

Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial



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Summary

Background Weight-loss drugs produce an additional mean weight loss of only 3–5 kg above that of diet and placebo over 6 months, and more effective pharmacotherapy of obesity is needed. We assessed the efficacy and safety of tesofensine—an inhibitor of the presynaptic uptake of noradrenaline, dopamine, and serotonin—in patients with obesity.

Methods We undertook a phase II, randomised, double-blind, placebo-controlled trial in five Danish obesity management centres. After a 2 week run-in phase, 203 obese patients (body-mass index 30–≤40 kg/m²) were prescribed an energy restricted diet and randomly assigned with a list of randomisation numbers to treatment with tesofensine 0.25 mg (n=52), 0.5 mg (n=50), or 1.0 mg (n=49), or placebo (n=52) once daily for 24 weeks. The primary outcome was percentage change in bodyweight. Analysis was by modified intention to treat (all randomised patients with measurement after at least one dose of study drug or placebo). The study is registered with ClinicalTrials.gov, number NCT00394667.

Findings 161 (79%) participants completed the study. After 24 weeks, the mean weight loss produced by diet and placebo was 2.0% (SE 0.60). Tesofensine 0.25 mg, 0.5 mg, and 1.0 mg and diet induced a mean weight loss of 4.5% (0.87), 9.2% (0.91), and 10.6% (0.84), respectively, greater than diet and placebo ($p < 0.0001$). The most common adverse events caused by tesofensine were dry mouth, nausea, constipation, hard stools, diarrhoea, and insomnia. After 24 weeks, tesofensine 0.25 mg and 0.5 mg showed no significant increases in systolic or diastolic blood pressure compared with placebo, whereas heart rate was increased by 7.4 beats per min in the tesofensine 0.5 mg group ($p = 0.0001$).

Interpretation Our results suggest that tesofensine 0.5 mg might have the potential to produce a weight loss twice that of currently approved drugs. However, these findings of efficacy and safety need confirmation in phase III trials.

Funding Neurosearch A/S, Denmark.

Introduction

The prevalence of obesity has increased to 15–35% of the adult population in most developed countries and in several developing countries,¹ resulting in an increasing number of people with diseases such as type 2 diabetes, cardiovascular disease, musculoskeletal disorders, and cancers. Weight loss of 5–10% of bodyweight, irrespective of how it is achieved, is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes.² Furthermore, major weight loss as a result of bariatric surgery (eg, 20–25% weight loss by gastric bypass) substantially reduces obesity comorbidities, increases longevity,³ and can often cure type 2 diabetes in patients who are obese.⁴ Non-pharmacological treatment can be effective, but the success rate in the long term is low.⁵ Pharmacological drugs for weight loss are effective in the long term, but after 1 year of treatment, the weight loss produced above that achieved by diet and lifestyle management is 2.9 kg for orlistat, 4.2 kg for sibutramine, and 4.7 kg for rimonabant.^{6,7} Pharmacotherapy with agents that are more effective has so far been limited because of adverse

effects and difficulties with tolerability.⁷ A gap is therefore evident between the efficacy provided by bariatric surgery and present pharmacotherapy for obesity management.

We report a phase II study on tesofensine—an inhibitor of the presynaptic uptake of noradrenaline, dopamine, and serotonin—that has been shown to be safe and effective in animal models and to produce unintended weight loss in obese patients with Parkinson's or Alzheimer's disease.⁸ In these patients, tesofensine produced a placebo-subtracted weight loss of about 4% over 14 weeks without any diet and lifestyle therapy, which is similar to the effect of sibutramine and rimonabant, but with no effect on blood pressure or mood. On the basis of these short-term results, we aimed to assess the weight-loss efficacy and safety in patients with obesity over 24 weeks.

Methods

Study design and patients

We undertook a randomised, double-blind, placebo-controlled, parallel-group, multicentre study of the effect of tesofensine on bodyweight in obese patients (body-mass index [BMI] 30–≤40 kg/m²). Five Danish obesity

Published Online
October 23, 2008
DOI:10.1016/S0140-6736(08)61525-1

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	Placebo (N=52)	Tesofensine		
		0.25 mg (N=52)	0.5 mg (N=50)	1.0 mg (N=49)
Women	38 (73%)	35 (67%)	34 (68%)	36 (74%)
White ethnic origin	51 (98%)	52 (100%)	49 (98%)	49 (100%)
Current smokers	40 (77%)	42 (81%)	37 (74%)	38 (78%)
Weight (kg)	104.3 (15.2)	102.7 (13.8)	101.1 (11.8)	102.4 (12.5)
Height (cm)	171 (10.0)	171 (9.1)	171 (8.6)	172 (9.1)
BMI (kg/m ²)	35.6 (2.9)	35.0 (2.9)	34.6 (2.6)	34.6 (2.7)
Waist (cm)	111.1 (9.8)	110.3 (10.4)	108.9 (10.0)	109.3 (10.2)

Data are number (%) or mean (SD). BMI=body-mass index.

