sinetrol®

Fat Shredding Technology™

WHITE PAPER

New clinical study results on body weight management

Fytexia

Increasing from year to year, the number of adults who currently have excess body fat is estimated to be 1.9 billion, including 600 million obese individuals (WHO). Excess fat mass is the most common chronic health problem worldwide and one of the greatest public health challenges of the 21st century.

Recognized as a cultural heritage by UNESCO, the Mediterranean diet is a modern nutritional lifestyle inspired by the traditional dietary patterns of Greece, Italy, Spain and southern France. Numerous known bioactive substances in this diet improve health and weight management. Giving up the paradigm of the miracle molecule, one of the challenges of innovation within the food supplement industry is now to combine each natural component and optimize positive effects by synergetic partners.

Fytexia designed Sinetrol® as a unique Mediterranean weight-loss ingredient. Sold in more than 30 countries, the polyphenol-rich patented formula is a leading ingredient in the weight management area.

Sinetrol® acts by way of Fat Shredding Technology™, an exclusive mechanism of action enhancing the rate of lipolysis. With weight-loss benefits demonstrated in two previous clinical studies, Fytexia has deepened the scientific evidence for Sinetrol® with a third clinical study. Altogether, Sinetrol® has been clinically shown to help with body-fat loss, leading to a healthier body composition, in more than 190 subjects.

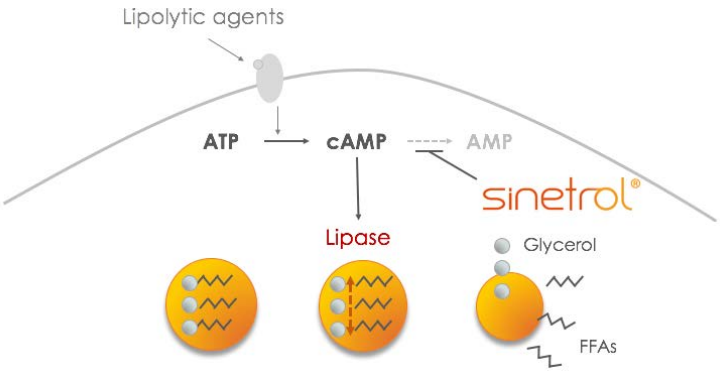
SUMMARY

sinetrol®

Fat Shredding Technology™

1- MECHANISM OF ACTION

Sinetrol® is a natural combination of polyphenols extracted from citrus and guarana targeting body weight management. Sinetrol® works as a safe and non-thermogenic fat burner to reduce the excess of fat mass.

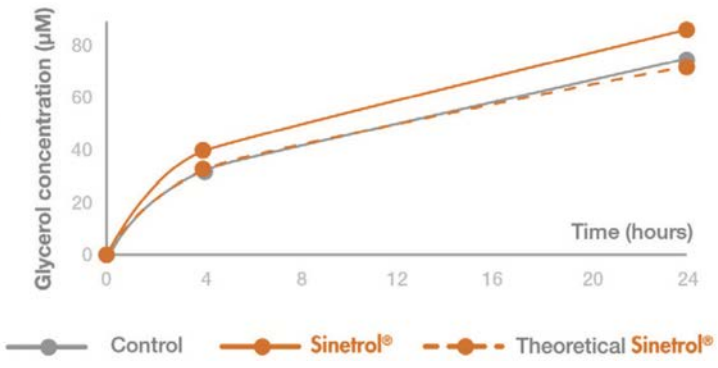


Fat Shredding Technology™

Lipolysis is a catabolic process leading to the breakdown of triglycerides stored in fat cells (adipocytes), releasing free fatty acids (FFAs) and glycerol.
Sinetrol® acts by way of the exclusive mechanism of Fat Shredding Technology™ (FST). Sinetrol® facilitates lipolysis through the inhibition of phosphodiesterase-4, the enzyme that catalyzes the hydrolysis of cyclic adenosine monophosphate (cAMP). Higher cAMP levels lead to an increased rate of triglyceride breakdown.

As highlighted in an *ex vivo* study, Sinetrol®, by way of the Fat Shredding Technology™, enhances the release of FFAs and glycerol, which results in a reduction in the volume of adipocytes. Acting together, polyphenols and caffeine in the patented formula of Sinetrol® provide higher lipolytic potency than when tested separately (theoretical Sinetrol®).

Lipolytic activity



sinetrol®
Fat Shredding Technology™

2- CLINICALLY PROVEN EFFICACY

Two double-blind randomized, *placebo*-controlled studies

900 mg/day of Sinetrol® in 2 capsules

	1	2
	Paris, France American Hospital	Paris, France American Hospital
	12 weeks	12 weeks
	20 subjects BMI: 27-33 Age: 22-55 years	95 subjects BMI: 26-29.9 Age: 22-45 years
	No diet	Normo-caloric diet *(Harris and Benedict)*
	Physical activity < 30 min/week	Physical activity < 30 min/week
	Impedance bioelectrical scale	VISCAN By Tanita®

WEIGHT LOSS

Body weight loss
(kg) ΔW1-W12

OVERWEIGHT & OBESE SUBJECTS

Body weight loss
(kg) ΔW1-W12

OVERWEIGHT SUBJECTS

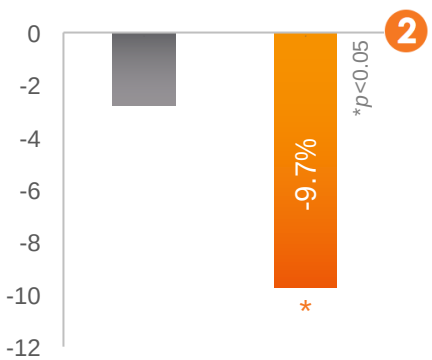
Placebo
Sinetrol®

The two first clinical studies were conducted in a healthy population of overweight or obese men and women. These studies demonstrated that the polyphenol-rich ingredient Sinetrol® is a safe solution for reducing excess of body weight:

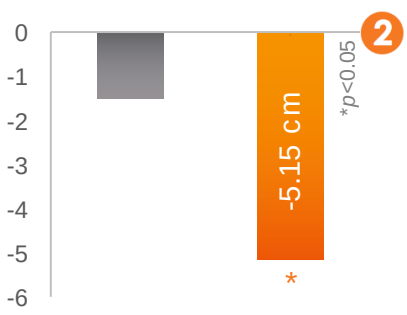
- The Sinetrol® group experienced a significant and progressive body weight loss during the trials, especially fat loss in the abdominal area.
- The silhouette of the supplemented group were improved with a significant reduction in waist and hip size.

SILHOUETTE SHAPING

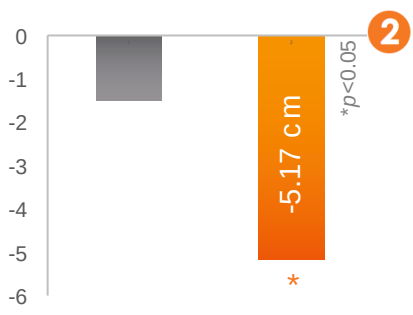
Abdominal fat reduction
(%) Δ W1-W12



Waist size reduction
(cm) ΔW1-W12



Hip size reduction
(cm) ΔW1-W12



NEW

sinetrol®
Fat Shredding Technology™

3- THIRD CLINICAL STUDY

Double-blind randomized, *placebo*-controlled study
900 mg/day of Sinetrol® in 2 capsules

Murcia, Spain
Research center, University of Murcia

77 subjects
BMI: > 25
Age: 29-52 years

16 weeks

Gold Standard: DXA
(Dual energy X-ray Absorptiometry)

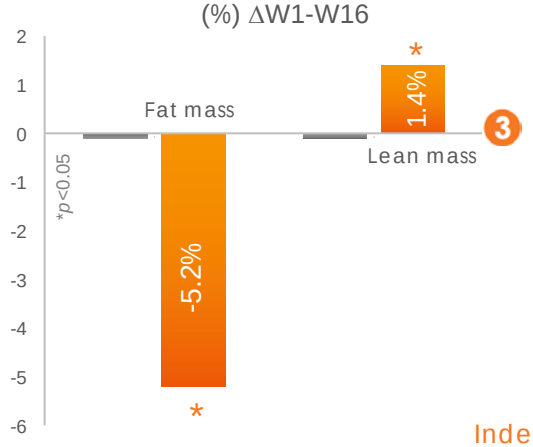
Normo-caloric diet
(Harris and Benedict)

