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ORIGINAL RESEARCH

Reduction of Excessive Visceral Fat and Safety with 52-Week Administration of Lipase Inhibitor Orlistat in Japanese: Long-Term Clinical Study

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ABSTRACT

Introduction: Orlistat is an inhibitor of pancreatic lipase and is used as an anti-obesity drug in many countries. However, there are no data available regarding the effects of orlistat on visceral fat (VF) accumulation in Japanese individuals. Therefore, this study aimed to analyze the efficacy and safety of 52 weeks of orlistat administration in Japanese individuals.

Methods: Orlistat 60 mg was administered orally three times daily for 52 weeks to Japanese participants with excessive VF accumulation and without dyslipidemia, diabetes mellitus, and hypertension (metabolic diseases). Participants were also counseled to improve their diet and to maintain exercise habits. We defined excessive VF accumulation as a waist circumference (WC) of $\geq$ 85 cm for males and $\geq$ 90 cm for females, which corresponds to a VF area of 100 cm^2. Adverse reactions, clinical laboratory tests, VF, WC, body weight (BW), etc., were monitored throughout the study period.

Results: VF, WC, and BW were significantly reduced at week 52 from baseline; the mean ± standard error rate of change was − 21.52% ± 1.89%, − 4.89% ± 0.45%, and − 5.36% ± 0.56%, respectively, and continued to reduce throughout the 52 weeks; these significantly reduced at whole term compared with baseline. Most adverse reactions were defecation-related symptoms such as oily spotting and flatus with discharge (flatus with small amounts of stool or oil) due to the pharmacologic effects of the lipase inhibitor. These symptoms were mostly mild, reversible, and recognizable by the participants; none were serious or severe. No participants discontinued by medical judgment about adverse reactions, and the drug could be administered continuously.

Conclusion: VF, WC, and BW were reduced from week 4 to week 52, indicating the effect of long-term orlistat administration. Moreover, it was well tolerated with an acceptable safety profile. Long-term administration of orlistat may be efficacious in reducing VF accumulation with safety when used in combination with diet and exercise.

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INTRODUCTION

Excessive accumulation of body fat is frequently associated with metabolic disorders, such as diabetes mellitus, hypertension, and dyslipidemia, and these disorders are known to cause coronary artery disease and cerebrovascular disorders [1, 2]. In addition, comorbidities such as sleep apnea, kidney damage, bone and joint diseases, and menstrual disorders can also occur with obesity [1, 2]. The Organisation for Economic Co-operation and Development has ranked obesity as the greatest emerging threat to public health worldwide and forecasted a sharp rise in medical expenditures based on the increased number of individuals with obesity-related diseases [3]. The increased incidence of dyslipidemia, diabetes mellitus, and hypertension caused by obesity as well as obesity-related cardiovascular diseases is a global problem, and prevention and treatment of obesity have been earnestly implemented in many countries. Although various indicators, including body weight, body mass index (BMI), waist circumference, and body fat, are considered for the assessment of obesity in Europe and the USA, BMI is the main indicator to identify individuals for treatment [4, 5].

In Japan, despite a low grade of obesity in comparison to the US and European populations, the incidence of dyslipidemia, diabetes mellitus, and hypertension (metabolic diseases) caused by obesity is relatively high, indicating that metabolic diseases caused by obesity can develop even with relatively mild obesity. Furthermore, body fat distribution types are divided into the visceral fat type and subcutaneous fat type, and metabolic diseases caused by obesity are more likely to be linked to visceral fat accumulation than subcutaneous fat accumulation [2].

Several clinical studies have demonstrated that the number of obesity-related cardiovascular risk factors increases with an increase in visceral fat accumulation [2, 6], suggesting a close relationship between excessive visceral fat and the development of metabolic diseases caused by obesity [7, 8]. The adverse health effects of visceral fat accumulation are mainly believed to result from insulin resistance caused by an insulin resistance factor, such as tumor necrosis factor-α, among others [2]. Several studies have also demonstrated that reductions in visceral fat accumulation and body weight lead to decreased risk of metabolic diseases caused by obesity [9, 10]. Therefore, visceral fat accumulation is used as an index for the diagnosis and treatment of obesity in Japan [2].

The initial management regimen for reducing visceral fat should start with lifestyle adjustments including improvements in diet and exercise [2]. Individuals with metabolic diseases should receive medical treatment from physicians, but those without metabolic diseases despite excessive visceral fat accumulation are generally required to manage their own health regimens by improving lifestyle. However, lifestyle improvements are often insufficient to achieve significant body weight loss, and long-term control of body weight is difficult to maintain [11–14]. Consequently, the development of new, effective, and safe methods to reduce visceral fat in Japanese participants with excessive visceral fat accumulation and without metabolic diseases is required.

One of the options is drug. There are several drugs affecting body weight, among which orlistat inactivates pancreatic lipase in the digestive tract, thereby inhibiting the absorption of dietary fat and enhancing the excretion of undigested fat in the stool, resulting in body weight reduction by decreasing energy uptake. Orlistat is available as both a prescription drug and an over-the-counter drug for weight loss in more than 120 countries of Europe and the USA. An important feature of orlistat is that it has no effect on the central nervous system; therefore, addiction or emotional side effects

are expected to be few. A clinical study conducted mainly in the white and black populations demonstrated that orlistat successfully reduced visceral fat [15]. Similar results would be expected in Japanese populations; however, data regarding the effects of orlistat on visceral fat in Japan are limited.

We confirmed from another study that administration of orlistat 60 mg three times daily for 24 weeks showed a reduction in visceral fat area, waist circumference, and body weight and was safe and tolerable in Japanese participants.

Due to orlistat's mechanism of action, the absorption of dietary fat-soluble vitamins could potentially be inhibited in individuals taking orlistat. Consequently, the over-the-counter formulation of orlistat (Alli®, GlaxoSmithKline, Brentford, UK) includes a warning in the package insert that recommends taking a multivitamin once a day at bedtime. In addition, defecation-related symptoms such as oily spotting and flatus with discharge can occur when taking orlistat. These effects may become particularly significant with extended use of orlistat; however, clinical evidence of the safety of long-term administration of orlistat in the Japanese population has not been reported.

