

Analysis of glucose biomarkers in phase I and phase II studies of survodutide in people with type 2 diabetes or living with overweight/obesity

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Objective

- To evaluate changes in insulin sensitivity, pancreatic islet cell function, and glucose biomarkers in participants with T2D or living with overweight/obesity from 3 phase I/II trials of survodutide in a post hoc analysis

Conclusions

- Survodutide was significantly associated with improved markers of insulin sensitivity, pancreatic islet cell function, and glucose biomarkers compared with placebo, in participants with T2D on concomitant metformin and in participants living with overweight/obesity
- These results demonstrate survodutide's beneficial impact on glycemic control

Introduction

- Survodutide (BI 456906) is a GCGR/GLP-1R dual agonist in clinical development for the treatment of obesity¹ and MASH with fibrosis²
- Its dual mechanism of action results in increased energy expenditure (due to GCGR agonism) and reduced energy intake (due to GLP-1R agonism)³
- In a phase II trial of participants with T2D (NCT04153929), survodutide elicited reductions in HbA1c of up to -1.71% in a dose-dependent manner after 16 weeks' treatment, compared with -1.47% for semaglutide (1 mg)⁴

Methods

- Data from 3 randomized, placebo-controlled, dose-finding survodutide trials were included in this analysis^{1,4,5}
- NCT04153929:** phase II trial of 413 adults (aged 18–75 years; BMI 25–50 kg/m²; T2D for ≥6 months; HbA1c 7.0–10.0%; on stable metformin therapy ≥1000 mg/day ≥3 months before screening) randomized to survodutide (up to 0.3, 0.9, 1.8, or 2.7 mg QW; 1.2 or 1.8 mg BIW), semaglutide (up to 1.0 mg QW), or PBO for 16 weeks, with an EoT visit at Week 17⁴
- NCT04667377:** phase II trial of 387 adults (aged 18–75 years; BMI ≥27 kg/m²; stable body weight [≥70 kg for females; ≥80 kg for males]; without diabetes) randomized to survodutide (up to 0.6, 2.4, 3.6, or 4.8 mg QW) or PBO for 46 weeks (20 weeks dose escalation, 26 weeks dose maintenance)¹
- NCT03591718:** phase I trial of 125 adults (aged 18–70 years; BMI 27–40 kg/m²; stable body weight [≥70 kg for females; ≥80 kg for males]) randomized to survodutide (up to 1.8, 2.4, or 3.0 mg QW over 6 weeks; up to 2.4 or 4.8 mg QW over 16 weeks), 2.4 mg BIW (over 16 weeks), or PBO escalated over 1, 2, or 4 weeks⁵
- Insulin resistance (HOMA-IR), β-cell function (HOMA-β), fasting insulin, FPG, non-FPG, HMW adiponectin, glucagon, and C-peptide levels were measured from BL to EoT
- Responses to treatment were measured using MMRM estimates with main effects for treatment, baseline, and visit, and interaction terms for treatment-by-visit and baseline by-visit, with an unstructured covariance matrix structure for repeated measurements within participants