Physical activity
No recommendation

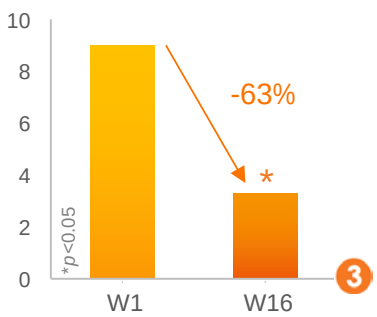
ANTHROPOMETRIC MEASURES

In this third trial, Sinetrol® again induced a significant weight loss. Moreover, the gold standard technology DXA used to measure the changes highlights that supplementing a normo-caloric diet with Sinetrol® led to the support of a healthy body composition: body fat decreased while lean mass increased. The supplemented group reduced their excess of fat mass by 63% compared to the theoretical fat mass.

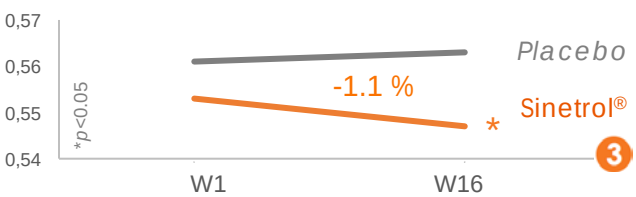
Body-fat & lean mass
(%) ΔW1-W16



Body-fat mass reduction
vs % theoretical fat mass



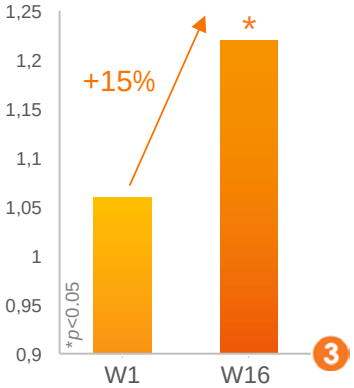
Index of Central Obesity (ICO)



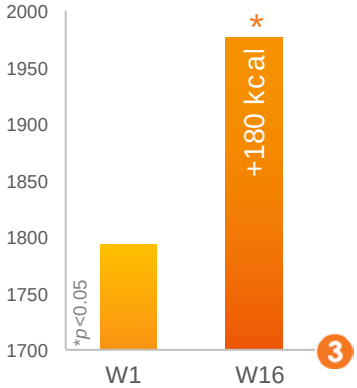
MECHANISTIC MARKERS

Blood measures confirmed the metabolic of action of the Fat Shredding Technology™: Sinetrol® was proven to enhance the release of free fatty acids from adipocytes signifying a higher rate of lipolysis.

Free fatty acid release
(mmol/L)



Resting energy expenditure
(expended kcalories/day)



4 - SCIENTIFIC CLINICAL REPORT

Third clinical study

ABSTRACT

Double-blind randomized, placebo-controlled study to evaluate the benefit of a polyphenol-rich fruit and seed extract formulation in managing body-fat loss and in improving body composition in overweight and obese subjects.

The objective of this study in 77 volunteers was to evaluate the benefit of Sinetrol® in managing body-fat loss and in improving body composition in overweight and obese subjects.

The primary outcome of this new clinical investigation is the body-fat mass loss (measured with DXA technology). Secondary outcomes correspond to the changes in anthropometry and body composition (DXA technology), as well as the modifications of rates of resting energy expenditure (Respiratory Exchange Ratio) after 16 weeks of supplementation as compared to placebo. To confirm the mechanism of action in human subjects, the changes in metabolic parameters, derived from enhanced lipolysis, were measured after 16 weeks of supplementation in comparison to those in the group who received placebo.

After 16 weeks, the primary outcome achieved both the objective and the 5% level of significance with an average body-fat loss (%BW) of 2 points ($p = 0.0003$) within the Sinetrol® population. All anthropometric and body composition parameters (BW, BMI, total lean mass, total fat mass, lean-to-fat mass ratio, ICO, and waist and hip circumferences) were significantly improved within the Sinetrol® group at the end of the studied period. Besides, resting energy expenditure also significantly increased within the Sinetrol® group. In terms of safety, there were no clinically significant changes in any of the laboratory parameters observed and no adverse events recorded.

Supplementation with Sinetrol® within the 16-week period led to a statistically significant loss of total body-fat mass. Moreover, the expertise in conducting body weight management related clinical investigations, resulted in no significant variation within the placebo group. Also, all the secondary outcomes improved with the Sinetrol® supplementation. Finally, the results prove that Sinetrol® has an excellent safety profile.

ETHICS

The study was reviewed and approved by the "Comité de Ética" of the UCAM before study initiation.

This clinical investigation was performed according to the protocol of the principles established in the current revised version of the Declaration of Helsinki (Seoul, 2008) and in accordance with the recommendations of Good Clinical Practice (1996) and guidelines from Good Epidemiological Practice (http://.ieatemp.com/goodEpiPractice.aspx). The Declaration of Helsinki can be obtained from the website of the World Medical Association in .wma.net/es/30publications/10policies/b3/17c_es.pdf.

Before enrolment, the investigator informed each subject about the objective, the intended effect, possible impacts and risks, as well as the exact chronological and procedural investigation process. The subjects were also informed about the fact that he/she may revoke his/her written consent at any time, and thereby terminate participation in the study.

The participant declared his/her agreement to all the conditions of the investigation by signing the informed consent form in the presence of the investigator who countersigned the form including the date and location.

1. RATIONALE

Excessive body weight is currently the most common chronic health problem worldwide and one of the greatest public health challenges of the twenty-first century. A major cause of overweight and obesity is known to be the accumulation of excessive body fat due to such causes as an imbalance between calorie consumption and energy expenditure, especially within populations with sedentary behaviours. In addition to causing various physical disabilities and psychological problems, overweight and obesity, especially when excess of fat is accumulated within the abdominal area, drastically increase a person's risk of developing a number of non-communicable diseases (NCDs), including metabolic syndrome (MS), cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM) (Aballay *et al.* 2013; Balkau *et al.* 2007; Cardoso-Saldana *et al.* 2010; Janus *et al.* 2007; Kaysen *et al.* 2009; Wadden & Phelan, 2002), which dramatically affect average life expectancy, making overweight and obesity the fifth leading risk factor for global death (WHO 2013). Nevertheless, overweight, obesity and their consequences are preventable.

During fat accumulation, throughout the progression of overweight or obesity, it has been reported that various metabolic effects associated with age-related changes in body composition and a decline in physical activity were involved with a significant propensity to lose skeletal muscle mass (SMM) (Kim *et al.* 2014). In addition, several authors observed a significant reduction of SMM in response to modified diets during weight loss intervention programs in overweight populations with excessive abdominal fat (Janssen & Ross 1999; Ross *et al.* 1996). Preserving SMM consequently appears to be essential when individuals with a medium- to long-term history of overweight or obesity decide to start a weight loss program (Cases *et al.* 2015).

While reducing abdominal fat mass and associated metabolic disorders appear as clear and crucial targets for the prevention of excess weight-related manifestations of NCDs (Shen *et al.* 2009), it is therefore critical that such body weight-loss programs participate to preserve a balanced body composition (lean/fat ratio). Hence, a precise measurement of the percentage of body fat in association with the lean mass ratio is considered the reference method for defining overweight or obesity. As the approach offering the highest sensitivity in determining the entire

body composition (both body fat & body lean mass), dual energy X-ray absorptiometry (DXA) appears is accordingly considered the gold standard methodology (Shawk *et al.* 2007). Yet, anthropometric indices, such as BMI, waist and hip circumferences and the index of central obesity (ICO), are still the most commonly used indicators for assessing abdominal overweight or obesity (Singh *et al.* 1998; Parikh *et al.* 2006; Mushtaa *et al.* 2011).