Therefore, we conducted a 52-week study to evaluate the efficacy and safety of long-term orlistat administration in Japanese participants with excessive visceral fat accumulation and without metabolic diseases.

METHODS

Participants

Japanese participants without metabolic diseases aged 18 years or older with excessive visceral fat accumulation were eligible for this study. We defined excessive visceral fat accumulation as a waist circumference $\geq$ 85 cm for males and $\geq$ 90 cm for females, which corresponds to a visceral fat area of 100 cm^2 [2]. Participants had not received medical treatment for obesity, diabetes mellitus, dyslipidemia, hypertension, hyperuricemia/gout, or fatty liver. Major exclusion criteria were the presence of secondary obesity; BMI $\leq$ 22.0 kg/m^2 (optimal BMI in Japan is defined as 22.0 kg/m^2 [16]); BMI $\geq$ 35.0 kg/m^2; judged necessary to treat with cyclosporine, warfarin, amiodarone, or other drugs capable of interfering with orlistat's effects during the study period; and presence of or a history of malabsorption syndrome, pancreatitis, cholestasis, cholecystitis, gallstones, kidney stones, or hyperoxaluria.

Study Design

This was an open-label, uncontrolled study to mainly evaluate the safety of 52-week administration of orlistat based on "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" [International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use—Efficacy 1 (ICH-E1) guidelines] [17], which requires 100 participants for 1-year administration. Accounting for possible dropouts, target enrollment was determined to be 120 participants. Participants were scheduled to take an oral capsule of orlistat 60 mg three times daily for 52 weeks with meals (during or within 1 h after breakfast, lunch, and dinner).

This study included a 12-week observation term and a 52-week treatment term. Participants were counseled to improve diet and to maintain exercise habits from the beginning of the observation term through the end of the study. All participants, except those whose waist circumference increased or reduced sufficiently during the observation term, moved on to the treatment.

Every 4 weeks, the participants underwent interviews, body measurements, blood pressure assessments, and routine clinical laboratory testing. Only glycated hemoglobin (HbA1c) was measured at the beginning of the observation term, at the beginning of treatment, and at treatment weeks 12, 24, 36, and 52. Body measurements consisted of height (measured only at the beginning of the observation term), body weight, and waist circumference. The measurement of waist circumference was performed according to the guidelines published by the

Japan Society for the Study of Obesity [2]. BMI was calculated from height and body weight. Visceral and subcutaneous fat areas were measured at the beginning of the observation term, at the beginning of treatment, and at treatment weeks 24 and 52 using computed tomography (CT) images of the umbilical plane with visceral fat area measurement software (FatScan Ver. 5.0, East Japan Institute of Technology Co., Ltd., Ibaraki, Japan). The imaging was performed according to the guidelines published by the Japan Society for the Study of Obesity [2]. Participants fasted for at least 10 h prior to body measurements, abdominal CT, and clinical laboratory tests.

Throughout the study period, participants were counseled to improve the quality of their diet and reduce their daily calorie intake by 200–400 kcal per day, depending on body weight. They recorded their achievement level of calorie reduction on a daily basis using the categories "almost attained," "partially attained," "attempted but not attained," and "not attempted." Participants were also advised to maintain their exercise habits without implementing significant changes throughout the study period.

Adverse events were defined as any unfavorable event or the presence or signs of medically unintended complications that occurred between the beginning and the end of treatment. All adverse events were recorded during physician examinations or by self-reporting from the participants. The investigator determined whether a causal relationship existed between the adverse event and investigational drug; all events except those that were judged to be "not related" were regarded as adverse reactions.

This study is registered with the Japan Pharmaceutical Information Center (identifier: JapicCTI-184004). It was implemented in accordance with Good Clinical Practice guidelines and the ethical principles of the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. Springer's policy concerning informed consent has been followed. This study was approved by the Institutional Review Board of each participating institution. After receiving sufficient explanation and achieving a full understanding of the study, all potential participants provided written consent to voluntarily participate in this study.

Assessments

End points for efficacy were the percent change and the amount of change in visceral fat area, waist circumference, body weight, BMI, and subcutaneous fat area from baseline to each study term; the achievement rates were 3% reduction in waist circumference and 3% reduction in body weight (defined as the percentage of participants whose waist circumference/body weight changed by − 3% or lower at each assessment compared with baseline); the achievement rates were 5% reduction in waist circumference and 5% reduction in body weight. "Baseline" was defined as the beginning of the treatment term; the primary study term was week 52 of the treatment.

The primary safety end point was the frequency of adverse reactions.

In addition, the clinical laboratory tests, blood pressure, compliance rate for dietary improvement (the level of calorie reduction on a daily basis using the categories was rated "almost attained, partially attained, or attempted but not attained"), and change in the number of metabolic disease risk factors from baseline to week 52 of treatment were assessed. Metabolic disease risk factors for diabetes mellitus, dyslipidemia, and hypertension were defined as blood glucose $\geq$ 126 mg/dl or HbA1c $\geq$ 6.5%; low-density lipoprotein (LDL) cholesterol $\geq$ 140 mg/dl, high-density lipoprotein (HDL) cholesterol $<$ 40 mg/dl, or triglycerides $\geq$ 150 mg/dl; and systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg, respectively.

Efficacy end points, compliance rate for dietary improvement, and change in metabolic disease risk factors were analyzed using the efficacy analysis set (full analysis set), and adverse reactions, clinical laboratory tests, and blood pressure were analyzed using the safety analysis set (all participants who were administered even one investigational drug and had

observed safety data after administration of the investigational drug).