Table 1: Baseline characteristics

management centres participated (Frederiksberg, Copenhagen, Hvidovre, Køge, and Aalborg). The study duration was 34 weeks, consisting of a run-in period of 2 weeks, a 24-week treatment period, and 8 weeks of follow-up, and was undertaken from Sept 1, 2006, to Aug 8, 2007. We included male and female patients with obesity aged between 18 and 65 years. They were recruited from waiting lists for treatment of obesity, and from advertising in the media. Women of childbearing potential had to be non-pregnant and use safe contraceptive methods (contraceptive pills, intrauterine device, or have been surgically sterilised). Smokers were allowed entry if smoking habits had been unchanged for at least 2 months.

We excluded participants if they used prescription drugs that could interfere with bodyweight or have interactions with tesofensine; misused or were dependent on any drug, including alcohol; were pregnant or lactating, or planned to become pregnant within the next 8 months; or

had endocrine, neurological, or psychiatric diseases, hepatic or renal dysfunction, untreated hypercholesterolaemia or hypertriglyceridaemia, diagnosed type 2 diabetes, untreated thyroid disease, malabsorptive intestinal disorders, weight change of more than 3 kg within 2 months before screening, surgically treated obesity, systemic infections or inflammatory diseases, cardiovascular disease or significant abnormalities on the electrocardiogram, uncontrolled hypertension, heart rate of more than 90 beats per min, HIV infection or serological evidence of active hepatitis B or C, cancer within the past 5 years (excluding treated basal cell carcinoma), clinically significant eye disorder, treatment with a drug with known ocular toxic effects, previous treatment with tesofensine, or treatment with an investigational drug within 30 days or five half-lives (whichever was longer) preceding the first dose of study drug. We did not exclude patients with a previous history of anxiety or depression if they had fully recovered, but those having a treatment requiring psychiatric disorder were excluded.

All participants provided written informed consent before any study-related procedures. This study was approved by the ethics committees for the Copenhagen and Frederiksberg Municipalities (now Region Copenhagen), Denmark; the Danish Medicines Agency; and The Data Protection Agency. The Trial was done in accordance with the International Conference on Harmonization/Good Clinical Practice (ICH/GCP) guidelines, and monitored by Cyncron Clinical Research Associates. Safety was monitored by a data monitoring committee, who made an interim analysis deeming it safe for the participants to continue the study.

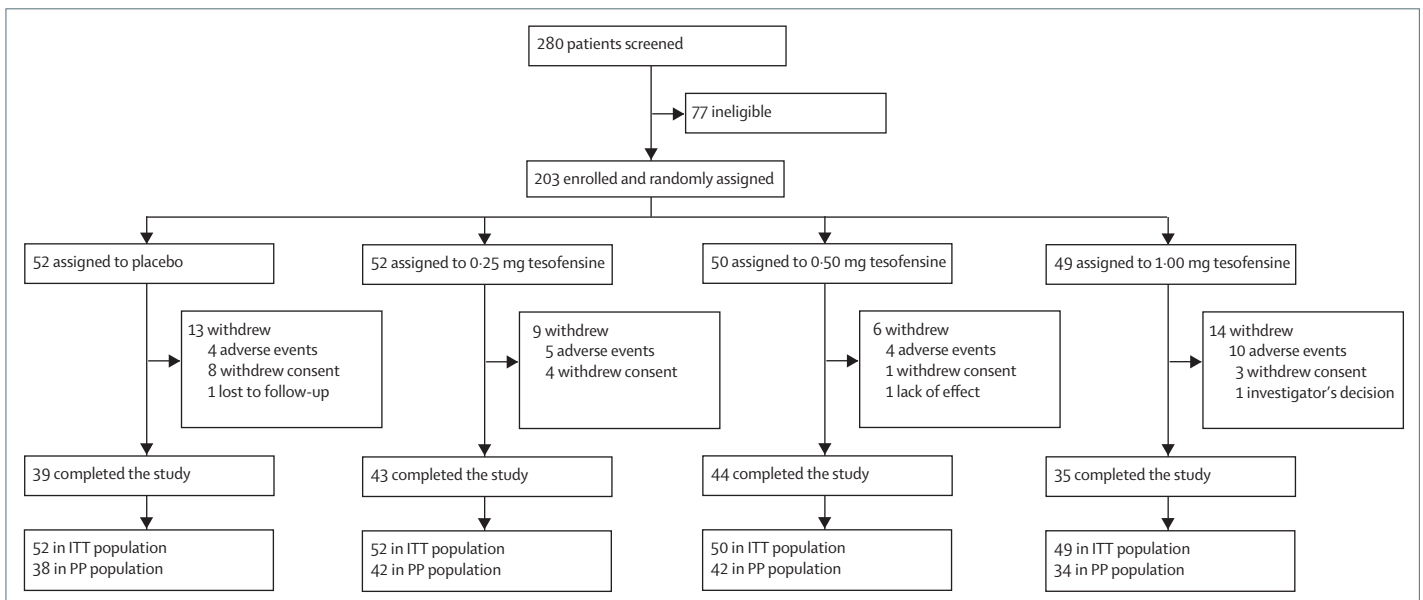


Figure 1: Trial profile

Study duration was 34 weeks, consisting of a run-in period of 2 weeks, a 24-week treatment period, and 8 weeks of follow-up. Some patients were excluded from the per-protocol population because of concomitant medication. ITT=intention to treat. PP=per protocol.