Among the most studied dietary patterns for health effects, it appears that adherence to a Mediterranean diet is correlated with a lower risk for NCDs. It has been assumed that some bioactive constituents of Mediterranean foods, namely polyphenols, are responsible for the observed health-promoting effects ascribed to this dietary style (Ros *et al.* 2014). The biological effects of polyphenols have been largely attributed to their antioxidant properties; however, recent data suggest that polyphenols can exert modulatory action in cells by interacting with the cell signalling machinery. Thus, several polyphenols can affect metabolic pathways involved in either appetite, adipogenesis, or energy homeostasis (Maydani & Hasan 2010). Hence, these bioactive constituents might be useful in the management of metabolic disorders generally associated with overweight and obesity.

The product to be investigated, Sinetrol® Xpur, is a proprietary combination of extracts from grapefruit and orange, providing Mediterranean polyphenols, and guarana providing natural caffeine.

In a 12-week double-blind, placebo-controlled trial (Dallas *et al* 2014) with 95 overweight subjects (BMI = 26.0–29.9), supplementation with Sinetrol® Xpur, in combination with a normo-caloric diet and 30 min/week of physical activity, induced a significant loss in body weight (-2.6 kg) associated with a decrease in body fat (-3.6%) and reductions in both waist and hip circumferences. Moreover, in a double-blind, placebo-controlled pilot trial (Cases *et al*. 2015) involving 25 overweight men, 12 weeks' of supplementation with Sinetrol® Xpur induced a significant decrease of body fat (-2.6%), while metabolic markers of muscle catabolism remained stable after 12 weeks, indicating preservation of SMM during fat loss.

Based upon these results, the aim of the present study was (1) to confirm the benefits of a supplementation with Sinetrol® Xpur in decreasing body-fat mass within a population including both overweight and obese subjects and (2), to confirm and evaluate the preservation of SMM during fat loss in integrating a reliable measure of body composition (fat mass and lean mass) using the DXA technology.

2. STUDY OBJECTIVE

The main objective of this 16-week double-blind, randomized, placebo-controlled study is improvement of total body weight, mainly as body-fat loss: at least a 2-point difference in body fat percentage between day 0 and day 112 (D0 and D112) within the Sinetrol® Xpur-supplemented group.

- Primary outcome: Total body-fat percentage loss versus body weight (BW) by DXA measurement.
- Secondary outcomes: Body-weight loss; body lean-mass gain; lean-to-fat mass ratio improvement; excess body-fat mass improvement *versus* theoretical fat mass; index of central obesity improvement; waist circumference & hip size improvement; resting exchange ratio (REE) improvement; metabolic parameters improvement; and change in caloric intake.

3. INVESTIGATIONAL PLAN

3.1 Overall study design and plan: description

The clinical investigation was a 16-week, double-blind, randomized, placebo-controlled study. All the subjects were instructed to ingest two capsules, one at breakfast time and one at lunch time. Thus, the daily dose was 2 capsules.

In addition, subjects were coached by a dietician to follow and maintain a nutritionally balanced and normal-calorie diet based on individual diet plans. Based on gender, body weight, age and height, the individual resting energy expenditure

(REE) was calculated from the revised equation of Harris-Benedict (Roza & Shizgal, 1984) and adjusted to their individual level of physical activity assessed with an oral interview.

The REE was calculated as follows:

Men	REE = 88.362 + (13.397 x weight(kg)) + (4.799 x height(cm)) - (5.677 x age(years))
Women	REE = 447.593 + (9.247 x weight(kg)) + (3.098 x height(cm)) - (4.330 x age(years))

REE was then adjusted according to the level of physical activity.

Little to no exercise	Daily kcalories needed = REE x 1.2
Light exercise (1-3 days per week)	Daily kcalories needed = REE x 1.375
Moderate exercise (3-5 days per week)	Daily kcalories needed = REE x 1.55
Heavy exercise (6-7 days per week)	Daily kcalories needed = REE x 1.725
Very heavy exercise (Twice per day)	Daily kcalories needed = REE x 1.9

Participants were encouraged to maintain their usual level of physical activity and to follow the individual diet throughout the 16-week intervention period. At the beginning and at the end of the study period, volunteers performed a 24-hour diet recall interview (2 interviews during the week and 1 during the weekend) to check compliance with instructions.

Volunteers submitted to 6 visits during the study:

Pre-inclusion visit (W_0):

- Oral and written information about the nature, purpose, and possible risks and benefits of the study provided to the subjects by the investigator.
- Written consent of the subject to participate; he/she understands the requirements of the clinical investigation and is willing to comply.
- Verification that the inclusion criteria are met and that there are no violations of the exclusion criteria.
- Assessment of anthropometrics.
- Blood sampling for the assessment of safety parameters.

Baseline visit (W1):

- Assessment of anthropometrics and body composition (DXA).
- Assessment of REE with indirect calorimetry.
- Interview for determination of calorie intake and nutritional coaching.

- Blood sampling for metabolic analyses.
- Issue of first capsule dispenser and instructions for correct use.
- Issue of pedometer and diary and instructions for their correct use.

Follow-up visits (W4, W8 and W12):

- Return of subject's diary.
- Return of any unused investigational product for compliance control.
- Questioning and documentation of possible occurrence of adverse events.
- Issue of next capsule dispenser for 4 weeks.

Final visit (W16):

- Assessment of anthropometrics and body composition (DXA).
- Assessment of REE with indirect calorimetry.
- Interview and determination of calorie intake.
- Blood sampling for metabolic analyses and safety parameters.
- Questioning and documentation of possible occurrence of adverse events.
- Return of any unused investigational product for compliance control.

3.2 Selection of study population

3.2.1 Inclusion criteria

- Age: 25 to 55 years.
- Overweight and obese subjects (25 $kg/m^2 \leq BMI \leq 42.5\ kg/m^2$).

3.2.2 Exclusion criteria

- A metabolic and/or chronic disease for which the subject is treated (diabetes, dyslipidaemia, thyroiditis, inflammatory disease, immunological disease, infectious disease, asthma, anxiety and depression, etc.).
- A food allergy to the ingredients of the test product (grapefruit, orange, caffeine and/or guarana).
- Involved in the prior 6 months in a chronic treatment program or a weight loss program, or have a history of eating disorders or been subjected to weight reduction surgery.

- Started or quit smoking, or have a high alcohol consumption.
- Pregnant, breastfeeding or wanting to have a baby.
- Menopausal women (no period since at least 12 months).

3.2.3 Removal of subjects from therapy

Subjects were free to discontinue their participation in the study at any time without prejudice to further intervention. Further, investigators could withdraw individual subjects at their discretion if it was judged necessary.

Specific reasons for discontinuing a subject from the study were:

- Intolerance to the investigational product.
- Required additional therapy due to other complaints which could influence the results of the investigation.
- Serious adverse events.
- Clinically significant illness or intake of concomitant medication according to exclusion criteria, which could influence the results of the investigation.
- Insufficient compliance by the subject.
- Withdrawal of informed consent.

3.3 Investigational product/supplementation

3.3.1 Supplementation administered

For the 16 weeks following randomization, subjects received either Sinetrol® Xpur or placebo and ingested one capsule with breakfast and one with lunch, daily.

3.3.2 Identity of the investigational product

Sinetrol® Xpur is a proprietary combination of fruit extracts. It is standardized to contain at least 20% polyphenols in the form of flavanones extracted from grapefruit (*Citrus paradisi* Macfad.) and orange (*Citrus sinensis* L.). The product also contains a source of caffeine delivered from an extract of guarana (*Paullinia cupana* Kunth).

The dry extract was packaged in red cellulose capsules (450 mg per capsule). Identical-looking capsules, each filled with 450 mg of maltodextrin, served as placebo.

3.3.3 Methods of assigning subjects to supplementation groups

The randomization number was generated using a simple block randomization of 1:1 with an additional stratification for sex (40% minimum and 60% maximum for each sex) with a separate randomization list.