Statistical Analysis

The percent change and amount of change in the visceral fat area, waist circumference, body weight, BMI, and subcutaneous fat area were analyzed using the paired *t* test. Achievement rates of 3% and 5% reductions in waist circumference and body weight from baseline were obtained by calculating the proportion of participants whose percent change was − 3% or lower and − 5% or lower, respectively; 95% two-sided confidence intervals (CIs) were also calculated. Differences in clinical laboratory tests and blood pressure from baseline to each term were analyzed using the Wilcoxon signed rank test. The change in the number of metabolic disease risk factors was analyzed using the Wilcoxon signed rank test. Because analyses other than the primary end point are also included to achieve the results or understand the cause, multiplicity was not considered, with a $p < 0.05$ considered significant. All analyses were performed using SAS 9.2 and SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

Among 241 potential participants selected for this study, 120 (the target enrollment number) were found to be eligible and subsequently received orlistat (Fig. 1). Six participants (5.0%) withdrew from the study during the treatment

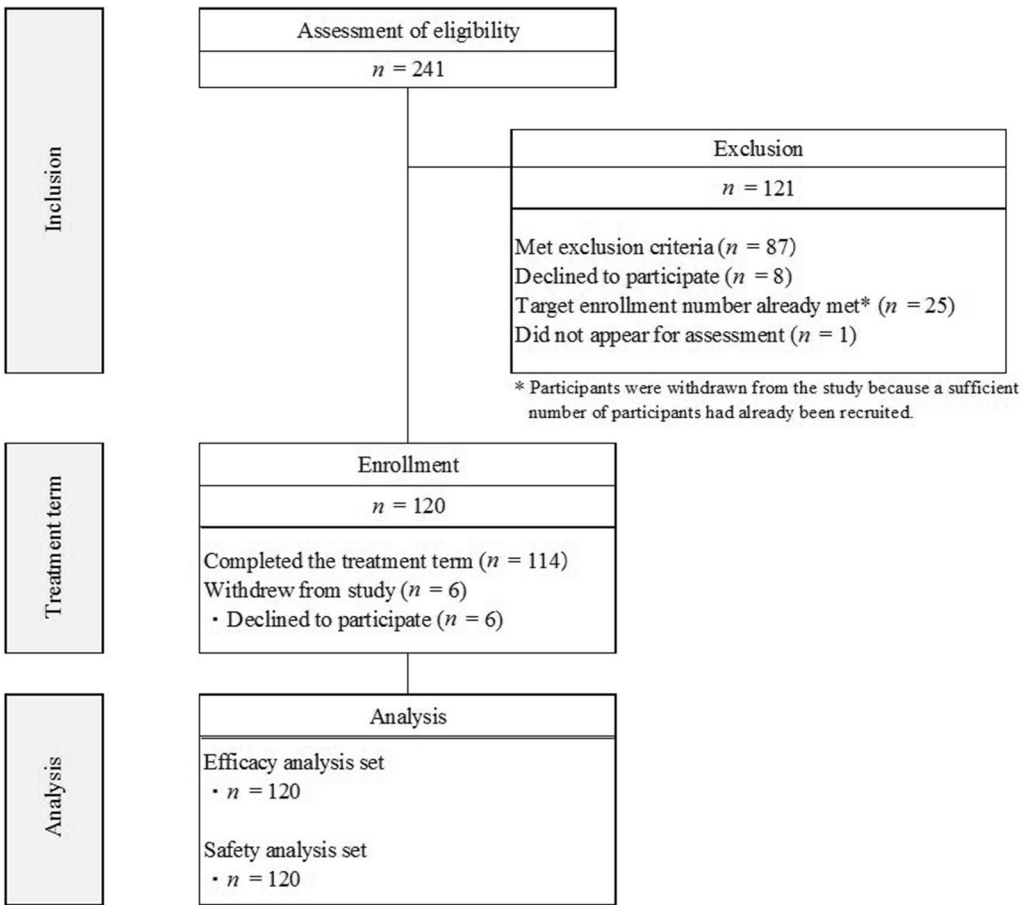

Fig. 1 Disposition of participants

term at their request. Of the 120 participants who received orlistat, none were excluded from the safety analysis set or the efficacy analysis set (both consisted of all 120 participants).

Baseline characteristics of the participants are shown in Table 1. The age of the participants was 47.3 ± 6.7 years [mean ± standard deviation (SD)], 22.5% were female, and visceral fat area was 130.90 ± 40.13 cm^2.

Efficacy

Efficacy End Points

Visceral fat area showed a significant change of − 21.52% ± 1.89% [mean ± standard error (SE)] from baseline to week 52 ($p < 0.001$; Fig. 2). The change in waist circumference from baseline to week 52 was − 4.89% ± 0.45%, and the change in body weight was − 5.36% ± 0.56%, both of which were significant reductions ($p < 0.001$ for all parameters; Figs. 3, 4). The visceral fat area, waist circumference, and body weight reduced during the 12-week observation term and reduced throughout the 52-week treatment term, with significant reductions in all three parameters at each period compared with baseline.

The amount of change in visceral fat area from baseline to week 52 was − 28.05 ± 2.71 cm^2 (mean ± SE); waist circumference reduced by − 4.73 ± 0.45 cm, and body weight reduced by − 4.22 ± 0.45 kg. BMI reduced by − 5.35% ± 0.56%, with the amount of change being − 1.46 ± 0.16 kg/m^2. Subcutaneous fat area reduced by − 14.84% ± 1.53%, with the amount of change being − 33.47 ± 3.82 cm^2. These reduc-

Table 1 Participant characteristics at baseline

Characteristic at the start of administration	*n* = 120
Age (years)[a]	47.3 ± 6.7 (29–61)
Gender	
Male[b]	93 (77.5)
Female[b]	27 (22.5)
Visceral fat area (cm^2)[a]	130.90 ± 40.13 (65.4–322.5)
Waist circumference (cm)[a]	96.86 ± 6.03 (85.0–115.5)
Body weight (kg)[a]	78.25 ± 8.75 (61.6–108.0)
Height (cm)[a]	169.76 ± 7.34 (149.8–185.8)
BMI (kg/m^2)[a]	27.16 ± 2.64 (22.5–33.8)

BMI body mass index, *SD* standard deviation
[a] Mean ± SD (min–max)
[b] *n* (%)

