Interim Data from INLIGHT: A Phase 1 Study of WVE-007 In Adults Living With Overweight and Obesity

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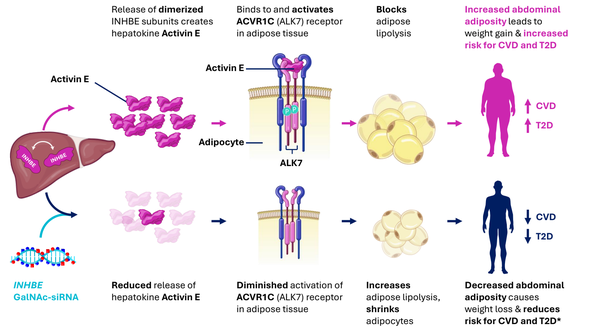
SUMMARY

- The INLIGHT™ trial (NCT06842186), a Phase 1/2a, randomized, double-blind, placebo-controlled study, was designed to evaluate investigational WVE-007, an *INHBE* *N*-Acetylgalactosamine (GalNAc)-conjugated siRNA, for the treatment of adults with overweight and obesity.
- There were some differences in baseline characteristics between the 240 and 400 mg groups.
- Single doses of WVE-007 were generally safe and well tolerated up to 600 mg.
- WVE-007 drove potent and durable reductions in serum Activin E levels, supporting the potential for once or twice-yearly dosing of WVE-007.
- Clinically meaningful improvements in body composition were observed at 3 and 6 months post-single 240 mg dose of WVE-007.
  - There was a statistically significant reduction in visceral fat at 6 months post-single 240 mg dose, along with reductions in total fat mass, and preservation of lean mass.
  - This was accompanied by reductions in body weight and waist circumference.
- 400 mg 3-month results emphasize impact of baseline body composition on therapeutic effect.
  - Post-hoc analysis of 3-month results demonstrates more robust visceral fat reductions in individuals with higher baseline visceral fat (>500 g).
- Overall, the data support continued evaluation of WVE-007 in the ongoing INLIGHT trial.

INTRODUCTION

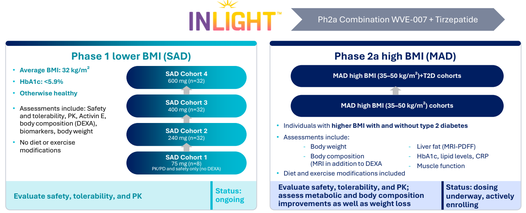
- WVE-007 is a GalNAc (*N*-Acetylgalactosamine)-conjugated small interfering RNA (siRNA) designed to lower the expression of *INHBE* (Inhibin βE) mRNA. *INHBE* is expressed in the liver and encodes the protein Activin E, a hepatokine that regulates adipocyte lipolysis.[1,2]
- *INHBE* loss-of-function carriers have a healthy metabolic profile, including lower abdominal obesity, lower triglycerides and HbA1c, and reduced risk for type 2 diabetes (T2D) and cardiovascular disease (CVD).[3-5] This suggests that lowering *INHBE* mRNA by ≥50% may provide therapeutic benefit for people living with overweight or obesity.
- Lowering *INHBE* mRNA with WVE-007 has the potential to reduce visceral fat via increased adipocyte lipolysis (**Figure 1**). Preclinical data demonstrated that *Inhbe*-lowering in mice can reduce visceral adipose accumulation, with preservation of muscle mass.[6]
- WVE-007 is being evaluated in the ongoing INLIGHT trial for its ability to lower circulating Activin E levels and for impacts on body weight and body composition in adults living with overweight or obesity (**Figure 2**).

Figure 1. *INHBE* is a therapeutic target for obesity with potential to impact type 2 diabetes and cardiovascular disease by reducing visceral fat



Model of how Activin E contributes to obesity and metabolic disease and hypothesized impact of siRNA-mediated knockdown of *INHBE* expression. *Consistent with the phenotype of *INHBE* heterozygous predicted loss-of-function carriers (reduced OR of T2D by 28% , reduced OR of CAD by 25%, reduced serum triglycerides, elevated HDL-c, visceral fat by MRI). OR: odds ratio; CAD: coronary artery disease; HDL-c: high-density lipoprotein cholesterol.

Figure 2. The INLIGHT trial is a Phase 1/2a clinical study evaluating WVE-007 in individuals living with overweight or obesity



National clinical trial number: NCT06842186. SAD: single-ascending dose; MAD: multiple-ascending dose; PK: pharmacokinetics; PD: pharmacodynamics; HbA1c: hemoglobin A1C; BMI: body mass index; DEXA: Dual-Energy X-ray Absorptiometry. DEXA was not evaluated for participants in Cohort 1.

- Dosing is underway in the Phase 2a multidose portion of the INLIGHT trial.
- Evaluation of WVE-007 in combination with tirzepatide was initiated in September 2026.