The label of the issued investigational product contained the randomization number. Randomization occurred at visit 1 (W1) when inclusion criteria were met, subjects complied with the protocol, and no violation of exclusion criteria had occurred. A 3-letter code was then attributed to each subject.

3.3.4 Blinding

As this clinical investigation was performed double blind, the investigator received sealed envelopes containing allocation information to Sinetrol® Xpur or placebo. The emergency envelopes were to be opened by the investigator in emergency cases in which the investigator suspected a causal relation with the investigational product that required unblinding.

For data and biological analyses, the scientists involved only had access to the random number labelled on samples. They did not have any information concerning the sex and the study arm.

3.4 Methods for assessment of benefit and safety variables

3.4.1 Safety analysis

After sampling, venous blood samples were transported on the same day in cooler boxes to a central laboratory (Complejo Hospitalario Universitario de Cartagena, Spain) for analysis of safety parameters, including:

- Serology: human immunodeficiency virus 1 & 2 (HIV 1 & 2), hepatits B virus (HBV), and hepatitis C virus (HCV).
- Hormones: human chorionic gonadotropin (hCG).
- Kidney function: urea, creatinine, sodium (Na), potassium (K), and glomerular filtration.

- Liver function: alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), and gamma-glutamyltransferase (gamma-GT).
- Heart rate: a polar heart rate band (Polar Electro Inc., NY, USA) was strapped over the volunteer's chest to measure heart rate while at rest.

3.4.2 Benefit variables

3.4.2.1 Body composition

Anthropometry:

Body weight (kg) was measured in subjects wearing light clothes and no shoes using calibrated weighing scales (Tanita Corporation, IL, USA).

Waist circumference (cm) was measured at the narrowest point between the lowest rib and the iliac crest using a non-stretchable tape.

Hip circumference (cm) was taken around the maximum circumference of the buttocks with a non-stretchable tape.

The ICO was calculated as the waist-to-height ratio.

Theoretical fat mass was calculated according to the equations of Deurenberg *et al.* (Deurenberg *et al.,* 1991):

Body fat (%): (1.20 x BMI) + (0.23 x age) – (10.8 x sex) -5.4; with sex=1 for men and sex=0 for women.

Dual-Energy X-ray Absorptiometry:

Body composition was assessed using DXA-scan of the whole body (XR-46; Norland Corp., Fort Atkinson, WI, USA). Discrimination of whole-body fat mass (FM) and lean mass (LM) was assessed with a computerized analysis of DEXA-scan (Software Illuminatus DXA 4.4.0, Visual MED, Inc. and Norland CooperSurgical Company).

3.4.2.2 Resting energy expenditure (REE)

REE was measured while the volunteer was at rest. Volunteer wore a mask to measure gas exchange using indirect calorimetry (MetaLyzer Cortex 3B, Leipzig, Germany).

3.4.2.3 Physical activity

The subjects were provided with a pedometer in order to assess the daily number of steps by detecting the motion of the subject's hip.

3.4.2.3 Diet

At the beginning and at the end of the study period, volunteers performed a 24-hour diet recall interview (2 interviews during the week and 1 during the weekend) to check compliance with individual recommended intake according to the revised equation of Harris-Benedict (Roza & Shizgal, 1984).

3.4.2.5 Metabolic outcomes

For metabolic analysis, 20 mL of blood was collected at baseline (W_1) and at the end of the study (W_{16}) from the basilica vein using a vacutainer system and 4 tubes of Terumo Venoject (Terumo, Leuven, Belgium) with EDTA, heparin or dry tube. Some samples were centrifuged at 3000 r.p.m for 10 minutes at 4°C. Immediately after centrifugation, plasma was extracted and proportionally divided in aliquots of 0.5 to 1 mL (Eppendorf tubes). Samples were frozen at -80° C for further analysis.

A total of 40 blood aliquots per volunteer (20 aliquots at baseline and 20 aliquots at the end of the study) were stored in a Serum Bank:

SERUM BANK	
Heparinized blood	8 x 750 µL plasma
	2 x 500 µL red blood cells
EDTA blood	6 x 500 µL plasma
Dry blood	4 x 2 mL serum

The first blood analysis performed included plasma concentration of fibrinogen, FFAs, leptin and adiponectin; additional metabolic outcomes will possibly be

analyzed in order to explore the mechanism of action of the supplement in more depth.

Quantification of FFAs was assessed with a colorimetric method on a Pentra 400 Chemistry Analyzer (Horiba ABX). Fibrinogen, leptin and adiponectin quantifications were assessed with Multiplex assay on a Luminex 100 LS (Luminex, Inc., Austin, TX) using commercial kits (Millipore, Billerica, MA).

3.5 Data quality assurance

During the clinical investigation, a monitor had regular contacts with the investigational site, including visits to verify that all data in the CRFs were completed and recorded in a timely manner and were consistent with the source data, that signed and dated informed consent forms were obtained from each subject at the time of enrollment, and that the study was being performed according the study protocol.

3.6 Statistical plan

3.6.1 Determination of sample size

The sample size calculation was based upon the results of a previous study with Sinetrol® Xpur (Dallas *et al.*, 2014). After 12 weeks of investigation, the study population (n = 95) showed a significant reduction in body fat of 3.6 ± 1.6 points difference (%) in the Sinetrol® Xpur group compared to 1.0 ± 0.7 points difference (%) in the placebo group; a result corresponding to a difference of 2.6 ± 0.1 between the groups.

Based on this result, the objective of the current study was to improve body composition by reaching a difference of total body fat variation (% BW) of at least -2.0 points within the Sinetrol® Xpur group after 16 weeks of supplementation as it was set for the primary outcome in the previous clinical study.

Since total body fat is significantly different between men and women in the general population, the use of a variance weighted by gender is required.

Given a significance level of 5%, a power of 80%, and a weighted variance of 2.82^2 = 7.95, a sample size of 32 subjects per group is required. Assuming a drop-out and failure rate of 40%, inclusion of 107 subjects was recommended.

3.6.2 Statistical analysis

Data was analysed using statistical package SPSS v20.0 for MAC. A descriptive analysis of the variables was performed to provide the mean, standard deviation, maximum and minimum ranges. Subsequently, an exploratory analysis of sample normality was performed with the Kolmogorov-Smirnov test and both Liliefors and Shapiro-Wilk tests for significance correction. A study of variables homoscedasticity and heteroscedasticity has also been performed.

The differences between groups and the effect of time were evaluated with a student t-test General Linear Model (pairwise comparison) in order to determine the intra- and inter-group differences. The level of significance was set at $p \leq 0.05$.

4. STUDY SUBJECTS

4.1 Disposition of subjects

During the length of time between March 2015 and September 2016, 107 subjects were enrolled.
58 subjects (58 of 107; 54%) were assigned to the Sinetrol® Xpur arm and 49 subjects (49 of 107; 46%) to the placebo arm.

4.1.1 Activity level at the beginning of the study (VCAS)

At the beginning of the study, all subjects declared to practice either no physical activity or to practice less than 1 time per week.

4.1.2 Recommended and reported calorie intake (VCAS)

At the beginning of the study, there were no significant differences in the VCAS population between the placebo and the Sinetrol® Xpur groups for the recommended calorie intakes ($p = 0.768$).

Recommended intake (kcal)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	2097	308	1593	2051	2860
Sinetrol® Xpur	43	2107	333	1593	2026	2860
Placebo	34	2086	276	1655	2053	2579
p-value		0.768				

There were also no significant differences in the VCAS population at the beginning of the study between the placebo and the Sinetrol® Xpur groups in regard to reported calorie intake ($p = 0.078$).