Results

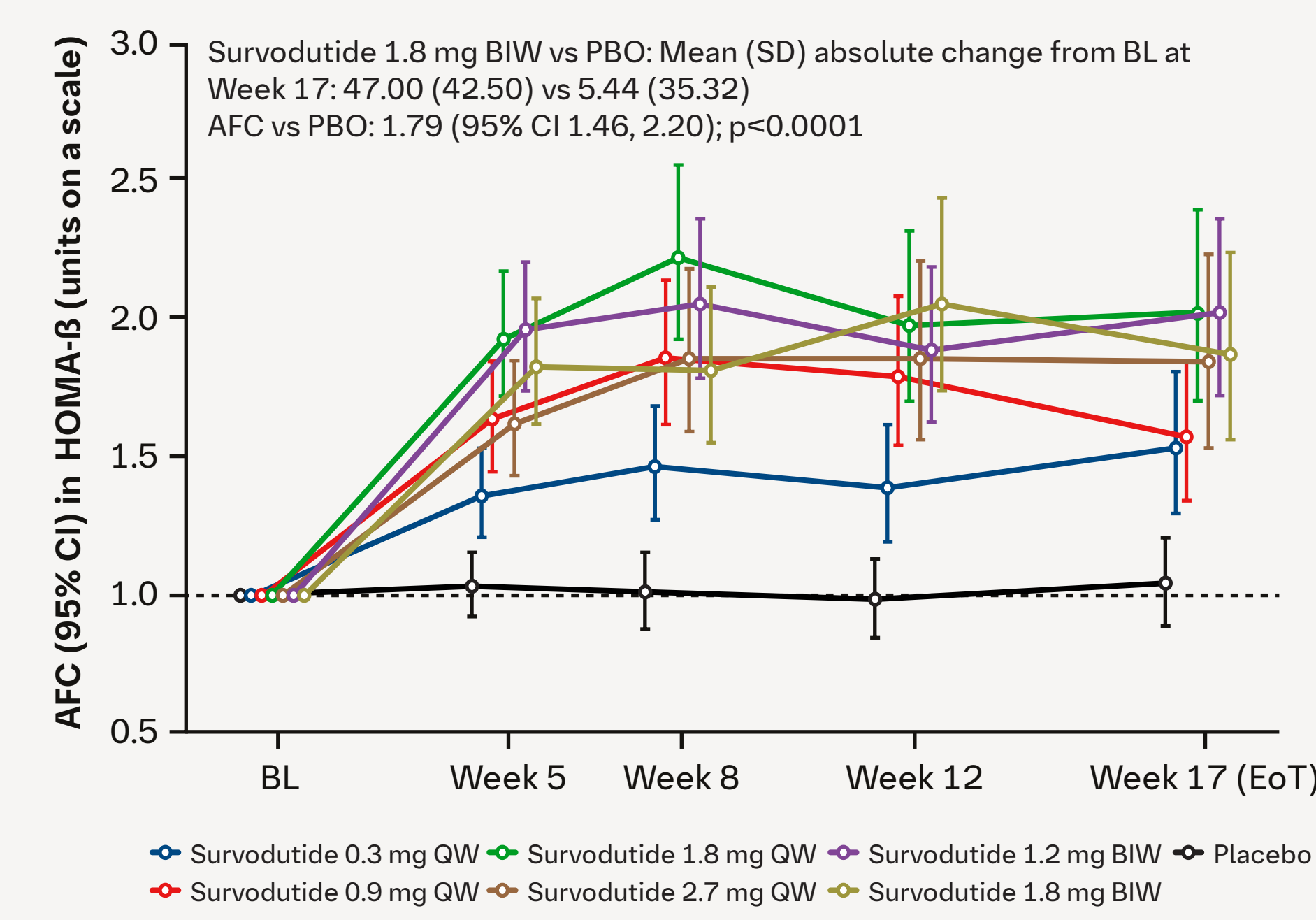
NCT04153929: phase II trial of survodutide in participants with T2D

Survodutide improved markers of β-cell function in participants with T2D

HOMA-β

- Survodutide was associated with significantly and rapidly increased HOMA-β vs PBO, suggestive of substantial improvements in β-cell function (Figure 1)