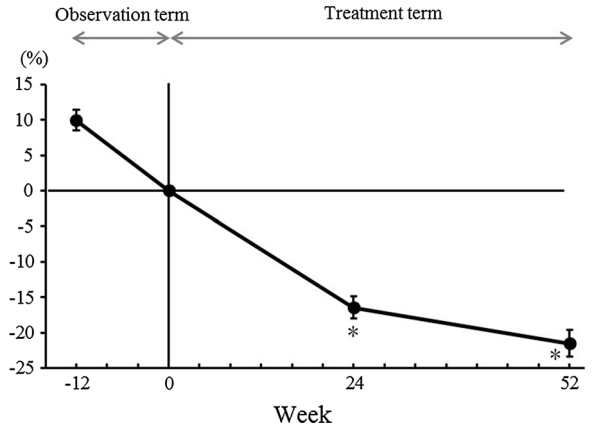

Fig. 2 Percent change in visceral fat area compared with baseline. Mean ± SE. *n* (week 52): 108. *Paired *t*-test, $p < 0.05$ compared with baseline. Visceral fat area reduced significantly at whole term compared with baseline. *SE* standard error

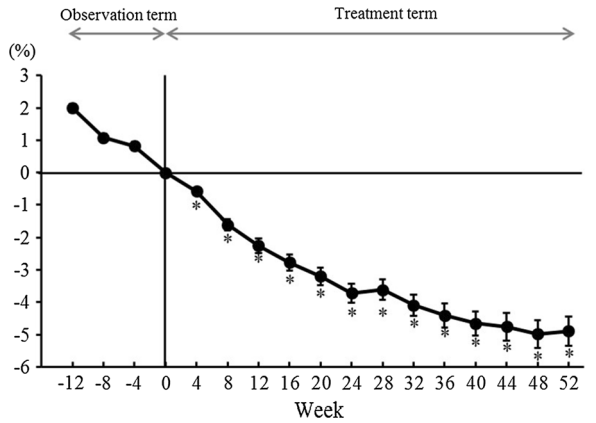

Fig. 3 Percent change in waist circumference compared with baseline. Mean ± SE. *n* (week 52): 108. *Paired *t*-test, $p < 0.05$ compared with baseline. Waist circumference reduced significantly at whole term compared with baseline. *SE* standard error

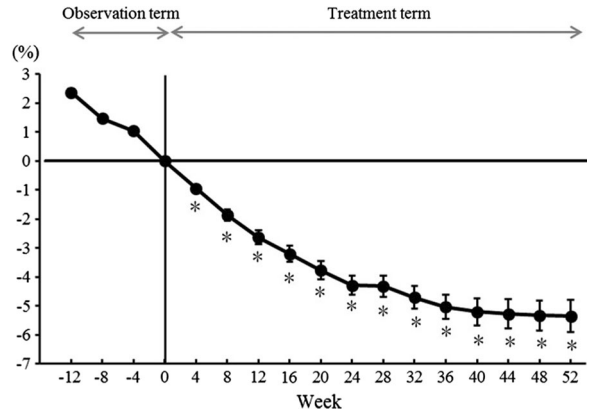

Fig. 4 Percent change in body weight compared with baseline. Mean ± SE. *n* (week 52): 108. *Paired *t*-test, $p < 0.05$ compared with baseline. Body weight reduced significantly at whole term compared with baseline. *SE* standard error

tions at week 52 were significant compared with baseline ($p < 0.001$ for all parameters; Table 2). Moreover, these parameters demonstrated significant reductions at each term compared with baseline.

At week 52 of the treatment term, the achievement rates of 3% and 5% reductions in body weight from baseline were observed in 67 of the 114 participants [58.8% (95% CI: 49.7–67.8%)] and in 54 of the 114 participants [47.4% (95% CI: 38.2–56.5%)], respectively. The achievement rates of 3% and 5% reductions in waist circumference were observed in 68 of the 114 participants [59.6% (95% CI: 50.6–68.7%)] and 47 of the 114 participants [41.2% (95% CI: 32.2–50.3%)], respectively.

Clinical Laboratory Tests

The changes in lipid parameters related to the development of metabolic diseases (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) during the treatment term are shown in Fig. 5. The change from baseline to week 52 was − 11.0 ± 2.0 mg/dl (mean ± SE) for total cholesterol, − 13.8 ± 1.8 mg/dl for LDL cholesterol, 3.1 ± 0.7 mg/dl for HDL cholesterol, and − 4.3 ± 4.3 mg/dl for triglycerides, and all parameters except triglycerides demonstrated significant changes from baseline ($p < 0.001$). Total cholesterol and LDL cholesterol demonstrated a trend of reduction throughout the treatment term, with significant reductions at each term compared with baseline. Other parameters associated with metabolic diseases (blood glucose, HbA1c, systolic blood pressure, and diastolic blood pressure) fluctuated within their normal ranges without notable changes (Supplemental Fig. S1).

Other Analyses of Efficacy

The change in the number of metabolic disease risk factors was assessed in 114 participants; six participants who withdrew from the study during the treatment term were excluded from analysis because of a lack of clinical data at week 52 (total cholesterol, LDL cholesterol, HDL

Table 2 Changes in parameters from baseline to week 52

Parameter	Mean ± SE	Parameter	Mean ± SE
Amount of change in visceral fat area (cm^2)	−28.05 ± 2.71[a]	Amount of change in waist circumference (cm)	−4.73 ± 0.45[a]
Amount of change in body weight (kg)	−4.22 ± 0.45[a]	Percent change in BMI (%)	−5.35 ± 0.56[a]
Amount of change in BMI (kg/m^2)	−1.46 ± 0.16[a]	Percent change in subcutaneous fat area (%)	−14.84 ± 1.53[a]
Amount of change in subcutaneous fat area (cm^2)	−33.47 ± 3.82[a]		

The amount of change in visceral fat area, waist circumference, and body weight as well as percent change and amount of change in BMI and subcutaneous fat area were significantly reduced at week 52 compared with baseline. *n* (week 52): 108
BMI body mass index, *SE* standard error
[a] Paired *t*-test, $p < 0.05$ compared with baseline