Reported intake (kcal)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	1881	507	341	1825	3316
Sinetrol® Xpur	43	1971	521	341	1952	3316
Placebo	34	1759	470	1019	1688	3107
p-value		0.078				

4.2 Dropouts and protocol deviations

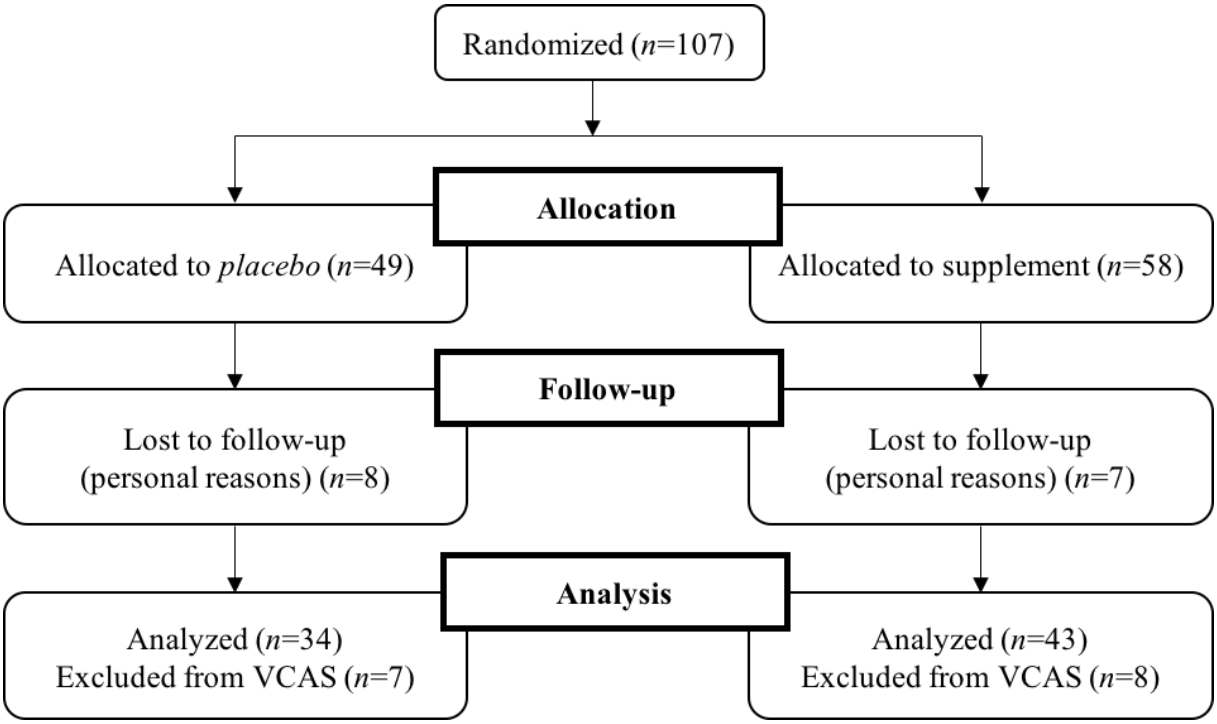
4.2.1 Dropouts

The dropout rate was 14.0% or 15 volunteers: 7 within the Sinetrol® Xpur-supplemented group (3 females and 4 males), and 8 within the placebo-supplemented group (5 females and 3 males) dropped out for personal reasons and were excluded from the VCAS population.

4.2.2 Protocol deviations

15 subjects were excluded from the VCAS population, 8 within the Sinetrol® Xpur-supplemented group (3 females and 5 males) and 7 within the placebo-supplemented group (3 females and 4 males) because of protocol deviations such as inconsistency of the DXA measurement or non-compliance to the protocol. These volunteers were excluded from the VCAS population.

4.2.3 VCAS population: CONSORT Flow Chart



5. BENEFIT EVALUATION

5.1 Data sets analyzed

According to dropouts and protocol deviations, a total of 30 subjects were excluded from the VCAS.

	TOTAL		Sinetrol® Xpur group		Placebo group	
	Number	Percentage	Number	Percentage	Number	Percentage
Study population	107	100%	58	54%	49	46%
VCAS	77	72%	43	56%	34	44%

5.2 Baseline characteristics

5.2.1 Age

There was no statistical difference in the VCAS population for age distribution between the Sinetrol® Xpur and the placebo group (p = 0.197).

Age (years)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	41.2	5.5	29	41	52
Sinetrol® Xpur	43	42.0	5.1	31	41	50
Placebo	34	40.3	5.9	29	40	52
p-value		0.197				

5.2.2 Gender

There was no statistical difference in the VCAS population for gender distribution between the Sinetrol® Xpur and the placebo group ($p = 0.685$).

Gender	*N*	Male		Female	
		Number	Percentage	Number	Percentage
TOTAL	77	36	47%	41	53%
Sinetrol® Xpur	43	21	49%	22	51%
Placebo	34	15	44%	19	56%
p-value	0.685				

5.2.3 Height

There was no statistical difference in the VCAS population for body height between the Sinetrol® Xpur and the placebo group ($p = 0.307$).

Height (m)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	169.3	9.3	150.6	167	192.0
Sinetrol® Xpur	43	170.2	10.4	150.6	169	192.0
Placebo	34	168.0	7.6	156.6	166	187.3
p-value		0.307				

5.2.4 Body weight at inclusion

There was no statistical difference in the VCAS population for body weight between the Sinetrol® Xpur and the placebo group ($p = 0.930$).

Body weight (kg)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	89.2	13.2	63.9	90.5	122.8
Sinetrol® Xpur	43	89.0	14.1	63.9	90.8	122.8
Placebo	34	89.3	12.2	67.7	88.7	115.6
p-value		0.930				

5.2.5 BMI at inclusion

There was no statistical difference in the VCAS population for BMI between the Sinetrol® Xpur and the placebo group ($p = 0.423$).

BMI (kg/m^2)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	30.0	3.7	24.6	29.3	39.9
Sinetrol® Xpur	43	29.7	4.0	24.6	28.4	39.9
Placebo	34	30.3	3.3	24.6	30.1	38.4
p-value		0.423				

5.2.6 Theoretical fat mass at inclusion

There was no statistical difference in the VCAS population for theoretical fat mass between the Sinetrol® Xpur and the placebo group ($p = 0.282$).

Theoretical FM (g)	*N*	Mean	SD	Min	Median	Max
TOTAL	77	32633	10033	17104	30333	64218
Sinetrol® Xpur	43	32042	9604	17104	30333	60873
Placebo	34	33382	10650	21574	29838	64218
p-value		0.282				

5.3 Benefit results

5.3.1 Primary outcome: Total body fat percentage loss (%BW)

At baseline (W_1), there was no statistical difference in the VCAS population in regard to total body fat mass (%BW) between the Sinetrol® Xpur and the placebo group ($p = 0.759$). At the end of the study (W_{16}), there was no statistical difference in the VCAS population for the total body fat mass (%BW) between the Sinetrol® Xpur and the placebo group ($p = 0.119$).

Regarding intragroup significance, there was no statistical difference for the total body fat mass (%BW) between W_1 and W_{16} in the placebo group ($p = 0.427$), while a statistical difference between W_1 and W_{16} was found in the Sinetrol® Xpur group ($p = 0.0003$).

The objective was to reach a –2.0 points total body fat mass (%BW) variation between W_1 and W_{16} in the Sinetrol® Xpur group. In the present study, a variation of -2.0 points was obtained; delta between both groups is statistically significant ($p = 0.016$).

Total body fat	W_1 (%BW)	W_{16} (%BW)	*p*-value (intragroup)	Delta W_1-W_{16} (%BW)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	38.7±8.4	36.7±8.5	0.0003*	- 2.0±3.5	- 5.2
Placebo	39.4±9.3	39.2±9.7	0.427	- 0.1±3.9	- 0.5
p-value (intergroup)	0.759	0.119		0.016*	

5.3.2 Secondary outcome: Body weight variation

At baseline (W_1), there was no statistical difference in the VCAS population regarding the body weight between the Sinetrol® Xpur and the placebo group ($p = 0.930$). At the end of the study (W_{16}), no statistical difference in the VCAS population regarding the body weight was found between the Sinetrol® Xpur and the placebo group ($p = 0.355$).

Regarding intragroup significance, no statistical difference for body weight between W_1 and W_{16} was found in the placebo group ($p = 0.338$), while a statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group ($p = 0.015$) was evident with a mean body-weight loss of 1.1 kg (-1.2%).