Procedures

From the start of a 2-week dietary run-in period, dieticians instructed all patients throughout the study in a diet providing a daily energy deficit of 300 kcal. The diet provided 20–25% of energy from fat, 20–25% from protein, and 50–60% from carbohydrate. Additionally, participants were given instructions to gradually increase their physical activity up to 30–60 min per day. Every week for the first 4 weeks, and subsequently every second week, patients attended group sessions at the centre, were trained by skilled dieticians in basic nutritional education and behavioural change for weight control, and received information reinforcing the diet.

At screening, all participants were allocated a screening number. Every site was provided with a list of randomisation numbers, consisting of a centre number and a participant number. Eligible participants were allocated the lowest available number at randomisation (baseline visit). The sequence of randomisation was computer generated by the monitoring company for a total of 400 patients with a block size of four, with the SAS Procedure PLAN. The treatment was double blinded, but no assessment was undertaken to test whether the blinding was effective. Randomisation data were kept strictly confidential, in sealed envelopes, which were accessible only to authorised people, until the time of unblinding. At baseline, patients were randomly assigned to tesofensine tablets containing 1.0 mg, 0.5 mg, or 0.25 mg of drug, or to a placebo, which was identical in appearance, taken orally once daily for a duration of 24 weeks. Clinical assessments were made at screening (–2 weeks), –1 week, baseline (0 weeks), weeks 1 and 2, and subsequently every second week until week 24 (end of treatment), and at follow-up (week 28 and week 32). Participants were planned to be enrolled and randomly allocated to one of four treatment groups with active trial drug or placebo.

The primary efficacy endpoint was percentage change in bodyweight. Secondary efficacy endpoints were changes in waist circumference, waist-hip ratio, body-mass index, dual-energy X-ray absorption, sagittal diameter, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, blood glucose fasting, haemoglobin A_{1c}, C-reactive protein, insulin, adiponectin, Baecke questionnaire, satiety and appetite questionnaire, profile of mood states, and quality of life. All blood samples were analysed in a central laboratory (Capio Diagnostik A/S, Copenhagen, Denmark). The questionnaires related to appetite,⁹ physical activity,¹⁰ and quality of life¹¹ were completed in the course of the study. Profile of mood states (POMS Brief)¹² was completed by all patients at baseline (week 0), week 12, and week 24. Safety measures were treatment emergent adverse events, vital signs (blood pressure, heart rate), ophthalmoscopy, electrocardiogram, laboratory assessments, and physical examination.

Dual-energy X-ray absorption scans were done by a standardised procedure in the morning, and we measured hip and waist diameters to the nearest 0.5 cm with the

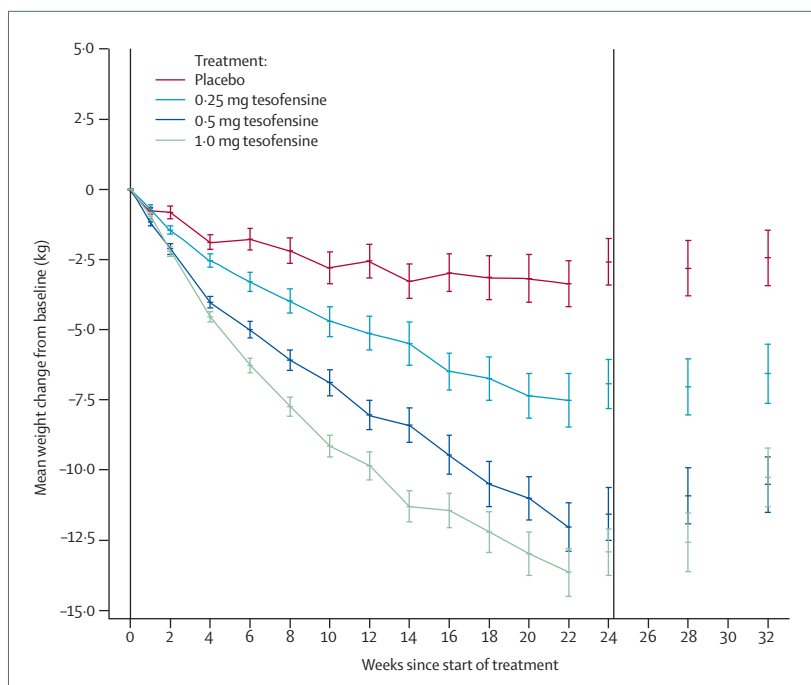


Figure 2: Mean change from baseline in bodyweight

Data are values for patients completing each scheduled visit, and last observation carried forward (values for the full intention-to-treat population with the last observations carried forward). Error bars show SE. Vertical lines indicate start and end of treatment.

patients standing with a non-extendable linen tape measure according to WHO recommendations.¹³

Statistical analysis

With the significance level of 5%, power 90%, and SD 5.5, a difference of 4.5 in percentage weight change would be detectable with 33 assessable patients per treatment group. With an expected drop-out rate of 33%, 50 participants were needed per treatment group. Hence we planned to enrol 200 individuals. The full analysis set was defined according to the modified intention-to-treat principle as all randomised patients with measurement after at least one dose of study drug or placebo. The per-protocol cohort consisted of all patients randomised and exposed to at least one dose of trial drug, who completed the trial and for whom no major protocol deviation occurred. The safety-analysis set consisted of all randomised participants who had taken at least one dose of the trial drug.