Figure 1. AFC in HOMA-β from BL to EoT*



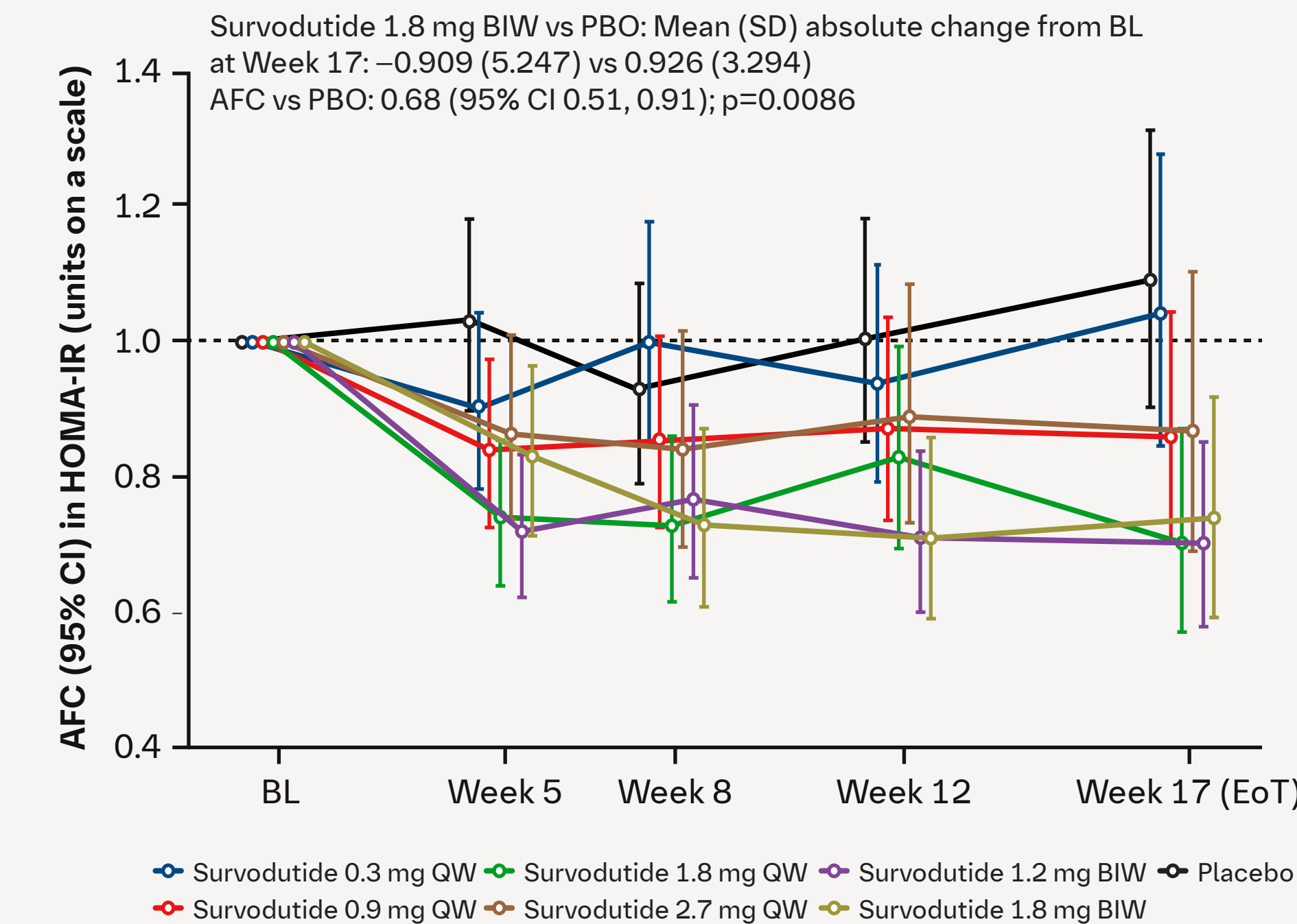
*1 participant was excluded due to a negative HOMA-β value

Survodutide improved markers of insulin sensitivity in participants with T2D

HOMA-IR

- Survodutide was associated with significantly reduced markers of insulin resistance vs PBO (Figure 2)

Figure 2. AFC in HOMA-IR from BL to EoT



Glucose biomarkers

- Survodutide was associated with a significantly reduced level of glucagon vs PBO
 - Mean (SD) absolute change in glucagon from BL at Week 17 for survodutide 1.8 mg BIW vs PBO: -15.07 (15.94) pmol/L vs -3.79 (8.92) pmol/L; AFC vs PBO (95% CI): 0.83 (0.76, 0.90); p<0.0001
 - There were no significant changes in levels of fasting insulin, C-peptide, or HMW adiponectin with survodutide vs PBO (data not shown)