Body weight (kg)	W_1 (kg)	W_{16} (kg)	*p*-value (intragroup)	Delta W_1-W_{16} (kg)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	89.0±14.1	87.9±13.8	0.015*	- 1.1±3.2	- 1.2
Placebo	89.3±12.2	89.1±12.5	0.338	- 0.2±3.1	- 0.2
p-value (intergroup)	0.930	0.355		0.117	

5.3.3 Secondary outcome: BMI variation

At baseline (W_1), there was no statistical difference in the VCAS population regarding the BMI between the Sinetrol® Xpur and the placebo group ($p = 0.358$). At the end of the study (W_{16}), no statistical difference was evident in the VCAS population for the BMI between Sinetrol® Xpur and the placebo group ($p = 0.112$).

Regarding intragroup significance, there was no statistical difference for BMI between W_1 and W_{16} in the placebo group ($p = 0.311$) while a statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group ($p = 0.023$) was evident with a mean BMI loss of -0.4 kg/m^2 (-1.0%).

BMI (kg/m^2)	W_1 (kg/m^2)	W_{16} (kg/m^2)	*p*-value (intragroup)	Delta W_1-W_{16} (kg/m^2)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	30.7±4.4	30.4±4.3	0.023*	-0.4±1.2	-1.0
Placebo	31.6±4.0	31.5±3.9	0.311	-0.1±1.1	-0.3
p-value (intergroup)	0.358	0.112		0.154	

5.3.4 Secondary outcome: Total body lean mass variation

At baseline (W_1), there was no statistical difference in the VCAS population regarding the total body lean mass between the Sinetrol® Xpur and placebo group ($p = 0.785$). At the end of the study (W_{16}), no statistical difference in the VCAS population regarding the total body lean mass was found between the Sinetrol® Xpur and placebo group ($p = 0.278$).

Regarding intragroup significance, there was no statistical difference for total body lean mass between W_1 and W_{16} in the placebo group ($p = 0.362$), while a statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group ($p = 0.006$) was found with a mean increase in total body lean mass of 0.7 kg (+1.4%).

Total body lean mass (g)	W_1 (g)	W_{16} (g)	*p*-value (intragroup)	Delta W_1-W_{16} (g)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	51810±12529	52518±12401	0.006*	+708±1746	+1.4
Placebo	51077±10438	50944±10429	0.362	-132±2168	-0.3
p-value (intergroup)	0.785	0.278		0.032*	

5.3.5 Secondary outcome: Total body fat mass variation

At baseline (W_1), there was no statistical difference in the VCAS population regarding the total body fat mass between the Sinetrol® Xpur and the placebo group ($p = 0.629$). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding total body fat mass between the Sinetrol® Xpur and the placebo group ($p = 0.104$).

Regarding intragroup significance, there was no statistical difference for total body fat mass between W_1 and W_{16} in the placebo group ($p = 0.444$) while a statistical difference became evident between W_1 and W_{16} in the Sinetrol® Xpur group ($p = 0.0002$) with a mean total reduction in body-fat of 1.8 kg (-5.2%).

Total body fat mass (g)	W_1 (g)	W_{16} (g)	*p*-value (intragroup)	Delta W_1-W_{16} (g)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	34201±8284	32411±8199	0.0002*	-1789±2996	-5.2
Placebo	35236±10412	35152±10761	0.444	-83±3413	-0.2
p-value (intergroup)	0.629	0.104		0.011*	

5.3.6 Secondary outcome: Beneficial variation of body composition

Beneficial variation of body composition refers to the variation between delta fat mass minus delta lean mass.

While there was no change in beneficial variation of body composition in the placebo group (+0.049 kg), the Sinetrol® Xpur group showed a beneficial variation of–2.5 kg after 16 weeks of supplementation; the delta between both groups is statistically significant (*p*=0.005).

Delta fat mass – delta lean mass (g)	Delta W_1-W_{16} (g)
Sinetrol® Xpur	-2498±3737
Placebo	+49±4821
p-value (intergroup)	0.005*

5.3.7 Secondary outcome: Lean-to-fat mass ratio

At baseline (W_1), there was no statistical difference in the VCAS population regarding the lean-to-fat mass ratio between the Sinetrol® Xpur and placebo group ($p = 0.881$). At the end of the study (W_{16}), no statistical difference was shown in the VCAS population for the lean-to-fat mass ratio between the Sinetrol® Xpur and placebo group ($p = 0.254$).

Regarding intragroup significance, no statistical difference for the lean-to-fat mass ratio between W_1 and W_{16} was found in the placebo group ($p = 0.234$), while a statistical difference was clearly evident between W_1 and W_{16} in the Sinetrol® Xpur group ($p = 0.00004$) with an increase in the mean lean-to-fat mass ratio of 0.13 (+8.1%).

LM/FM	W_1	W_{16}	*p*-value (intragroup)	Delta W_1-W_{16}	Delta W_1-W_{16} (%)
Sinetrol® Xpur	1.61±0.6	1.74±0.7	0.00004*	+0.13±0.19	+8.1
Placebo	1.59±0.6	1.63±0.8	0.234	+0.04±0.31	-2.5
p-value (intergroup)	0.881	0.254		0.064	

5.3.8 Secondary outcome: Percentage excess FM vs theoretical FM

At baseline (W_1), there was no statistical difference in the VCAS population in regard to the percentage of excess FM vs theoretical FM between the Sinetrol® Xpur and the placebo group ($p = 0.465$). At the end of the study (W_{16}), no statistical difference in the VCAS population for the percentage excess FM vs theoretical FM was evident between Sinetrol® Xpur and the placebo group ($p = 0.230$).

Regarding intragroup significance, there was no statistical difference for percentage of excess FM vs theoretical FM between W_1 and W_{16} in the placebo group ($p = 0.416$), while a statistical difference became evident between W_1 and W_{16} in the Sinetrol® Xpur group ($p = 0.0002$) with a mean percentage decrease of excess FM vs theoretical FM of 5.7 points (-63.3% of the excess fat mass).

Percentage excess FM *vs* theoretical FM	W_1 (%)	W_{16} (%)	*p*-value (intragroup)	Delta W_1-W_{16}	Delta W_1-W_{16} (%)
Sinetrol® Xpur	9.0±15.4	3.3±16.9	0.0002*	-5.7±9.7	-63.3
Placebo	6.6±13.1	6.2±16.4	0.416	-0.4±11.4	-6.1
p-value (intergroup)	0.465	0.230		0.015*	

5.3.9 Secondary outcome: ICO (Index of Central Obesity) variation

At baseline (W_1), there was no statistical difference in the VCAS population for the ICO between the Sinetrol® Xpur and the placebo group ($p = 0.577$). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding the ICO between the Sinetrol® Xpur and the placebo group ($p = 0.117$).

Regarding intragroup significance, there was no statistical difference for ICO between W_1 and W_{16} in the placebo group ($p = 0.234$) while a statistical difference between W_1 and W_{16} was found in the Sinetrol® Xpur group ($p = 0.023$) with a mean ICO reduction of 0.006 points (-1.1%).

ICO (points)	W_1 (points)	W_{16} (points)	*p*-value (intragroup)	Delta W_1-W_{16} (points)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	0.553±0.06	0.547±0.06	0.023*	-0.006±0.02	-1.1
Placebo	0.561±0.05	0.563±0.05	0.234	+0.002±0.01	+0.4
p-value (intergroup)	0.577	0.117		0.025*	

5.3.10 Secondary outcome: Waist circumference variation

At baseline (W_1), there was no statistical difference in the VCAS population for waist circumference between Sinetrol® Xpur and the placebo group (p = 0.980). At the end of the study (W_{16}), no statistical difference in the VCAS population for waist circumference was evident between the Sinetrol® Xpur and the placebo group (p = 0.266).

Regarding intragroup significance, no statistical difference was found for waist circumference between W_1 and W_{16} in the placebo group (p = 0.235) while a statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.018) became evident with a mean reduction in waist circumference of 1.1cm (-1.3%).