For the primary efficacy analysis, the comparisons of the three dose groups with placebo were tested by analysis of variance. The model included visit, centre, and treatment group as fixed effects, and baseline value as covariate. We also adjusted the model for participant variation and heterogeneity in error variation between treatment groups. A two-sided 95% CI for the difference in adjusted means between treatment groups is given.

For other efficacy analyses we compared the proportion of patients with a weight loss of 5 kg or more and 10 kg or

more for the three dose groups against placebo through a logistic regression analysis, with treatment and centre as fixed effects and weight at baseline as covariate. We did analyses of change from baseline to end of treatment for all secondary endpoints (eg, waist circumference) similarly to the primary endpoints.

We compared the number of patients with adverse events between the treatment groups by Fisher's exact test (pair-wise comparisons). We analysed change from baseline in vital signs in the same way as for the primary analysis.

The study is registered with ClinicalTrials.gov, number NCT00394667.

Role of the funding source

The study was designed by an external advisory board with the corresponding author as chairman and

representatives from the main sponsor. Data were collected by the monitoring company (Cyncron) and were assessed jointly by the statistician, the authors, and the sponsor. The data were interpreted and the report written by the authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The treatment groups had much the same demographic and baseline characteristics (table 1). Figure 1 shows the trial profile. 203 patients (143 [70%] of whom were women) were randomly assigned to double-blind treatment, and 161 (79%) completed the 24-week treatment (figure 1). 42 (21%) participants withdrew during the 24 weeks (figure 1), with fewer patients withdrawing in the tesofensine 0.5 mg group than in the tesofensine 1.0 mg

	Placebo	Tesofensine			Odds ratio (95% CI)		
		0.25 mg	0.5 mg	1.0 mg	0.25 mg tesofensine	0.5 mg tesofensine	1.0 mg tesofensine
Weight reduction of 5 kg or more							
<5 kg	32 (71%)	20 (41%)	6 (13%)	4 (9%)	4.0 (1.6–9.9; p=0.0023)	20.9 (6.8–64.3; p<0.0001)	31.5 (9.0–111.0; p<0.0001)
≥5 kg	13 (29%)	29 (59%)	41 (87%)	42 (91%)			
Weight reduction of 10 kg or more							
<10 kg	42 (93%)	32 (65%)	22 (47%)	12 (26%)	9.5 (2.4–37.4; p=0.0013)	23.0 (5.8–42.0; p<0.0001)	57.7 (13.7–242.0; p<0.0001)
≥10 kg	3 (7%)	17 (35%)	25 (53%)	34 (74%)			

Data are number of patients in the intention-to-treat analysis set with an end of treatment visit (%), unless otherwise indicated. p values are for comparison with placebo.

Table 2: Proportion of patients achieving a weight loss of 5 kg or more, or 10 kg or more

	Placebo	Tesofensine			p vs placebo		
		0.25 mg	0.5 mg	1.0 mg	0.25 mg	0.5 mg	1.0 mg
Bodyweight (kg)*	-2.2 (-3.5 to -0.9)	-6.7 (-8.0 to -5.4)	-11.3 (-12.7 to -9.9)	-12.8 (-14.1 to -11.6)	<0.0001	<0.0001	<0.0001
Body fat (kg)†	-2.3 (-3.8 to -0.9)	-5.5 (-6.9 to -4.1)	-9.2 (-10.6 to -7.8)	-9.8 (-11.2 to -8.4)	0.0014	<0.0001	<0.0001
Fat-free mass (kg)	0.1 (-0.4 to 0.6)	-0.9 (-1.5 to -0.2)	-2.3 (-3.0 to -1.5)	-2.7 (-3.4 to -2.0)	0.016	<0.0001	<0.0001
Waist circumference (cm)	-2.4 (-4.2 to -0.7)	-5.9 (-7.8 to -4.0)	-9.4 (-11.1 to -7.7)	-9.3 (-11.0 to -7.6)	0.007	<0.0001	<0.0001
Sagittal diameter (cm)	-0.5 (-1.1 to 0.1)	-2.1 (-2.7 to -1.6)	-3.4 (-3.9 to -2.8)	-3.6 (-4.1 to -3.0)	0.0001	<0.0001	<0.0001
Triglycerides (mmol/L)	0.07 (-0.14 to 0.27)	-0.12 (-0.28 to 0.03)	-0.31 (-0.43 to -0.19)	-0.32 (-0.43 to -0.21)	0.13	0.0016	0.001
Total cholesterol (mmol/L)	0.27 (0.05 to 0.49)	-0.08 (-0.27 to 0.12)	-0.08 (-0.27 to 0.12)	0.01 (-0.17 to 0.19)	0.016	0.016	0.062
LDL cholesterol (mmol/L)	0.15 (-0.04 to 0.33)	-0.10 (-0.26 to 0.06)	-0.01 (-0.17 to 0.14)	0.04 (-0.11 to 0.19)	0.041	0.17	0.36
HDL cholesterol (mmol/L)	0.09 (0.04 to 0.14)	0.08 (0.03 to 0.13)	0.11 (0.06 to 0.16)	0.13 (0.08 to 0.19)	0.83	0.51	0.23
Plasma glucose (mmol/L)	-0.05 (-0.20 to 0.10)	-0.05 (-0.16 to 0.07)	-0.16 (-0.28 to -0.04)	0.03 (-0.14 to 0.20)	0.92	0.26	0.45
Insulin (pmol/L)	-3.1 (-13.1 to 6.8)	-5.0 (-14.4 to 4.5)	-20.9 (-29.2 to -12.6)	-8.9 (-22.4 to 4.6)	0.78	0.005	0.48
Haemoglobin A _{1c} (%)	-0.02% (-0.07 to 0.04)	-0.06% (-0.11 to -0.01)	-0.08% (-0.14 to -0.03)	-0.14% (-0.19 to -0.10)	0.19	0.06	0.0002
Adiponectin (µg/ml)	-0.39 (-1.23 to 0.44)	0.57 (-0.30 to 1.44)	1.29 (0.42 to 2.15)	1.71 (0.83 to 2.59)	0.10	0.005	0.0005
Systolic blood pressure (mm Hg)*	1.3 (-2.1 to 4.7)	1.4 (-1.4 to 4.1)	0.9 (-2.2 to 4.0)	6.8 (3.7 to 9.8)	0.98	0.85	0.018
Diastolic blood pressure (mm Hg)*	1.5 (-0.5 to 3.4)	2.9 (1.2 to 4.6)	3.0 (1.0 to 5.0)	5.8 (3.5 to 8.0)	0.27	0.27	0.004
Heart rate (beats per min)*	0.4 (-1.6 to 2.4)	4.7 (2.8 to 6.6)	7.8 (4.6 to 10.9)	8.5 (5.1 to 11.8)	0.0018	0.0001	<0.0001