NCT04667377: phase II trial of survodutide in participants living with obesity

HOMA-β

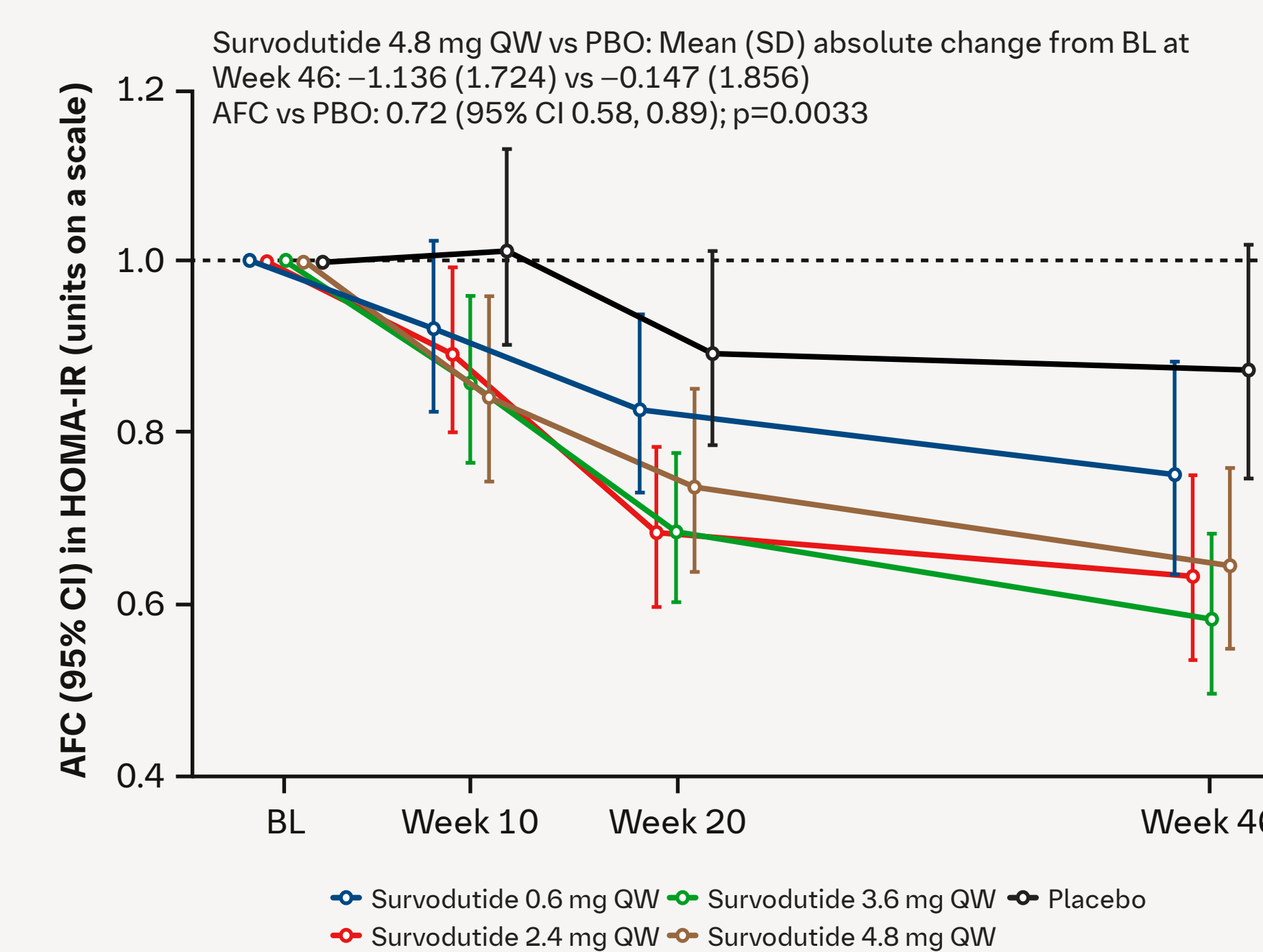
- There was no significant change in HOMA-β with survodutide vs PBO, most likely due to the normoglycemia of the participants in this study
 - Mean (SD) absolute change from BL at Week 46 for survodutide 4.8 mg QW vs PBO: -20.50 (109.78) vs 2.15 (136.30); AFC vs PBO (95% CI): 1.01 (0.83, 1.23); p=0.9053

