Co-administration of tesofensine/metoprolol: Improvements in body weight and liver fat content in overweight or obese subjects with type 2 diabetes

Grit Andersen[1], Tim Heise[1], Berit Edsberg[2], Daniela Lamers[1], Thomas A. Jacobsen[2], Leona Plum-Mörschel[3], Roman V. Dvorak[2]
[1]Profil, Neuss, Germany, [2]Saniona A/S, Ballerup, Denmark, [3]Profil, Mainz, Germany

Poster #857

INTRODUCTION

- It has been confirmed that weight reduction is an effective therapy for T2D.
- However, few patients achieve that reduction only through diet and therefore weight reduction remains an area of unmet medical need for these patients.
- Tesofensine, a serotonin, norepinephrine, and dopamine reuptake inhibitor has previously been investigated in a Phase 2 study in patients with obesity and showed clinically and statistically significant weight loss at all three administered doses [Astrup et al., 2008].
- However, a dose-related increase in HR and to smaller extent BP were observed, which raised the question of a potential elevated CV risk of this compound.
- Given the need for neutral or beneficial CV safety profile in these patients, it has been decided to combine tesofensine with metoprolol, a selective β1-adrenergic blocker, in order to deliver a product with a favorable benefit/risk profile.

OBJECTIVES

- The objectives of this trial were to compare the effects of co-administration of tesofensine/metoprolol treatment vs. placebo on 24-hour mean heart rate, blood pressure, body weight, glycaemic endpoints and body composition in patients with T2D.
- This poster focuses on the results related to the changes in body weight, glycaemic endpoints and body composition.
- Regarding results related to the effects on 24-hour mean heart rate and blood pressure you are kindly requested to visit poster #851.

STUDY DESIGN AND PATIENTS

- Double-blind, randomized, placebo-controlled, multi-dose, parallel study in subjects with T2D.
- Study conducted at two sites in Germany (Profil Neuss and Profil Mainz).
- 12 visits, including two in-house visits and seven out-patient visits.
- Each subject was randomized to one of two parallel treatment arms, 0.5 mg/d tesofensine + 100 mg/d metoprolol or placebo tablets in the morning over 90 consecutive days.
- Heart rate was monitored by telemetry over 24 hours and through a quiet hour during in-house visits at baseline and at the end of treatment.
- 24-hour heart rate as the primary endpoint was measured every minute and the mean was recorded every hour.
- Comparison of systolic and diastolic blood pressure were done as three measurements at each of six different time points (morning, pre-breakfast, noon, pre-dinner, evening, and midnight). For each of the six time points the mean value was calculated.
- Body weight was measured with calibrated scales at baseline (two measurements) and at the end of treatment.
- Waist circumference was measured using a tape measure.
- Liver fat content was measured in a subset of patients (Profil Neuss) using MRS at the German Diabetes Center, Düsseldorf.

STATISTICAL ANALYSIS

- Statistical analysis was done with an analysis of covariance (ANCOVA) model with fixed effects of treatment and study site and baseline as co-variate.
- Safety endpoints were analysed by means of descriptive statistics.

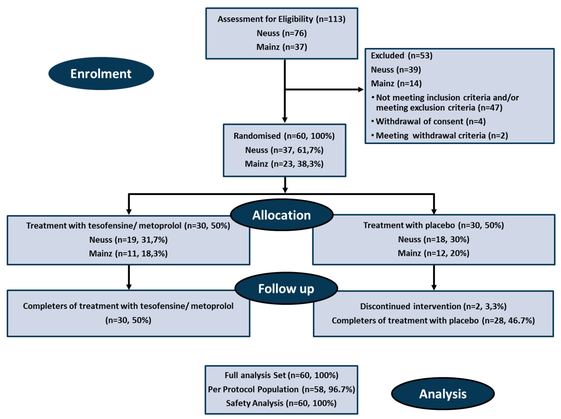

Figure 1. Patient flow and distribution diagram.