Data are mean (95% CI). The pair-wise comparisons of the treatment groups at end-of-treatment were done via adjusted means through repeated measurement of analysis of variance (ANOVA) including all measurements from week 1 until week 24 (marked with *), or ANOVA of change from baseline to week 24. The model includes visit (only for repeated measures), centre, and treatment group in the fixed effects, and the baseline value as a covariate. The model is also adjusted for patient variation and inhomogeneity in error variation between treatment groups. †Body-fat mass and fat-free mass were measured by dual-energy X-ray absorption scan, and the sum does therefore not equal bodyweight measured by a scale on a subsequent day.

Table 3: Changes from baseline to week 24 in bodyweight, body composition, fat distribution, and metabolic and haemodynamic variables

group ($p=0.048$; figure 1), but results were not statistically different from the placebo group ($p=0.13$).

We recorded a slight weight loss during the run-in phase (mean 1.1 kg [SD 0.6], $p<0.0001$). In the intention-to-treat population, change in bodyweight in the placebo group was 2.0% ($p<0.0001$) from baseline to 6 months, but was greater in all tesofensine groups (figure 2). The adjusted mean weight reduction above that of placebo was 4.5% (4.5 kg [SE 0.87], $p<0.0001$) for 0.25 mg tesofensine, 9.2% (9.1 kg [0.91], $p<0.0001$) for 0.5 mg tesofensine, and 10.6% (10.6 kg [0.84], $p<0.0001$) for 1.0 mg tesofensine. The outcome for those who completed the study was much the same (4.7% [SE 0.96], 9.2% [0.98], 10.4% [0.97], respectively; $p<0.0001$). The difference in weight loss between tesofensine 0.5 mg and 1.0 mg was not significant ($p=0.11$).

The proportion of patients who achieved more than 5 kg or more weight loss was increased more than three times compared with placebo by the highest doses of tesofensine, and the proportion of those losing 10 kg or more of initial bodyweight was increased around ten times by such doses (table 2). The reduction in bodyweight produced by tesofensine was mainly due to a reduction in body fat, as evidenced by a reduction in waist circumference and sagittal diameter (table 3). After discontinuation of treatment (ie, from week 24 to 32), bodyweight increased significantly in all tesofensine groups: by 0.50% (SE 0.40) in the placebo group, 0.82% (0.38) in 0.25 mg tesofensine group, 2.26% (0.38) in 0.5 mg tesofensine group, and 3.81% (0.43) in 1.0 mg tesofensine group. The weight regain exceeded that of placebo in the tesofensine 0.5 mg group (1.76% [SE 0.53]; $p=0.0013$) and the 1.0 mg tesofensine group (3.31% [0.57]; $p<0.0001$).

Consistent with the weight loss, tesofensine reduced fasting triglyceride and total cholesterol concentrations, but only the 0.25 mg dose produced a significant decrease in LDL cholesterol (table 3). Tesofensine treatment also had a beneficial effect on glucose metabolism in this non-diabetic population. Although plasma glucose was not affected, we recorded reductions in plasma insulin and haemoglobin A_{1c}, and an increase in adiponectin (table 3). Tesofensine 0.25 mg and 0.50 mg had no effect on blood pressure, whereas tesofensine 1.0 mg significantly increased systolic and diastolic blood pressure (table 3). Furthermore, tesofensine had a dose-related effect on heart rate (table 3). Neither sex nor age was a significant covariate in any of the above effect measures (data not shown).