Survodutide improved markers of insulin sensitivity in participants living with obesity

HOMA-IR

- Survodutide was associated with significantly reduced markers of insulin resistance vs PBO (Figure 3)

Figure 3. AFC in HOMA-IR from BL to EoT



Glucose biomarkers

- Survodutide was associated with significantly increased HMW adiponectin and reduced C-peptide, fasting insulin, and FPG vs PBO (Table 1)
- The change from BL in non-FPG levels with survodutide 4.8 mg QW vs PBO was -0.0 vs 0.6 mmol/L, respectively

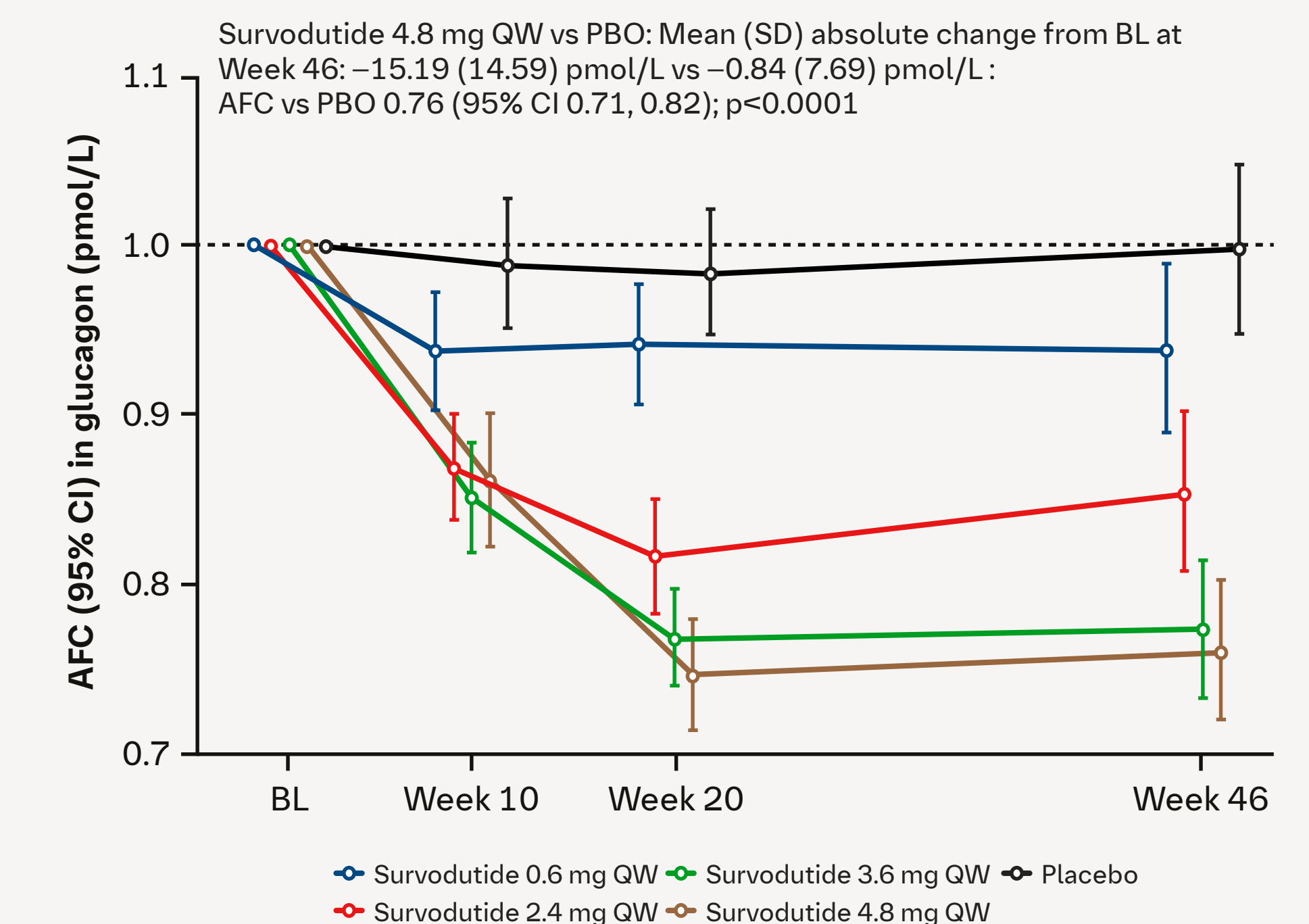
Table 1. Glucose biomarkers at Week 46

| Glucose biomarker | Absolute change from BL, mean (SD) | AFC vs PBO (95% CI) | p-value |
|--------------------------------|------------------------------------|---------------------|----------|
| HMW adiponectin (μg/L) | | | |
| Survodutide 0.6 mg QW | -52.9 (2038.1) | 1.08 (0.84, 1.38) | 0.5651 |
| Survodutide 2.4 mg QW | 548.3 (4127.1) | 1.18 (0.92, 1.51) | 0.1922 |
| Survodutide 3.6 mg QW | 1003.3 (3079.2) | 1.32 (1.04, 1.69) | 0.0251* |
| Survodutide 4.8 mg QW | 1921.6 (3023.8) | 1.37 (1.08, 1.75) | 0.0099* |
| Placebo | -149.3 (2983.6) | - | - |
| C-peptide (nmol/L) | | | |
| Survodutide 0.6 mg QW | -0.065 (0.250) | 0.94 (0.81, 1.08) | 0.3758 |
| Survodutide 2.4 mg QW | -0.187 (0.370) | 0.83 (0.72, 0.95) | 0.0081* |
| Survodutide 3.6 mg QW | -0.078 (0.340) | 0.87 (0.76, 1.00) | 0.0510 |
| Survodutide 4.8 mg QW | -0.100 (0.297) | 0.87 (0.76, 1.00) | 0.0506 |
| Placebo | 0.009 (0.274) | - | - |
| Fasting insulin (mIU/L) | | | |
| Survodutide 0.6 mg QW | -2.96 (5.14) | 0.91 (0.74, 1.12) | 0.3634 |
| Survodutide 2.4 mg QW | -6.83 (15.14) | 0.76 (0.62, 0.93) | 0.0092* |