Table 1. Baseline characteristics

Baseline Characteristics	Placebo N=18	75 mg N=6	240 mg N=24	400 mg N=24
Age at consent (years)	35.2 (8.8)	38.3 (3.7)	40.5 (11.2)	39.4 (9.4)
Gender,				
Male	10 (55.6)	2 (33.3)	15 (62.5)	17 (70.8)
Female	8 (44.4)	4 (66.7)	9 (37.5)	7 (29.2)
Weight (kg)	95.0 (12.5)	97.4 (15.5)	97.7 (17.0)	95.6 (11.4)
BMI (kg/m²)	31.8 (2.4)	32.5 (2.8)	32.1 (2.9)	30.9 (1.7)
Waist circumference (cm)	103.2 (8.7)	105.0 (8.4)	106.4 (10.9)	105.2 (8.0)
Total fat mass (kg)	34.7 (5.4)	NA	34.2 (9.0)	33.5 (5.9)
Lean mass (kg)	57.5 (11.1)	NA	58.4 (10.8)	59.4 (10.5)
Visceral fat mass (kg)	0.9 (0.5)	NA	1.0 (0.6)	0.7 (0.5)

All values are mean (SD) or N (%). Total fat mass, lean mass and visceral fat mass were measured by DEXA in the 240 mg and 400 mg cohorts. Lean mass equals tissues excluding bone and fat. Visceral fat is measured in the android region. Placebo column includes participants randomized to placebo across three cohorts shown.

- There were differences in baseline characteristics in gender, BMI, and visceral fat mass, with the 400 mg group having fewer females, lower mean BMI, and lower visceral fat mass than the 240 mg group (**Table 1**).

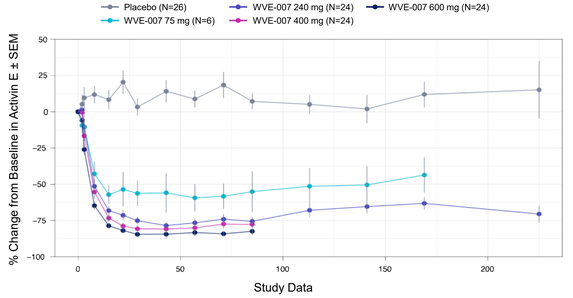
Table 2. Safety

TEAE Category	Placebo N=26 n (%)	75 mg N=6 n (%)	240 mg N=24 n (%)	400 mg N=24 n (%)	600 mg N=24 n (%)
Any TEAE	19 (73.1)	3 (50.0)	20 (83.3)	17 (70.8)	15 (62.5)
Mild	9 (34.6)	2 (33.3)	13 (54.2)	9 (37.5)	9 (37.5)
Moderate	9 (34.6)	1 (16.7)	7 (29.2)	8 (33.3)	6 (25.0)
Severe	1 (3.8)	0	0	0	0
Any drug-related TEAE	3 (11.5)	1 (16.7)	9 (37.5)	9 (37.5)	10 (41.7)
Mild	3 (11.5)	1 (16.7)	9 (37.5)	9 (37.5)	10 (41.7)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
Any serious TEAE	0	0	0	0	0
Any TEAE leading to discontinuation	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0

TEAE: treatment-emergent adverse event; LFT: liver function test. Placebo includes participants randomized to placebo across all cohorts. Data as of February 27, 2026.

- WVE-007 was generally safe and well tolerated through 600 mg (**Table 2**).
- There were no discontinuations from treatment, serious TEAEs, or deaths.
- All TEAEs in the treatment group were mild or moderate, and all study drug related AEs were mild.
- There were no clinically meaningful changes in lipids or other clinical laboratory measurements including LFTs.

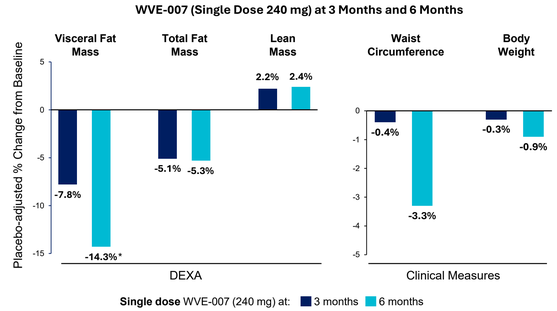
Figure 3. WVE-007 led to dose-dependent, potent, and durable reductions in serum Activin E



Serum Activin E data are sample means with SEM. Change from baseline was analyzed using a mixed model for repeated measures (MMRM). All MMRM baseline and placebo comparisons from Day 8 onwards are p<0.003.

- Activin E protein levels were reduced in all groups (75, 240, 400, and 600 mg) relative to placebo, with a mean maximum reduction of up to 88%. Reductions in Activin E were dose-dependent (**Figure 3**).
- This effect on Activin E was durable through at least 7 months, with substantial reductions in serum Activin E protein levels compared with placebo. This supports the potential for once or twice-yearly dosing with WVE-007.