The profile of mood states did not show any effect of tesofensine on total mood disturbance, tension or anxiety, depression or dejection, or fatigue or inertia compared with placebo (data not shown). However, tesofensine 1.0 mg increased anger and hostility ($p=0.018$), and both 0.5 mg and 1.0 mg doses increased confusion ($p=0.015$ and $p=0.0003$, respectively). All tesofensine doses improved vigour and activity compared with placebo ($p=0.0093$ for 25 mg dose, $p=0.0002$ for 50 mg dose, and

	Placebo	Tesofensine		
		0.25 mg	0.5 mg	1.0 mg
All adverse events	49 (94%)	48 (92%)	49 (96%)	49 (100%)
Serious adverse events	4 (8%)	2 (4%)	1 (2%)	4 (6%)
Drug-related adverse events	31 (60%)	40 (77%)	45 (90%)	45 (92%)
Gastrointestinal				
Nausea	5 (9.6%)	9 (17.3%)	10 (20.0%)	11 (22.4%)
Vomiting	1 (1.9%)	3 (5.8%)	3 (6.0%)	2 (4.1%)
Dry mouth	6 (11.5%)	12 (23.1%)	21 (42.0%)	29 (59.2%)
Toothache	0	3 (5.8%)	1 (2.0%)	2 (4.1%)
Abdominal pain	0	1 (1.9%)	1 (2.0%)	6 (12.2%)
Discomfort	2 (3.8%)	4 (7.7%)	0	1 (2.0%)
Abdominal pain, upper	0	4 (7.7%)	0	0
Flatulence	1 (1.9%)	2 (3.8%)	5 (10.0%)	0
Diarrhoea	3 (5.8%)	7 (13.5%)	4 (8.0%)	9 (18.4%)
Constipation	4 (7.7%)	5 (9.6%)	1 (2.0%)	8 (16.3%)
Faeces hard	2 (3.8%)	5 (9.6%)	7 (14.0%)	5 (10.2%)
Faecaloma	1 (1.9%)	2 (3.8%)	0	3 (6.1%)
Sleep disturbances				
Insomnia	1 (1.9%)	2 (3.8%)	6 (12.0%)	13 (26.5%)
Dyssomnia	0	3 (5.8%)	1 (2.0%)	1 (2.0%)
Sleep phase rhythm disturbance	2 (3.8%)	0	2 (4.0%)	6 (12.2%)
Hypervigilance	0	0	2 (4.0%)	3 (6.1%)
Affective changes				
Mood altered	2 (3.8%)	3 (5.8%)	2 (4.0%)	7 (14.3%)
Mood elevated	0	1 (1.9%)	0	1 (2.0%)
Depressed mood	0	1 (1.9%)	3 (6.0%)	3 (6.1%)
Major depression	0	0	0	1 (2.0%)
Anxiety	0	0	1 (2.0%)	0
Cardiovascular				
Palpitations	1 (1.9%)	2 (3.8%)	3 (6.0%)	3 (6.1%)
Hot flush	0	2 (3.8%)	3 (6.0%)	2 (4.1%)
Neurological				
Dizziness	2 (3.8%)	1 (1.9%)	5 (10.0%)	6 (12.2%)
Headache	21 (40.4%)	16 (30.8%)	17 (34.0%)	13 (26.5%)
Migraine	3 (5.8%)	2 (3.8%)	1 (2.0%)	1 (2.0%)

Data are number of events (%). All adverse events reported by more than 5% in any group are reported, except for affective changes for which all events are reported. Additionally, key adverse events pertinent to mood changes and anxiety are reported.

Table 4: Adverse events per treatment group

$p=0.0003$ for 1.0 mg dose). Patients in the placebo group had a 3.2% (SE 4.4) improvement in total weight-related quality-of-life score (IWQOL-Lite), whereas tesofensine 0.25 mg had a 16.9% (4.2) improvement ($p=0.02$), 0.5 mg had a 20.8% (4.2) improvement ($p=0.005$), and 1.0 mg also had a 20.8% (4.4) improvement ($p=0.007$). The effect was due to significant improvements in physical function and self-esteem (all tesofensine doses versus placebo $p<0.02$), whereas we recorded no effects on sexual life, public distress, or work (data not shown).

The most common adverse events caused by tesofensine were of gastrointestinal origin (dry mouth, nausea,

abdominal pain, constipation, hard faeces, diarrhoea). These events were recorded mainly, apart from nausea and dry mouth, in the 1.0 mg tesofensine group (table 4). Insomnia, sleep disturbance, and dizziness were also greater with tesofensine than with placebo, especially in the tesofensine 1.0 mg group. Mood changes seemed to occur more frequently in patients given tesofensine than in those given placebo, but these changes included altered and elevated mood and depressed mood, and occurred particularly with the highest doses of tesofensine (table 4). The highest frequency of mood changes was in the tesofensine 1.0 mg group (table 4). We recorded no trends to depressive disorders or anxiety for tesofensine 0.25 mg or 0.50 mg, although numbers are small and do not allow a robust conclusion.

The proportion of patients who had serious adverse events did not differ between tesofensine and placebo (table 4). However, more patients in the tesofensine group than in the placebo group had adverse events related to the intervention, and in the tesofensine 1.0 mg group more patients discontinued treatment as a result (table 5). Eight (16%) patients in the tesofensine 1.0 mg group had treatment emerging adverse events with probable or definite relation to study drug, which was more than in any other group (table 5).