| Survodutide 3.6 mg QW | -4.25 (7.64) | 0.80 (0.65, 0.98) | 0.0282* |
| Survodutide 4.8 mg QW | -4.03 (7.22) | 0.76 (0.62, 0.93) | 0.0075* |
| Placebo | -0.75 (7.47) | - | - |
| FPG (mmol/L) | | | |
| Survodutide 0.6 mg QW | -0.27 (0.75) | 0.96 (0.93, 1.00) | 0.0290* |
| Survodutide 2.4 mg QW | -0.51 (0.52) | 0.91 (0.88, 0.94) | <0.0001* |
| Survodutide 3.6 mg QW | -0.54 (0.56) | 0.91 (0.88, 0.94) | <0.0001* |
| Survodutide 4.8 mg QW | -0.42 (0.53) | 0.91 (0.89, 0.95) | <0.0001* |
| Placebo | 0.02 (0.59) | - | - |

*p<0.05 was considered statistically significant

- Survodutide was associated with a significantly reduced level of glucagon vs PBO (Figure 4)

Figure 4. AFC in glucagon from BL to EoT



NCT03591718: phase I trial of survodutide in participants living with obesity

HOMA-IR

- Survodutide was associated with reduced markers of insulin resistance vs PBO
 - Mean (SD) absolute change from BL at Week 16 for survodutide 2.4 mg BIW vs PBO: -1.014 (1.190) vs 0.305 (1.466)



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Abbreviations

AFC, adjusted fold change; BIW, twice-weekly; BL, baseline; BMI, body mass index; CI, confidence interval; EoT, end of treatment; FPG, fasting plasma glucose; GCGR, glucagon receptor; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, glycated hemoglobin; HMW, high molecular weight; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; MASH, metabolic dysfunction-associated steatohepatitis; mIU, milli-international units; MMRM, Mixed Model for Repeated Measures; PBO, placebo; QW, once-weekly; SD, standard deviation; T2D, type 2 diabetes

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Disclosures

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