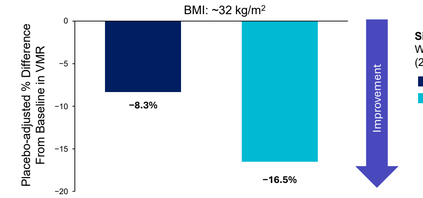
Figure 4. A single dose of WVE-007 drove clinically meaningful improvements in body composition at 3 and 6 months



Placebo-adjusted % change from baseline were estimated using an MMRM model with fixed effects for treatment group, visit, treatment-by-visit interaction, and baseline as a covariate; estimates were based on geometric mean ratios. Stats: *p<0.05.

- A single 240 mg dose of WVE-007 led to a 7.8% reduction in visceral fat mass (placebo-adjusted) at 3 months, as measured by DEXA. This decrease was further reduced at 6 months post-dose, to 14.3% (p<0.05) (**Figure 4**).
- Waist circumference was reduced by 3.3% (placebo-adjusted) at 6 months post-dose.
- Total fat mass was reduced by 5.1% at 3 months and 5.3% at 6 months (placebo-adjusted) post-240 mg single dose of WVE-007.
- Lean mass was preserved, with placebo-adjusted changes of +2.2% at 3 months and +2.4% as 6 months post-240 mg single dose of WVE-007.
- Body weight reductions of 0.3% and 0.9% (placebo-adjusted) were observed at 3 and 6 months, respectively, post single 240 mg dose of WVE-007.

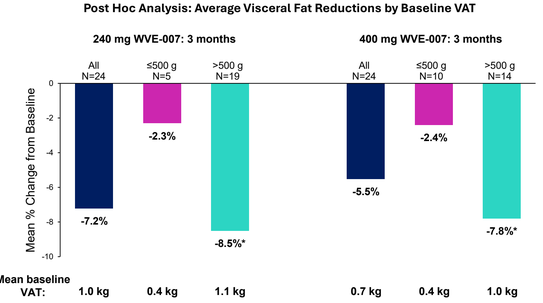
Figure 5. WVE-007 improved body composition by VMR at 3 months and 6 months



Placebo-corrected VMR calculated based on changes from baseline in visceral fat and lean mass at 3 and 6 months.

- Visceral fat-to-muscle ratio (VMR) is an established measure of body composition that integrates harmful visceral fat and beneficial lean mass in a single index.
- Lower VMR is associated with decreased risks of MASH / MAFLD,[7,8] T2D,[9] and cardiometabolic disorders (e.g., dyslipidemia, hypertension).[7,9]
- A post-hoc analysis demonstrated improvements in body composition as measured by VMR at 3 and 6 months post-single 240 mg dose of WVE-007 (**Figure 5**).

Figure 6. 400 mg 3-month results emphasize the impact of baseline body composition on therapeutic effect



*p<0.05. ns: not significant. Mean % CFB values are the arithmetic mean of individual % CFB and were tested within each subgroup against zero using a one-sample t-test. Placebo-adjusted % CFB were estimated using an MMRM model with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline as a covariate; estimates were based on geometric mean ratios.

- 3 months following a single 400 mg dose of WVE-007, there was a 5.0% reduction in visceral fat, a 0.7% reduction in total fat, and preservation of lean mass (-0.2%) (placebo-adjusted).
- A post-hoc analysis of the 3-month results was conducted to analyze average visceral fat reductions by baseline VAT (**Figure 6**):
  - 10 / 24 (42%) treated patients in the 400 mg group had healthy levels of baseline VAT (≤500 g).[10]
  - In the 240 mg dose group, there was a 8.5% reduction in visceral fat (p<0.05) in individuals with higher baseline VAT, compared to 2.3% reduction in individuals with healthy baseline levels of VAT (ns).
  - In the 400 mg dose group, there was a 7.8% reduction in visceral fat (p<0.05) in individuals with higher baseline VAT, compared to 2.4% reduction in individuals with healthy baseline levels of VAT (ns).

References: 1. Adam RC et al., *PNAS* 2023 Aug 8;120(32):e2309967120; 2. Griffin JD et al., *Mol Metab.* 2023 Dec;78:101830; 3. Akbari P et al., *Nat Commun.* 2022 Aug 23;13(1):4844; 4. Deaton AM et al., *Nat Commun.* 2022 Jul 27;13(1):4319; 5. Suglyama M et al., *PLoS ONE* 2018;13(3): e0194798; 6. Yang HC et al., *Obesity* 2025 Nov; https://doi.org/10.1002/oby.70101; 7. Zhang S et al., 2023 *Diabetes Metab Res Rev.* 39(2):e3597; 8. Liu C, et al., 2024 *Lipids Health Dis.* 23(1):104; 9. Wang Q, et al., 2019 *Diabetes Metab Syndr Obes.* 12:1399-1407; 10. Burridge K, et al. 2022 *Obes Pillars.*1:100007.
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