Discussion

This phase II study shows that tesofensine is very effective in producing weight loss in obese patients over 6 months. Because of an overall low drop-out rate of 21%, results are

	Placebo (N=52)		Tesofensine					
	Patients (%)	Events	0.25 mg (N=52)		0.50 mg (N=50)		1.00 mg (N=49)	
			Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
All adverse events	3 (6%)	3	4 (8%)	8	3 (6%)	8	8 (16%)	11
Ear and labyrinth disorders	0	0	0	0	0	0	1 (2%)	1
Vertigo	0	0	0	0	0	0	1 (2%)	1
Endocrine disorders	1 (2%)	1	0	0	0	0	0	0
Pituitary-dependent Cushing's syndrome	1 (2%)	1	0	0	0	0	0	0
Gastrointestinal disorders	0	0	2 (4%)	3	1 (2%)	1	1 (2%)	1
Abdominal discomfort	0	0	1 (2%)	1	0	0	0	0
Abdominal pain upper	0	0	1 (2%)	1	0	0	0	0
Constipation	0	0	0	0	0	0	1 (2%)	1
Flatulence	0	0	1 (2%)	1	0	0	0	0
Nausea	0	0	0	0	1 (2%)	1	0	0
General disorders and administration site conditions	0	0	1 (2%)	2	1 (2%)	1	0	0
Chest pain	0	0	1 (2%)	1	0	0	0	0
Fatigue	0	0	0	0	1 (2%)	1	0	0
Oedema peripheral	0	0	1 (2%)	1	0	0	0	0
Nervous system disorders	0	0	1 (2%)	1	1 (2%)	2	2 (4%)	2
Dizziness	0	0	0	0	1 (2%)	1	0	0
Headache	0	0	1 (2%)	1	1 (2%)	1	0	0
Sleep phase rhythm disturbance	0	0	0	0	0	0	1 (2%)	1
Syncope	0	0	0	0	0	0	1 (2%)	1
Psychiatric disorders	1 (2%)	1	1 (2%)	1	2 (4%)	2	4 (8%)	5
Depression	0	0	0	0	2 (4%)	2	0	0
Hypervigilance	0	0	0	0	0	0	1 (2%)	0
Mood altered	1 (2%)	1	1 (2%)	1	0	0	4 (8%)	4
Skin and subcutaneous tissue disorders	1 (2%)	1	1 (2%)	1	1 (2%)	2	1 (2%)	1
Acne	1 (2%)	1	0	0	0	0	0	0
Dermatitis allergic	0	0	0	0	1 (2%)	1	0	0
Pain of skin	0	0	0	0	1 (2%)	1	1 (2%)	1
Rash	0	0	1 (2%)	1	0	0	0	0
Vascular disorders	0	0	0	0	0	0	1 (2%)	1
Hypertension	0	0	0	0	0	0	1 (2%)	1

Preferred term is coded in MedDRA (Medical Dictionary for Regulatory Activities). Data are number of patients (% in treatment group having the event), or number of events.

Table 5: Treatment emerging adverse events with probable or definite relation to study drug, leading to discontinuation of treatment

much the same whether the analysis is based on the intention-to-treat population or patients who completed the study. Our results should be compared with the 2.9 kg net weight loss produced by orlistat over 6 months, to the 4.2 kg net weight loss by sibutramine, and the 4.7 kg net weight loss by rimonabant.^{6,7} The lowest dose of tesofensine that we tested produced a weight loss similar to that of sibutramine and rimonabant treatment over 6–24 months.⁶ However, one should keep in mind that this is a study of small size, and the very positive findings cannot be directly compared with those produced by much larger phase III studies on currently approved compounds. Our findings need to be confirmed in larger phase III trials, and direct head-to-head comparison with approved weight-loss compounds is needed before any conclusion about comparative efficacy can be made.

Weight loss in the placebo group levelled out after 16 weeks but continued in the tesofensine groups; thus even greater weight loss could be achieved with longer duration of treatment. Efficacy of tesofensine was also shown by an almost ten times higher proportion of the patients achieving more than 10% weight loss in the two groups with the highest dose compared with placebo. After the pharmacological treatment was discontinued we recorded only a slight tendency to weight regain at 4 and 8 weeks of follow-up. The long half-life (roughly 230 h) of tesofensine accounts for the little weight regain.

The weight loss produced by tesofensine 0.5 mg and 1.0 mg was around 10 kg over 6 months, which is a daily loss of bodyweight of about 55 grams, corresponding to an energy deficit of around 400 kcal per day (1650 kJ per day). From the measurements of appetite recordings, tesofensine produced a dose-related suppression of hunger and increased satiety (data not shown), but increased energy expenditure might have contributed to the negative energy balance. Tesofensine shares the re-uptake inhibition of noradrenaline and serotonin with sibutramine, and it also exhibits some of the same adverse events and haemodynamic effects—eg, increased heart rate. Sibutramine exerts a small thermogenic effect in higher doses,^{14,15} and the thermogenic effect of sibutramine might be partly responsible for the increase in heart rate—ie, a haemodynamic effect of increased sympathetic nervous system activity and increased tissue heat production. Studies to explore the thermogenic properties of tesofensine are in progress (ClinicalTrials.gov, number NCT00428415).

The measurements of body composition and fat distribution showed that no excessive loss of lean body tissue occurred, and that the expected loss of abdominal fat during reduced caloric intake took place. Tesofensine had beneficial effects on glucose metabolism, suggesting a reduction in insulin resistance that is consistent with the weight loss produced. We recorded effects of tesofensine on adiponectin, insulin, haemoglobin A_{1c}, but no significant reduction in fasting glucose. The most probable explanation for this finding is that in this cohort of

non-diabetic patients, improvements in insulin resistance will mainly be seen as reductions in insulin concentrations because their plasma glucose concentrations are fairly normal and regulated by the insulin secretion. The slight reduction seen in haemoglobin A_{1c} might suggest postprandial glucose concentrations were decreased, but this tenet remains to be assessed in future studies.