Waist circumference (cm)	W_1 (cm)	W_{16} (cm)	p-value (intragroup)	Delta W_1-W_{16} (cm)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	94.2±11.3	93.0±10.8	0.018*	-1.1±3.4	-1.3
Placebo	94.2±9.9	94.5±9.6	0.235	+0.3±2.2	+0.3
p-value (intergroup)	0.980	0.266		0.020*	

5.3.11 Secondary outcome: Hip circumference variation

At baseline (W_1), no statistical difference was found in the VCAS population regarding hip circumference between the Sinetrol® Xpur and placebo group (p = 0.384). At the end of the study (W_{16}), there was no statistical difference in the VCAS population for hip circumference between Sinetrol® Xpur and the placebo group (p = 0.080).

Regarding intragroup significance, there was no statistical difference for hip circumference between W_1 and W_{16} in the placebo group (p = 0.159) while a statistical difference was found between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.002) with a mean reduction in hip circumference of 1.2 cm (-1.2%).

Hip circumference (cm)	W_1 (cm)	W_{16} (cm)	p-value (intragroup)	Delta W_1-W_{16} (cm)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	109.0±7.2	107.7±6.7	0.002*	-1.2±2.6	-1.2
Placebo	110.5±8.2	110.1±8.0	0.159	-0.4±2.2	-0.4
p-value (intergroup)	0.384	0.080		0.070	

5.3.12 Secondary outcome: Resting Energy Expenditure (REE)

At baseline (W_1), no statistical difference in the VCAS population regarding the REE between the Sinetrol® Xpur and placebo group (p = 0.695) was found. At the end of the study (W_{16}), there was no statistical difference in the VCAS population for the REE between the Sinetrol® Xpur and the placebo group (p = 0.174).

Regarding intragroup significance, there was no statistical difference for REE between W_1 and W_{16} in the placebo group (p = 0.459) while a statistical difference between W_1 and W_{16} was found in the Sinetrol® Xpur group (p = 0.012) with a mean increase in REE of 181 kcal/d (+10.1%).

REE (kcal/d)	W_1 (kcal/d)	W_{16} (kcal/d)	p-value (intragroup)	Delta W_1-W_{16} (kcal/d)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	1794±476	1976±495	0.012*	+181±425	+10.1
Placebo	1841±355	1849±473	0.459	+8±376	+0.4
p-value (intergroup)	0.695	0.174		0.063	

5.3.13 Secondary outcome: Metabolic parameters

5.3.13.1 Fibrinogen

At baseline (W_1), there was no statistical difference in the VCAS population regarding the concentration of fibrinogen between the Sinetrol® Xpur and the placebo group (p = 0.073). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding the fibrinogen concentration between the Sinetrol® Xpur and the placebo group (p = 0.169).

Regarding intragroup significance, no statistical difference for fibrinogen concentration between W_1 and W_{16} was shown in the placebo group (p = 0.067) while a statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.001) became evident with a mean reduction in the concentration of fibrinogen of 21 mg/dL (-5.7%).

Fibrinogen (mg/dL)	W_1 (mg/dL)	W_{16} (mg/dL)	p-value (intragroup)	Delta W_1-W_{16} (mg/dL)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	387±58	365±68	0.001*	-21±42	-5.7
Placebo	360±63	381±66	0.067	+21±73	+5.8
p-value (intergroup)	0.073	0.169		0.001*	

5.3.13.2 Free Fatty Acids (FFAs)

At baseline (W_1), there was no statistical difference in the VCAS population regarding the concentration of FFAs between the Sinetrol® Xpur and the placebo group (p = 0.715). At the end of the study (W_{16}), no statistical difference was shown in the VCAS population regarding the concentration of FFAs between the Sinetrol® Xpur and placebo group (p = 0.075).

Regarding intragroup significance, no statistical difference for the concentration of FFAs was evident between W_1 and W_{16} in the placebo group (p = 0.146) while a statistical difference was found between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.009) with a mean increase in the concentration of FFAs of 0.16 mmol/L (+15.1%).

FFAs (mmol/L)	W_1 (mmol/L)	W_{16} (mmol/L)	p-value (intragroup)	Delta W_1-W_{16} (mmol/L)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	1.06±0.40	1.22±0.35	0.009*	+0.16±0.41	+15.1
Placebo	1.03±0.44	1.10±0.36	0.146	+0.07±0.34	+6.8
p-value (intergroup)	0.715	0.075		0.176	

5.3.13.3 Leptin

At baseline (W_1), there was no statistical difference in the VCAS population regarding the leptin concentration between the Sinetrol® Xpur and the placebo group (p = 0.997). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding the leptin concentration between the Sinetrol® Xpur and the placebo group (p = 0.254).

Regarding intragroup significance, there was no statistical difference for leptin concentration between W_1 and W_{16} in the placebo group (p = 0.080), and no statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.261).

Leptin (ng/mL)	W_1 (ng/mL)	W_{16} (ng/mL)	p-value (intragroup)	Delta W_1-W_{16} (ng/mL)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	9.06±6.60	8.68±7.31	0.261	-0.38±3.83	-4.2
Placebo	9.05±7.47	9.87±7.36	0.080	+0.82±2.98	+9.1
p-value (intergroup)	0.997	0.254		0.084	

5.3.13.3 Adiponectin

At baseline (W_1), no statistical difference in the VCAS population regarding the concentration of adiponectin was evident between the Sinetrol® Xpur and the placebo group (p = 0.999). At the end of the study (W_{16}), there was no statistical difference in the VCAS population regarding the adiponectin concentration between the Sinetrol® Xpur and the placebo group (p = 0.397).

Regarding intragroup significance, there was no statistical difference for adiponectin concentration between W_1 and W_{16} in the placebo group (p = 0.161), and no statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.415).

Adiponectin (µg/mL)	W_1 (µg/mL)	W_{16} (µg/mL)	p-value (intragroup)	Delta W_1-W_{16} (µg/mL)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	20.19±14.50	20.45±17.33	0.415	-0.26±7.79	+1.3
Placebo	20.20±14.11	19.25±13.06	0.161	-0.95±4.88	-4.7
p-value (intergroup)	0.999	0.397		0.238	

5.4 Follow-up of protocol requirements

5.4.1 Recommended and reported dietary intake

At baseline (W_1), there was no statistical difference in the VCAS population regarding the recommended dietary intake between the Sinetrol® Xpur and the placebo group (p = 0.768). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding the recommended dietary intake between the Sinetrol® Xpur and the placebo group (p = 0.906).

Regarding intragroup significance, there was no statistical difference for recommended intake between W_1 and W_{16} in the placebo group (p = 0.383) while a statistical difference between W_1 and W_{16} was found in the Sinetrol® Xpur group (p = 0.012) with a mean reduction in the recommended dietary intake of 15 kcal/d.

Recommended intake (kcal)	W_1 (kcal)	W_{16} (kcal)	p-value (intragroup)
Sinetrol® Xpur	2107±333	2092±329	0.012*
Placebo	2086±276	2084±281	0.383
p-value (intergroup)	0.768	0.906	

At baseline (W_1), there was no statistical difference in the VCAS population regarding the reported dietary intake between the Sinetrol® Xpur and the placebo group (p = 0.078). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding the reported dietary intake between the Sinetrol® Xpur and the placebo group (p = 0.440).

Regarding intragroup significance, there is a statistical difference for reported dietary intake between W_1 and W_{16} in the placebo group (p = 0.015) while there is no statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.194).

Reported intake (kcal)	W_1 (kcal)	W_{16} (kcal)	p-value (intragroup)
Sinetrol® Xpur	1971±521	1904±508	0.194
Placebo	1759±470	1885±522	0.015*
p-value (intergroup)	0.078	0.440	

Comparing the recommended intake and the reported intake at baseline (W_1), the Sinetrol® Xpur group intake is 6.5% lower than the recommendation, while the placebo group is 15.7% lower; however, at the end of the study (W_{16}), the reported intake within the placebo group is only 9.5% lower than the recommendation, which is less than a 10% difference and thus acceptable. The Sinetrol® Xpur group intake, at the end of the study, is 9.0% lower than the recommended intake which is still an acceptable difference.