RESULTS

Both groups had very similar baseline and demographic characteristics. The difference between treatment arms in bodyweight, BMI and waist was driven by a single individual with weight=157 kg in the active treatment arm.

Most subjects were of Caucasian origin (59, 98.3%) and one subject was of African origin (1.7%). Twenty-one (21) subjects (35.0%) were female and 39 subjects (65.0%) were male. Female/male gender distribution was 15/15 in the TES0+MET arm, 6/24 in the placebo arm, 15/22 at Profil Neuss and 6/17 at Profil Mainz.

Parameter [Unit]	Statistics	TESO+MET (N=30)	Placebo (N=30)	Overall (N=60)
Age [Years]	Mean (SD)	62 (7)	64 (5)	64 (6)
	Median (min-max)	63 (44-70)	66 (52-70)	65 (44-70)
Weight [kg]	Mean (SD)	99.2 (19.3)	93.7 (12.6)	96.4 (16.4)
	Median (min-max)	94.1 (73.5-174.4)	89.8 (75.8-125.6)	91.0 (73.5-174.4)
Height [cm]	Mean (SD)	170 (8)	174 (9)	172 (9)
	Median (min-max)	172 (158-190)	174 (154-194)	172 (154-194)
BMI [kg/m²]	Mean (SD)	34.2 (6.1)	31.0 (3.8)	32.6 (5.3)
	Median (min-max)	34.4 (27.3-59.0)	30.2 (27.0-44.1)	31.5 (27.0-59.0)
Waist Circumference [cm]	Mean (SD)	114 (13)	109 (9)	111 (12)
	Median (min-max)	113 (95-154)	107 (94-140)	110 (94-154)
Pulse [b/min]	Mean (SD)	67 (7)	65 (9)	66 (8)
	Median (min-max)	66 (56-87)	65 (50-85)	66 (50-87)
SBP [mmHG]	Mean (SD)	132 (7)	136 (5)	134 (7)
	Median (min-max)	134 (118-140)	138 (120-140)	136 (118-140)
DBP [mmHG]	Mean (SD)	84 (5)	83 (5)	84 (5)
	Median (min-max)	85 (72-90)	83 (70-90)	85 (70-90)

Table 1. Patient characteristics at baseline.

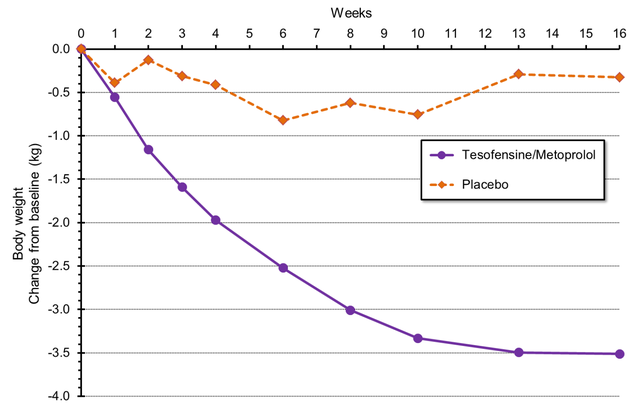

Figure 2. Treatment with TESO+MET showed a progressive and statistically significant reduction in body weight compared to subjects in the placebo group.

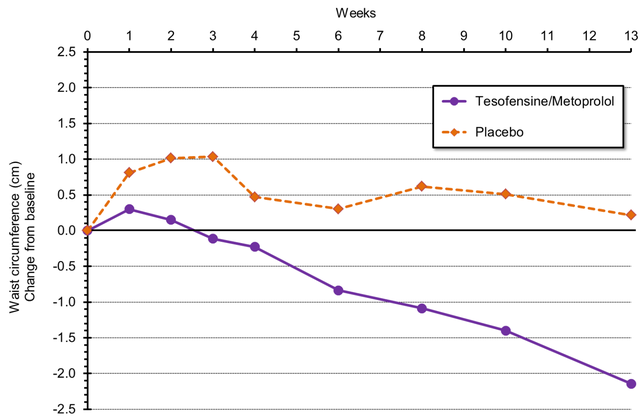

Figure 3. Treatment with TESO+MET led to a significant reduction in mean waist circumference compared to placebo.