Additionally, plasma triglycerides and total cholesterol were lowered, although we recorded a significant effect on LDL-cholesterol only for the 0.25 mg dose. This finding is somewhat similar to the effects of sibutramine and rimonabant, which both failed to reduce LDL cholesterol despite a weight loss of 4–5 kg in larger phase III and IV studies.^{6,16–19} In our study, three factors might have contributed to this result. First, some improvements could have occurred during the 1 kg weight loss during the run-in period, making further improvements less likely. Second, the present study included only obese patients with fairly normal blood lipids. Third, our study might not have had sufficient statistical power to detect effects on LDL cholesterol in all doses of tesofensine.

We recorded no significant effects of tesofensine on HDL cholesterol. HDL cholesterol is transiently lowered during weight loss when the patients are in negative energy balance, but it normally increases to above initial concentrations when weight loss plateaus. We noted that weight loss still occurred at the end of the study, so the assessment of the effect of tesofensine on HDL cholesterol might need a longer trial duration.

Sibutramine produces a sustained rise in blood pressure and heart rate, at least in normotensive patients with obesity,^{6,16} whereas a slight reduction in blood pressure might be seen in patients with cardiovascular disease and hypertension.²⁰ We recorded an effect on blood pressure with tesofensine 1.0 mg only (table 4), whereas the 0.5 mg dose did not produce any significant increase. However, in view of the mechanism of action and the small study size, the 0.5 mg dose could increase diastolic blood pressure when assessed in larger trials. Sibutramine increases heart rate by 4–6 beats per min,^{6,16} which is similar to tesofensine 0.25 mg, whereas tesofensine 0.5 mg and 1.0 mg increased heart rate by 7.4 and 8.1 beats per min, respectively. Thus the potential for tesofensine 0.25 mg and 0.50 mg is to produce a weight loss better than that of sibutramine but without effects on blood pressure and with an increasing effect on heart rate. The effect on heart rate will be an important safety issue in obese individuals who are at increased cardiovascular risk, and needs special attention in future trials.

The adverse events produced by tesofensine are consistent with its mechanism of action—ie, re-uptake inhibition of noradrenaline, serotonin, and dopamine. The most frequently observed adverse effects were nausea, dry mouth, insomnia, dizziness, diarrhoea, and constipation, which were mainly reported in the tesofensine

1.0 mg group. Insomnia, nausea, dry mouth, and constipation are more common in patients receiving the noradrenaline and serotonin reuptake inhibitor sibutramine (occurring at frequency rates of 7–20%) than in those receiving placebo.⁶

Bupropion, a dopamine and noradrenaline reuptake inhibitor, produces weight loss in animals and in obese individuals.²¹ Frequent adverse events are insomnia and other sleep problems, and dry mouth. Other less frequent side-effects are increased restlessness, agitation, and anxiety.²² Tesofensine did not seem to increase measured levels of anxiety as assessed by the profile of mood states scale, or anxiety reported as an adverse event. However, there might be a tendency for more agitation and mood changes (table 5), although the actual number of patients was small and events were reported mainly in the tesofensine 1.0 mg group. With the increased focus on psychiatric adverse events produced by the weight-loss compound rimonabant (a cannabinoid-1 receptor blocker)—ie, anxiety, depressive mood disorders, and suicidality^{7,18,19}—a more comprehensive assessment of these potential effects of tesofensine is warranted in planned trials.

In conclusion, this phase II study suggests that 0.5 mg and 1.0 mg doses of tesofensine produce weight losses of more than double that of the placebo-subtracted weight loss from the currently approved anti-obesity drugs, but that little additional weight loss is achieved by increasing the dose from 0.5 mg to 1.0 mg. Tesofensine 1.0 mg had more effects on blood pressure, produced more adverse events, and had more adverse events that lead to discontinuation of treatment than did tesofensine 0.5 mg. The adverse event profile of tesofensine 0.5 mg is promising, and haemodynamic effects are similar to or slightly weaker than those of sibutramine. We conclude that tesofensine 0.5 mg, once daily for 6 months, has the potential to produce twice the weight loss as currently approved drugs; however, larger phase III studies are needed to substantiate our findings.

Contributors

AA was involved in the study design and wrote the report. All authors reviewed and validated data and final analyses. AA had full access to the complete set of data. All the named authors participated in the study, contributed to the interpretation of data and revision of the report, and approved the final version.

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Conflict of interest statement

AA receives an honorarium as a consultant and for membership of the Tesofensine Advisory Board for Neurosearch. AA and TJJ own shares in Neurosearch A/S purchased on the stock exchange. TML has received one travel grant from Neurosearch A/S. JPK, LB, and SM declare that they have no conflict of interest.

Acknowledgments

Neurosearch A/S, Denmark was the main sponsor of this study. Additional funding for the research was provided by EU grant EC-FP6 (contract number: LHM-CT-2003-503041) and by the Center for Pharmacogenomics, University of Copenhagen, Denmark.

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