5.4.2 Daily steps variation (pedometer)

At baseline (W_1), no statistical difference in the VCAS population regarding the mean daily steps was evident between the Sinetrol® Xpur and placebo group (p = 0.449). At the end of the study (W_{16}), no statistical difference was found in the VCAS population regarding the mean daily steps between the Sinetrol® Xpur and the placebo group (p = 0.481).

Regarding intragroup significance, there was no statistical difference for mean daily steps between W_1 and W_{16} in the placebo group (p = 0.130), and no statistical difference between W_1 and W_{16} in the Sinetrol® Xpur group (p = 0.399).

Taken together, the level of physical activity, assessed with recording of daily steps, is stable throughout the course of the study with no significant differences, both between and within groups.

Daily steps (steps)	W_1 (steps/day)	W_{16} (steps/day)	*p*-value (intragroup)	Delta W_1-W_{16} (steps/day)	Delta W_1-W_{16} (%)
Sinetrol® Xpur	7236±2289	7310±2682	0.399	+74±1859	+1.0
Placebo	6826±2267	7280±2612	0.130	+455±2202	+6.7
p-value (intergroup)	0.449	0.481		0.213	

6. SAFETY EVALUTION

6.1 Clinical laboratory values

6.1.2 Liver function parameters

There was no clinically significant difference within and between the Sinetrol® Xpur and the placebo group for liver function parameters; all were within the healthy range at baseline (W_1) and at the end of the study (W_{16}).

Alanine transaminase (ALT)	W_1 (U/L)	W_{16} (U/L)	*p*-value (intragroup)	Delta W_1–W_{16} (U/L)	Delta W_1–W_{16} (%)
Reference values*	7 to 55 U/L				
Sinetrol® Xpur	26.0±12.9	22.6±11.7	0.013*	-3.4±9.8	-13.1
Placebo	21.5±8.7	20.9±8.2	0.330	-0.6±7.2	-2.8
p-value (intergroup)	0.107	0.253		0.097	
Aspartate aminotransferase (AST)	W_1 (U/L)	W_{16} (U/L)	*p*-value (intragroup)	Delta W_1–W_{16} (U/L)	Delta W_1–W_{16} (%)
Reference values*	8 to 48 U/L				
Sinetrol® Xpur	21.4±5.3	20.6±8.2	0.256	-0.8±8.1	-3.7
Placebo	20.1±5.5	19.5±4.2	0.271	-0.6±5.5	-3.0
p-value (intergroup)	0.324	0.252		0.461	
Gamma-Glutamyltransferase (GGT)	W_1 (U/L)	W_{16} (U/L)	*p*-value (intragroup)	Delta W_1–W_{16} (U/L)	Delta W_1–W_{16} (%)
Reference values*	6 to 48 U/L				
Sinetrol® Xpur	23.1±13.2	23.0±13.3	0.447	-0.1±6.8	-0.4
Placebo	19.5±12.0	20.2±12.1	0.212	+0.7±4.6	+3.6
p-value (intergroup)	0.247	0.189		0.282	

*www.mayoclinic.org

6.1.3 Renal function parameters

There was no clinically significant difference within and between the Sinetrol® Xpur and the placebo group for renal function parameters; all were within the healthy range at baseline (W_1) and at the end of the study (W_{16}).

Urea	W_1 (mg/dL)	W_{16} (mg/dL)	*p*-value (intragroup)	Delta W_1–W_{16} (mg/dL)	Delta W_1–W_{16} (%)
Reference values*	15 to 46 mg/dL				
Sinetrol® Xpur	31.7±7.9	31.8±8.2	0.483	0.0±7.3	0.3
Placebo	36.4±8.9	33.0±7.7	0.009*	-3.4±7.1	-9.3
p-value (intergroup)	0.025*	0.265		0.028*	
Creatinine	W_1 (mg/dL)	W_{16} (mg/dL)	*p*-value (intragroup)	Delta W_1–W_{16} (mg/dL)	Delta W_1–W_{16} (%)
Reference values*	0.6 to 1.3 mg/dL				
Sinetrol® Xpur	0.76±0.16	0.78±0.15	0.152	+0.02±0.10	+2.6
Placebo	0.81±0.18	0.75±0.16	0.011*	-0.06±0.13	-7.4
p-value (intergroup)	0.269	0.211		0.003*	
Sodium (Na)	W_1 (mmol/L)	W_{16} (mmol/L)	*p*-value (intragroup)	Delta W_1–W_{16} (mmol/L)	Delta W_1–W_{16} (%)
Reference values*	135 to 145 mmol/L				
Sinetrol® Xpur	140.8±3.4	140.6±2.3	0.391	-0.1±3.3	- 0.1
Placebo	141.2±1.3	141.2±2.1	0.467	0.0±2.3	- 0.0
p-value (intergroup)	0.510	0.152		0.442	
Potassium (K)	W_1 (mmol/L)	W_{16} (mmol/L)	*p*-value (intragroup)	Delta W_1–W_{16} (mmol/L)	Delta W_1–W_{16} (%)
Reference values*	3.6 to 5.2 mmol/L				
Sinetrol® Xpur	4.3±0.5	4.4±0.4	0.187	+0.1±0.4	+2.3
Placebo	4.3±0.3	4.3±0.2	0.417	0.0±0.4	0.0
p-value (intergroup)	0.777	0.199		0.340	

*www.mayoclinic.org

6.2 Heart rate

There was no significant difference within and between the Sinetrol® Xpur and the placebo group for resting heart rate at baseline (W_1) and at the end of the study (W_{16}).

Heart rate (b.p.m)	W_1 (b.p.m)	W_{16} (b.p.m)	*p*-value (intragroup)	Delta W_1–W_{16} (b.p.m)	Delta W_1–W_{16} (%)
Sinetrol® Xpur	70.8±9.1	70.6±8.8	0.449	-0.2±9.6	-0.3
Placebo	72.1±10.7	72.3±9.1	0.474	+0.1±7.6	+0.3
p-value (intergroup)	0.635	0.258		0.448	

6.3 Adverse events

Neither adverse events nor side effects were recorded throughout the course of the study.

7. OVERALL CONCLUSIONS

The intention of this investigation was to evaluate benefit — primarily as total body-fat loss — from a 16-week supplementation with Sinetrol® Xpur in a randomized double-blind, placebo-controlled study conducted in overweight and obese subjects. The primary endpoint was reached. The Sinetrol® Xpur-supplemented group showed a significant loss in body-fat mass (%BW; -2.0 points), while body-fat mass (%BW) of the placebo group remained stable after 16 weeks.

The secondary endpoints focused on the evaluation of the benefit of Sinetrol® Xpur on body composition (fat mass variation, lean mass variation, lean-to-fat mass ratio) and anthropometrics (waist and hip circumferences). All those secondary endpoints were significantly improved after 16 weeks of supplementation with Sinetrol® Xpur, whereas the placebo group failed to show any positive variation in the same parameters. Taken together, these results confirmed the weight management benefits of Sinetrol® Xpur which is able to positively rebalance body composition by decreasing body-fat mass while significantly increasing lean mass; thereby improving the lean-to-fat mass ratio. Linked-anthropometric parameters were all improved in the supplemented group while no positive shifts were seen within the placebo group.

In summary, it has been shown that supplementation with Sinetrol® Xpur within a 16-week period induces beneficial changes in body composition in positively rebalancing the total lean and fat mass. In addition, the supplementation did not induce any adverse nor side effects.

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APPENDICE

Abbreviations

BMI	Body Mass Index
BW	Body Weight
CVD	Cardiovascular Disease
DXA	Dual energy X-ray Absorptiometry
FFAs	Free Fatty Acids
FM	Fat Mass
ICO	Index of Central Obesity
LM	Lean Mass
NCD	Non Communicable Disease
REE	Resting Energy Expenditure
VCAS	Valid Case Analysis Set
SMM	Skeletal Muscle Mass

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