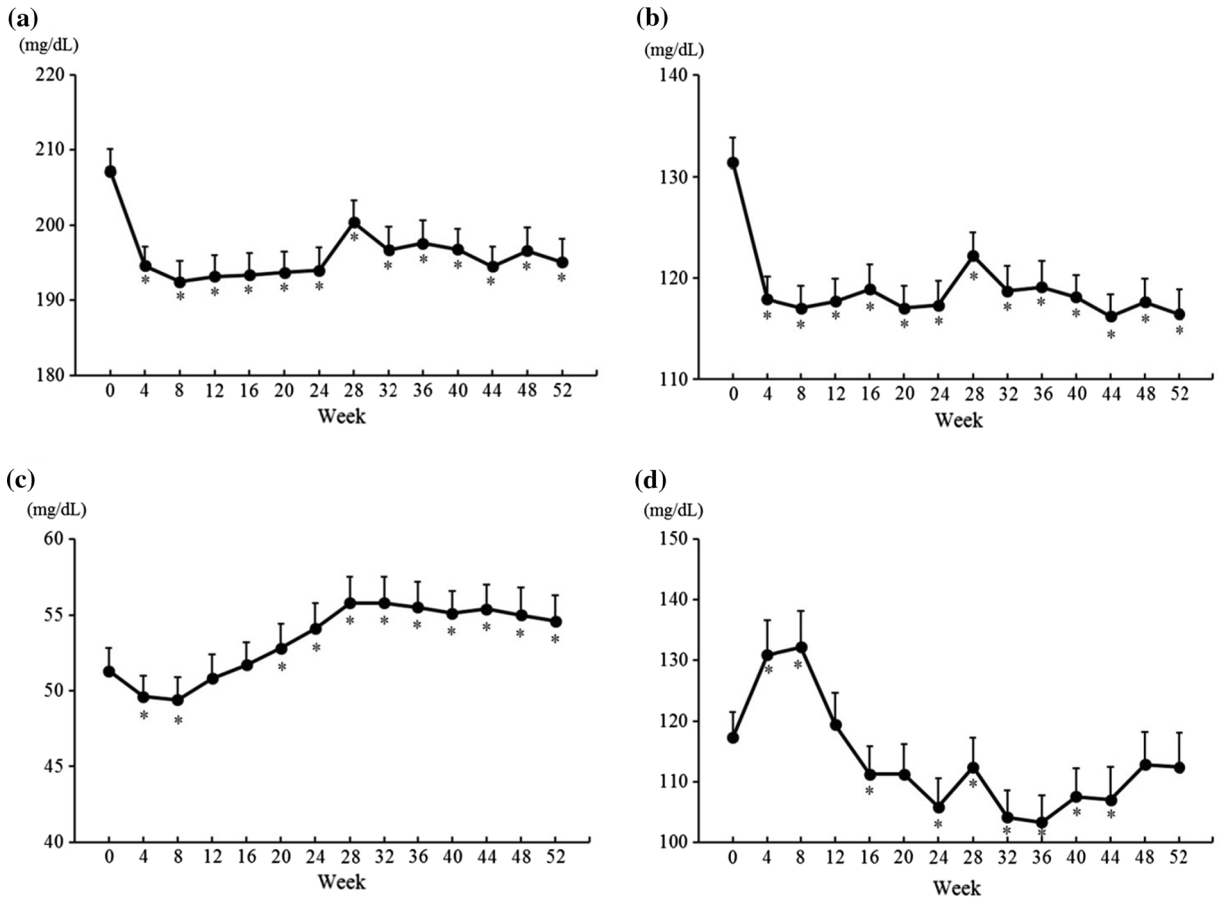

Fig. 5 Changes in lipid parameters. Mean ± SE. *n* (week 52): **a** 114, **b** 114, **c** 114, **d** 113. *Paired Wilcoxon test, $p < 0.05$ compared with baseline. **a** Total cholesterol; **b** LDL cholesterol; **c** HDL cholesterol; **d** triglycerides. Total cholesterol and LDL cholesterol reduced throughout the treatment term with significant reductions compared with baseline at whole term until week 52 of treatment. *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SE* standard error

cholesterol, triglycerides, blood glucose, HbA1c, systolic blood pressure, or diastolic blood pressure). Results showed that a significant improvement was observed ($p = 0.004$), and 26 of the 64 participants (40.6%) who had one or more risk factors at baseline had zero risk factors at week 52 of the treatment term (Table 3). Moreover, all seven participants with two risk factors at baseline had fewer risk factors at week 52.

With respect to the compliance rate for dietary improvement, more than 90% of participants had a rate of 100% throughout the treatment term. In the remaining participants, none had a compliance rate < 80%.

Safety and Tolerability

The incidence of adverse reactions is shown in Table 4. There were 142 adverse reactions observed in 73 of the 120 participants (60.8%). Of these, 133 were episodes of defecation-related symptoms such as oily spotting and flatus with discharge due to the pharmacologic effects of the lipase inhibitor, observed in 70 participants (58.3%). Additionally, there were two incidences of hepatic function abnormal in two participants (1.7%), two incidences of hyperuricemia in one participant (0.8%), and a single incidence of hyperbilirubinemia, dysuria,

Table 3 Changes in metabolic disease risk factors

Term	Baseline				Wilcoxon signed-rank test[a]
	0	1	2	Total (%)	
Week 52 of treatment					
0	40	24	2	66 (57.9)	$S = -205.5$
1	9	30	5	44 (38.6)	$p = 0.004$
2	1	2	0	3 (2.6)	
Undeterminable	0	1	0	1 (0.9)	
Total (%)	50 (43.9)	57 (50.0)	7 (6.1)	114	

A significant reduction in the number of metabolic disease risk factors was observed ($p = 0.004$), and 26 of the 64 participants who had one or more risk factors at baseline (40.6%) had zero risk factors at week 52 of the treatment term. Moreover, all seven participants with two risk factors at baseline had fewer risk factors at week 52

[a] Undeterminable is excluded

cough, skin erosion, and liver function test abnormal in one participant (0.8%). The severity of these adverse reactions was categorized as follows: 140 mild episodes in 73 participants (60.8%) and two moderate episodes in one participant (0.8%). No serious or severe adverse reactions were observed. Only two adverse reactions required medical treatment (gastritis and skin erosion), which resolved with pharmacologic intervention. There were no remarkable differences in the frequency of adverse reactions with respect to participant baseline characteristics (age, gender, BMI, etc.).