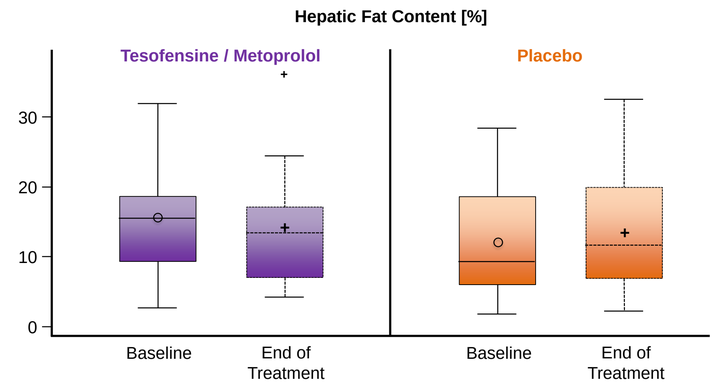

Figure 4. Treatment with TESO+MET led to a numerically decrease in liver fat content, whereas an increase was observed with placebo.

Parameter [Unit]	TESO+MET		Placebo		Difference in change from baseline (95% CI)	p-value
	Baseline	EOT	Baseline	EOT		
Body weight [kg]	99 ± 19	96 ± 20	94 ± 12	93 ± 13	-3.5 (-4.7; -2.3)	<.0001
Waist circumference [cm]	114 ± 13	112 ± 13	109 ± 9	108 ± 9	-2.3 (-3.9; -0.7)	0.0070
HbA1c [%]	7.5 ± 0.5	7.3 ± 0.6	7.7 ± 0.4	7.4 ± 0.7	0.05 (-0.2; 0.3)	0.7240
1.5-Anhydroglucitol [mg/L]	9.8 ± 6.0	11.8 ± 6.1	6.7 ± 3.6	8.2 ± 5.0	0.8 (-0.9; 2.5)	0.3290
FGP [mg/dL]	161 ± 30	158 ± 34	163 ± 28	157 ± 25	2 (-10; 14)	0.7331
Liver fat content [%]	16 ± 8	14 ± 8	12 ± 8	13 ± 9	-2.7 (-5.5; 0.1)	0.0625
Cholesterol [mmol/L]	5.2 ± 1.0	4.9 ± 0.8	4.7 ± 0.8	4.5 ± 0.7	0.08 (-0.2; 0.4)	0.5920
HDL [mmol/L]	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	-0.02 (-0.1; 0.1)	0.6613
LDL [mmol/L]	3.4 ± 0.9	3.3 ± 0.7	2.9 ± 0.6	2.9 ± 0.5	0.13 (-0.1; 0.4)	0.2537
Triglycerides [mmol/L]	2.2 ± 1.0	1.8 ± 0.8	2.0 ± 0.7	1.8 ± 0.7	-0.07 (-0.3; 0.2)	0.5722

Table 2. Summary table of efficacy results.

SAFETY

- **For safety results please refer to Poster #851**

CONCLUSION

- Co-administration of TESO+MET over 90 consecutive days compared to placebo resulted in a statistically significant reduction in both body weight and waist circumference.
- Co-administration of TESO+MET trended to improve liver fat content.
- Co-administration of TESO+MET had no effect on glycemic endpoints or lipids.
- Co-administration of TESO+MET showed favorable tolerability and safety profile.
- This study demonstrates that a tesofensine/metoprolol co-administration significantly reduces body weight as well as waist circumference and trends to improve liver fat in patients with T2D without any negative effects on heart rate and blood pressure.

REFERENCES

Astrup et al., 2008. Lancet 372:1906-1913

SPONSOR

This study was sponsored by Saniona A/S, Denmark and registered at clinicaltrials.gov under the number NCT02737891.