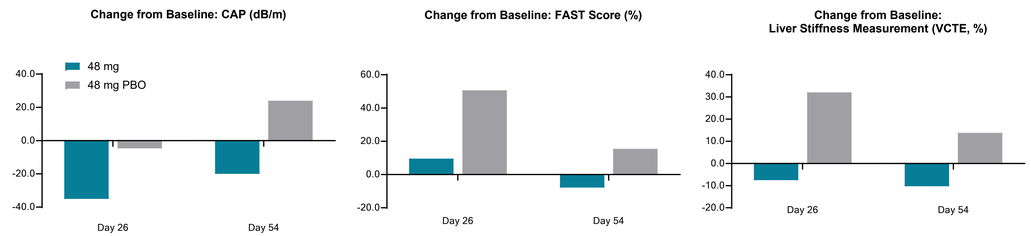



* p<0.05 vs. Pooled PBO, # p<0.05 vs. 48 mg PBO

* p<0.05 vs. Pooled PBO; § at Day 33

### FibroScan-based assessments† suggested liver-related improvements at Day 54

- **Controlled attenuation parameter**: **−20.0 dB/m** at Day 54 vs. **+24.0 dB/m** with placebo
- **Liver stiffness measurement**: **−10.3%** by VCTE at Day 54 vs. **+13.8%** with placebo
- **FAST score**: Directional improvement from baseline observed at Day 54




Baseline CAP values differed by analysis set: Day 26, 307/334 dB/m; Day 54 extension, 291/339 dB/m for 48 mg/PBO n: Day 26, 48 mg = 4, PBO = 3; Day 54, 48 mg = 3, PBO = 1

Baseline FAST scores differed by analysis set: Day 26, 0.108/0.144; Day 54 extension, 0.083/0.210 for 48 mg/PBO n: Day 26, 48 mg = 4, PBO = 3; Day 54, 48 mg = 3, PBO = 1

Baseline LSM scores differed by analysis set: Day 26, 6.48/5.13 kPa; Day 54 extension, 5.30/5.95 for 48 mg/PBO n: Day 26, 48 mg = 4, PBO = 3; Day 54, 48 mg = 3, PBO = 1

† Only FibroScan results that passed QC review were included in the analysis

## Conclusions

- **DA-1726 was generally well tolerated up to 48 mg, with no new safety signals**
- **Most GI AEs were mild-to-moderate and transient, even without dose titration**
- **Despite glucagon receptor activation, no clinically meaningful mean changes in heart rate or QTcF were observed in this short Phase 1 cohort, supporting continued evaluation.**
- **Clinically meaningful and significant weight loss was observed at the 48 mg, without plateau**
- **Exploratory FibroScan findings suggested early liver-related improvements, supporting long-term evaluation**
- **Ongoing Phase 1 Part 3a/3b dose-titration studies will evaluate longer-term treatment**