The incidence of adverse reactions by time is shown in Fig. 6. Of the 142 adverse reactions that occurred during the treatment term, 92 (64.8%) occurred during the first 4 weeks (0–35 days) of the treatment term. Subsequently, there were one (0.7%) to 10 (7.0%) adverse reactions per assessment interval (Fig. 6a). Similar results were observed for defecation-related symptoms, with 90 of the 133 adverse reaction episodes (67.7%) occurring in the first 4 weeks of the treatment term and subsequently one (0.8%) to 10 (7.5%) adverse reactions per assessment interval (Fig. 6b).

As mentioned above, defecation-related symptoms were the most common adverse reactions. Specifically, those symptoms that occurred in ≥ 5% of participants included oily spotting [46 episodes in 41 participants (34.2%)], flatus with discharge [37 episodes in 28 participants (23.3%)], fatty/oily stool [11 episodes in 11 participants (9.2%)], fecal incontinence [nine episodes in eight participants (6.7%)], and liquid stool [six episodes in six participants (5.0%)]. These symptoms were mostly mild, reversible, and recognizable by the participants; none were serious or severe. No participants were advised by the physician to withdraw from treatment.

No adverse reactions related to fat-soluble vitamin deficiencies were observed, and no participants required treatment or vitamin supplementation. Changes in vitamin A (retinol), vitamin D (25-OH vitamin D), and vitamin E (tocopherol) during the treatment term are shown in Fig. 7. Significant differences were observed, with a change from baseline to week 52 of the treatment term of 34.8 ± 87.1 ng/ml (mean ± SD) for vitamin A, 2.36 ± 5.11 ng/ml for vitamin D, and − 0.081 ± 0.197 mg/dl for vitamin E ($p < 0.001$ for all parameters). Notably, only vitamin E showed a reduction. Although vitamin E levels at whole term after week 4 were lower than those at baseline, the levels did not continue to reduce. Further, the observed changes were within the normal ranges, and no other remarkable changes were observed. All other laboratory tests showed

Table 4 Incidence of adverse reactions

Number of participants included in the analysis	*n* = 120	
Event	**Number of episodes**	**Number of cases (%)**
Total	142	73 (60.8)
Defecation-related symptoms		
Subtotal	133	70 (58.3)
Fecal incontinence	9	8 (6.7)
Oily spotting	46	41 (34.2)
Flatus with discharge	37	28 (23.3)
Fecal urgency	5	5 (4.2)
Oily evacuation	4	4 (3.3)
Fatty/oily stool	11	11 (9.2)
Liquid stool	6	6 (5.0)
Increased defecation	3	3 (2.5)
Soft stool	3	3 (2.5)
Decreased defecation	3	3 (2.5)
Abdominal distension	1	1 (0.8)
Abdominal pain	3	3 (2.5)
Flatulence	1	1 (0.8)
Gastritis	1	1 (0.8)
Hepatobiliary disorders		
Subtotal	3	2 (1.7)
Hepatic function abnormal	2	2 (1.7)
Hyperbilirubinemia	1	1 (0.8)
Metabolism and nutrition disorders		
Subtotal	2	1 (0.8)
Hyperuricemia	2	1 (0.8)
Renal and urinary disorders		
Subtotal	1	1 (0.8)
Dysuria	1	1 (0.8)
Respiratory, thoracic, and mediastinal disorders		
Subtotal	1	1 (0.8)
Cough	1	1 (0.8)
Skin and subcutaneous tissue disorders		
Subtotal	1	1 (0.8)
Skin erosion	1	1 (0.8)
Investigations		
Subtotal	1	1 (0.8)
Liver function test abnormal	1	1 (0.8)

changes within their normal ranges, with no notable changes or safety concerns.

DISCUSSION

This study was the first to evaluate the efficacy and safety of 52-week administration of orlistat (60 mg, administered three times daily) in Japanese participants with excessive visceral fat accumulation and without metabolic diseases.

In terms of efficacy, 52-week administration of orlistat 60 mg reduced the visceral fat area in Japanese participants with excessive visceral fat accumulation and without metabolic diseases; these effects continued after 24 weeks, which is a new finding. At week 52 of the treatment term, the change from baseline in visceral fat area was − 21.52% ± 1.89% (mean ± SE). The visceral fat area reduced during the 12-week observation term as a result of improvement in diet and maintenance of exercise habits, and it continued to reduce gradually throughout the entire 52-week treatment term without returning to baseline levels. Significant reductions in visceral fat area were observed at whole term compared with baseline. Additionally, the subcutaneous fat area reduced, and waist circumference, which consists of visceral fat and subcutaneous fat, also decreased. These results suggest that the use of orlistat reduces the risk of developing metabolic diseases resulting from excessive visceral fat accumulation by

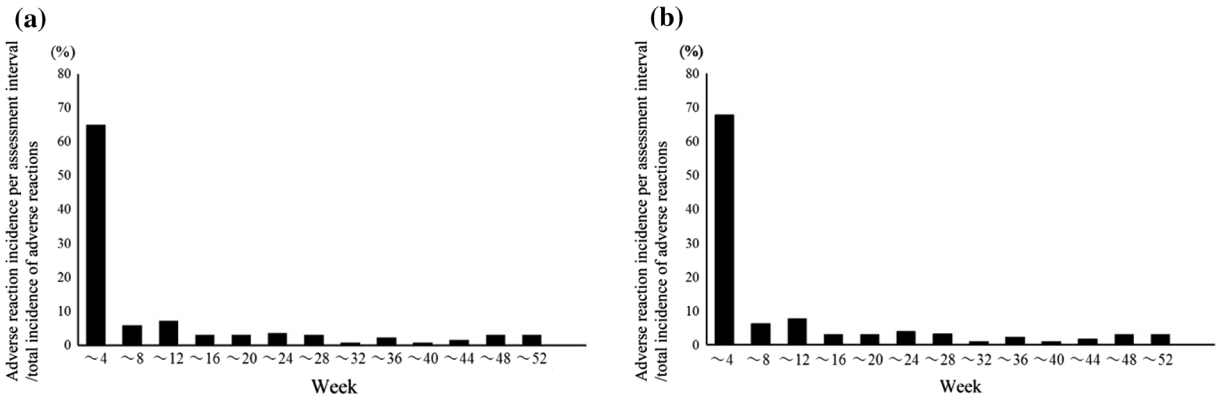

Fig. 6 Incidence of adverse reactions by time. Percentages are calculated as the number of adverse reactions per assessment interval over the total number of adverse reactions during the entire treatment term. **a** Incidence of all adverse reactions; **b** incidence of defecation-related adverse reactions. In both **a** and **b**, the majority of adverse reactions occurred within the first 4 weeks (0–35 days) of treatment; frequency of adverse reactions did not increase with longer administration time

