Co-administration of tesofensine/metoprolol: Improvement in heart rate with significant body weight reduction in overweight or obese subjects with type 2 diabetes

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Poster #851

INTRODUCTION

- Obesity and closely related type 2 diabetes (T2D) are major health problems, which has globally reached epidemic proportions.
- Even though many therapeutic options are already available, none of them has a direct effect on the underlying pathophysiology and as a result new alternatives are needed as both standalone therapeutics or to be combined with existing therapies.
- 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 potentially 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 more 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 effects on 24-hour mean heart rate and blood pressure.
- Regarding results related to the effects on body composition and other secondary efficacy endpoints you are kindly requested to visit poster #857.

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.

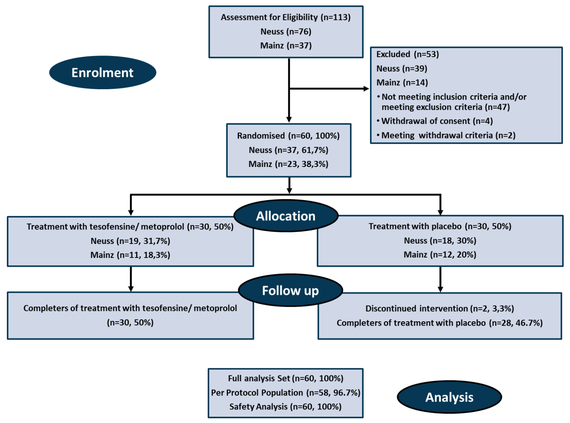

Figure 1. Patient flow and distribution diagram.

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.

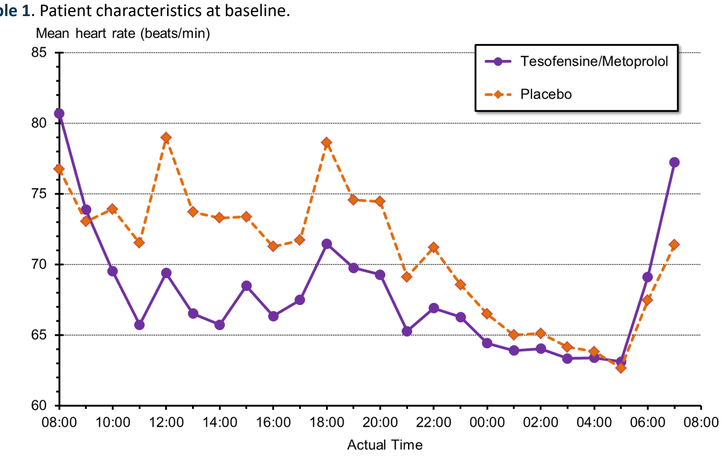

Figure 2. Treatment with TESO+MET led to a significant reduction in mean 24-hour heart rate profile compared to placebo.

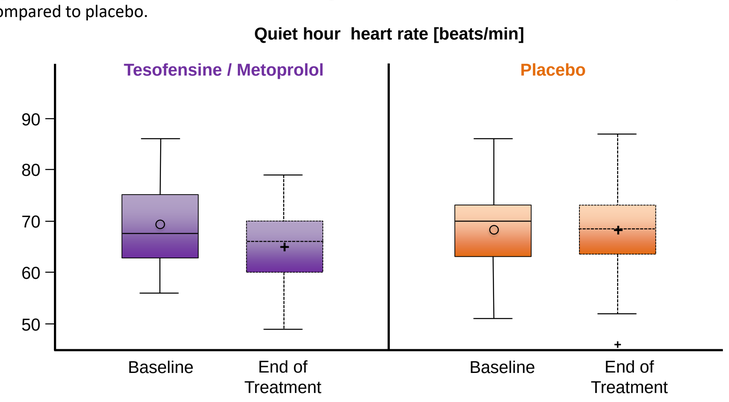

Figure 3. Treatment with TESO+MET led to a significant reduction in the quiet hour heart rate compared to placebo.

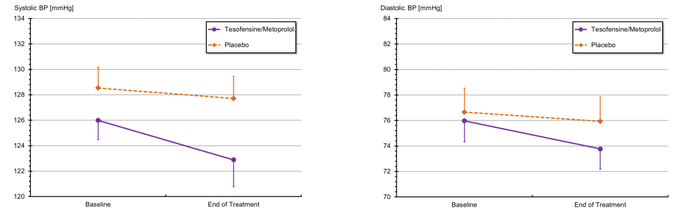

Figure 4. Treatment with TESO+MET led to a numerical, but statistically non-significant, reduction in both systolic and diastolic blood pressure.

Parameter [Unit]	TESO+MET		Placebo		Difference in change from baseline (95% CI)	p-value
	Baseline	EOT	Baseline	EOT		
24-h HR [bpm]	72 ± 7	68 ± 7	70 ± 8	70 ± 9	-3.8 (-6.4; -1.3)	0.0038
Quiet hour HR [bpm]	69 ± 8	65 ± 7	68 ± 8	68 ± 9	-4.3 (-7.1; -1.3)	0.0048
SBP [mmHg]	126 ± 8	123 ± 12	129 ± 9	127 ± 10	-3.1 (-7.5; 1.2)	0.152
DBP [mmHg]	76 ± 9	74 ± 9	77 ± 10	76 ± 10	-2.1 (-4.9; 0.7)	0.138
Body weight [kg]	99 ± 19	96 ± 20	94 ± 12	93 ± 13	-3.5 (-4.7; -2.3)	<.0001

Table 2. Summary table of results.

SAFETY

- 58 out of 60 randomized patients completed the trial – both discontinuations were in the placebo arm.
- No serious adverse events occurred with TESO+MET – one with placebo.
- There were no clinically meaningful findings in the laboratory parameters or ECG
- TESO+MET was well tolerated and most frequent adverse events were nausea, hyperhidrosis, headache, dry mouth, fatigue, and dizziness.

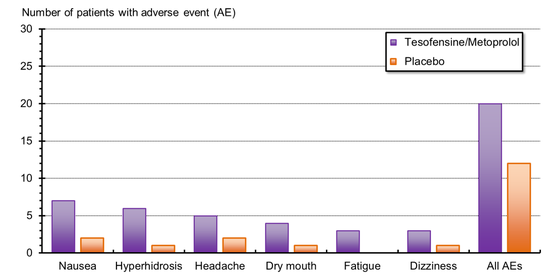

Figure 5. Incidence of the most frequent adverse events.

CONCLUSION

- Co-administration of TESO+MET over fully mitigated the increases in heart rate and blood pressure observed with tesofensine alone while significantly reducing body weight.
- 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 (please refer to Poster #857).
- No new or unexpected safety findings have been observed in the study.
- Considering incidence, kind and severity of the reported AEs, the safety profile of tesofensine/metoprolol did not raise any concerns.
- Hypoglycaemic episodes did not occur during the study.
- There were no concerns with respect to vital signs, physical examination, ECG results and clinical laboratory assessments.
- These results provide basis for further studies with TESO+MET combination in the areas where reduction in urge to eat, body weight and body fat may provide meaningful clinical benefits.

REFERENCES

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

SPONSOR

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