enhancing the effects of lifestyle improvement in Japanese participants with excessive visceral fat accumulation and without metabolic diseases. Orlistat, therefore, may be a useful option for early intervention in obesity. Moreover, based on orlistat's mechanism of action, it is conceivable that the suppression of dietary fat absorption enhances the utilization of lipids in the body, which may further lead to reductions in visceral fat and body weight. Reduction in waist circumference can be attributed to subsequent abdominal fat reduction.

In Europe and the US, a 60-mg formulation of orlistat for administration three times daily is available without a prescription. Multiple reports have confirmed the safety and efficacy of orlistat in individuals with severe obesity in these countries, and significant body weight changes were observed as well in a previous study (orlistat was administered three times daily for 104 weeks at a dose of 60 mg to severely obese patients with BMIs between 30 and 44 kg/m^2 [18]).

Central appetite suppressants, such as lorcaserin and the combination of bupropion and naltrexone, are used as anti-obesity drugs in Europe and the USA. Significant body weight reductions have been demonstrated in clinical studies for lorcaserin (in obese patients with BMI 30–45 kg/m^2 or those with BMI $\geq$ 27 kg/m^2 with hypertension and/or dyslipidemia) [19] and the combination of bupropion and naltrexone (in obese patients with BMI $\geq$ 30 kg/m^2 or those with BMI $\geq$ 27 kg/m^2 with hypertension and/or dyslipidemia) [20]. Furthermore, the frequency of headache, nausea, and dizziness was higher in the lorcaserin group compared with placebo; the combination of bupropion and naltrexone caused nausea, headache, constipation, dizziness, and dry mouth [21]. However, because orlistat has very little absorption in the body, these symptoms were not observed in individuals taking orlistat (with the exception of constipation).

Waist circumference was used to select participants for this study, and, as a result, participants with a visceral fat area $<$ 100 cm^2 were included in this study (19.2%) (as in another study [6]). Notably, not only was the visceral fat area reduced in these participants, but waist circumference, which serves as a surrogate index for visceral fat, was also reduced.

Orlistat inhibits the absorption of dietary fat by 25%–30% [15] and is therefore presumed to reduce the concentration of lipids in the blood. In this study, all lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) showed significant differences compared with baseline at some terms. However, only total cholesterol and LDL cholesterol levels showed a reducing trend throughout the 52-week treatment term with significant

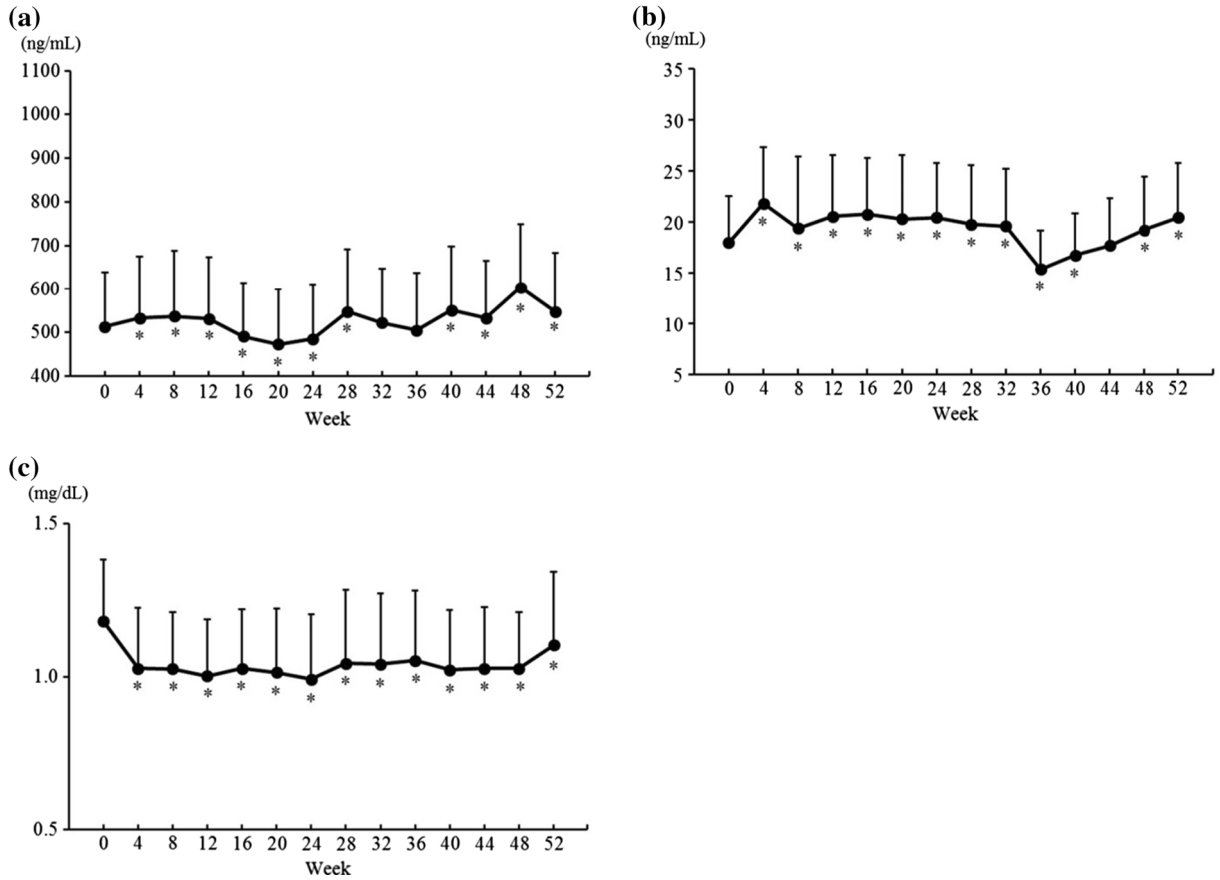

Fig. 7 Changes in fat-soluble vitamin concentrations. Mean ± SD. *n* (week 52): **a** 114, **b** 114, **c** 114. *Paired Wilcoxon test, $p < 0.05$ compared with baseline. **a** Vitamin A (retinol); **b** vitamin D (25-OH vitamin D); **c** vitamin E (tocopherol). Although all parameters showed significant differences compared with baseline at a certain term, all changes were within their normal ranges. No notable changes in terms of safety were observed. *SD* standard deviation

reductions from baseline at whole term. In a meta-analysis by Tian Hu et al., participants receiving a low-carbohydrate diet showed a greater increase in HDL cholesterol and a reduction in triglycerides compared with those receiving a low-fat diet, but experienced less reduction in total cholesterol and LDL cholesterol compared with those receiving a low-fat diet [22]. Orlistat, then, likely did not affect HDL cholesterol or triglycerides, which are more likely to be affected by carbohydrate intake than fat intake, as orlistat's mechanism of action inhibits the absorption of food-derived fat.

It is well established that body weight loss inhibits the progression of metabolic diseases resulting from insulin resistance in individuals with obesity [2]. In this study, the effects of orlistat on blood glucose levels and blood pressure were not clear, partly because most of the participants had both normal blood glucose and normal blood pressure at baseline. However, it may be reasonable to expect that orlistat prevents the aggravation of blood glucose and blood pressure imbalances in the long term. Moreover, in this study, 26 of the 64 participants with one or more risk factors at baseline (40.6%) had no risk factors at week 52 of treatment, and all seven participants who had two or

more risk factors at baseline had fewer risk factors at week 52.

By demonstrating reductions in total cholesterol, LDL cholesterol, visceral fat area, waist circumference, and the number of metabolic disease risk factors, the clinical significance of orlistat as a potential benefit for Japanese participants with excessive visceral fat accumulation and without metabolic diseases was confirmed. Furthermore, a study suggesting high blood pressure, high blood glucose, and abnormal lipid metabolism to be cardiovascular risk factors [6] showed reductions in the number of metabolic disease risk factors as well as visceral fat area with the use of orlistat, which may ultimately lead to a reduced risk of cardiovascular diseases.

In terms of safety, 142 adverse reactions in 73 of the 120 participants (60.8%) were observed. However, most of these [133 episodes in 70 participants (58.3%)] were defecation-related symptoms such as oily spotting and flatus with discharge due to the pharmacologic effects of the lipase inhibitor. The majority of these symptoms were mild, reversible, and recognizable by the participant; none were serious or severe. Few adverse reactions required medical treatment, and no participants were advised by the investigator to withdraw from treatment. The frequency of adverse reactions observed in this study does not exceed that observed in previous studies of orlistat 60 mg conducted in other countries as an over-the-counter drug (including defecation-related adverse reactions) [23]; therefore, it is reasonable to assume that orlistat is also sufficiently tolerable with self-management in the Japanese population. Moreover, among the 133 defecation-related adverse reactions that occurred during the treatment term, the majority (90 episodes, 67.7%) occurred during the first 4 weeks of the treatment term, and most of these participants were able to continue the 52-week term (a few participants withdrew from the study at their request).

Because orlistat inhibits the absorption of dietary fat by inactivating lipase, a lipolytic enzyme, the absorption of fat-soluble vitamins such as A, D, and E could also be inhibited. No adverse reactions related to fat-soluble vitamin deficiencies were observed, and no participants required treatment or vitamin supplementation. In this study, levels of vitamin A and vitamin D at week 52 were higher than those at baseline; levels of vitamin E, however, decreased by -0.081 ± 0.197 mg/dl (mean $\pm$ SD). Although there was a statistically significant reduction in vitamin E at week 52 of the treatment term, levels did not subsequently continue to reduce. Therefore, it is doubtful that this change is clinically meaningful. Further, the observed changes in this study were within the normal ranges, and no other remarkable changes were observed. All other laboratory tests showed changes within their normal ranges, and no notable changes were observed with regard to safety.

Throughout the treatment term of this study, $>90\%$ of participants had a compliance rate of 100% for dietary improvement. Among the remaining participants, none had a compliance rate $< 80\%$. Therefore, orlistat can also be a useful option when used as a complement to diet and maintenance of exercise habits in the long term.

The open-label design and lack of a control group are limitations of this study and may have contributed to observational bias of the investigators and high expectations of participants.

In this study, we selected participants and measured the efficacy based on waist circumference. Thus, it is conceivable that users of orlistat can monitor feasibility of drug use and its effects by using their waist circumference as an indicator. Considering the fact that orlistat 60 mg is already available as an over-the-counter drug in several countries, for Japanese participants with excessive visceral fat accumulation and without metabolic diseases, orlistat is expected to provide significant potential benefits.

CONCLUSIONS

It was confirmed that the 52-week administration of orlistat 60 mg three times daily was effective in reducing the visceral fat area and waist circumference and was sufficiently

tolerated by Japanese participants with excessive visceral fat accumulation and without metabolic diseases when their diet was improved and exercise habits were maintained. The longer orlistat is administered, the more visceral fat is expected to decrease; moreover, it may lead to reductions in risk factors for metabolic diseases caused by obesity.

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Compliance with Ethics Guidelines. The study was implemented in accordance with Good Clinical Practice guidelines and the ethical principles of the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. Springer's policy concerning informed consent has been followed. This study was approved by the Institutional Review Board of each participating institution. After receiving a sufficient explanation and achieving a full understanding of the study, all potential participants provided written consent to voluntarily participate in the study.

Data Availability. The data sets generated during and/or analyzed during the current study are not publicly available because of confidentiality reasons but are available from the corresponding author on reasonable request.

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