Original Article

A Comparative Analysis of the Pharmacodynamic and Pharmacokinetic Properties of 2 Controlled-Release Formulations Versus a Marketed Orlistat Product

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Abstract

A new modified-release oral formulation combines acarbose and orlistat (MR-OA) to enhance efficacy and reduce adverse effects through controlled drug release. This study aims to compare the pharmacodynamic properties of the orlistat component of MR-OA (MR-O) with a conventional orlistat product, Xenical (Conv-O), analyzing the percentage of fecal fat excretion. In addition, the pharmacokinetic properties of the complete formulation, MR-OA, were compared with Conv-O. In Part I of the study, 20 healthy volunteers were randomized in a single-blind, crossover trial to take MR-O or Conv-O (120-mg orlistat) 3 times daily for 9 days. Fecal fat was measured at baseline and after each treatment. MR-O and Conv-O similarly increased fecal fat percentage from 3.8% to 13.5%, confirming pharmacodynamic equivalence. Adverse events were few and generally rated as mild. In Part II, participants received MR-OA and then Conv-O, with blood samples collected for 12 hours to measure orlistat and acarbose levels. Orlistat's peak concentration stayed below 5 ng/mL, and acarbose plasma levels were mostly undetectable, indicating minimal systemic absorption. This shows that the new weight loss product MR-OA retains the dietary energy loss pathway used in Conv-O. Consistent with previous studies, minimal systemic absorption of orlistat and acarbose was observed for MR-OA, confirming that no significant alteration of the original substances occurs when modifying their release.

Keywords

local mode of action, modified-release, obesity treatment, orlistat, weight loss

In the growing market for obesity treatments, there is a demand for drug products that complement the current glucagon-like peptide-1 receptor agonists by offering a different mode of action.[1] "EMP16" is an oral capsule that uses modified-release and combines the 2 well-known drug substances orlistat and acarbose (MR-OA). The rationale for modifying the release of orlistat and acarbose is to enhance the efficacy of the treatment compared with the conventional dosage forms by controlling the site and extent of drug release, delaying the breakdown of fats and carbohydrates. This increase in efficacy has been demonstrated in two 6-month trials in which MR-OA treatment was associated with clinically significant weight loss along with additional improvements in secondary health outcomes.[2]

The next step was to show that bioequivalence to the conventional drug still was present despite the MR pattern used. Since orlistat (and acarbose) has limited systemic absorption, a conventional pharmacokinetic (PK) comparison to demonstrate bioequivalence

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Table 1. Dietary Fat Intake and Fecal Fat Excretion, Part I (n = 16)

Assessment (unit)	Run-in	MR-O	Conv-O
Dietary fat intake, relative energy (%/day)			
Mean (SD)	28.3 (2.76)	28.4 (2.33)	28.3 (2.28)
90% CI	(27.3-29.4)	(27.5-29.3)	(27.4-29.2)
Dietary fat intake, absolute amounts (g/day)			
Mean (SD)	54.0 (7.52)	52.4 (6.93)	52.6 (7.34)
90% CI	(51.1-56.9)	(49.6-55.1)	(49.8-55.4)
Fecal fat excretion (g/100 g)			
Mean (SD)	3.80 (1.83)	13.5 (3.84)	13.3 (4.81)
90% CI	(3.00-4.60)	(11.8-15.2)	(11.1-15.4)

CI, confidence interval; Conv-O, conventional orlistat; MR-O, orlistat component of modified-release orlistat and acarbose; SD, standard deviation.

Table 2. Orlistat in Blood Plasma, PK Parameters, Part II (n = 18)

Assessment (unit)	MR-OA	Conv-O
t_{max} (hour)		
Median (minimum, maximum)	5.0 (2.5, 6.5)	3.7 (1.0, 6.0)
C_{max} (ng/mL)		
Mean (SD)	5.13 (2.79)	1.35 (1.27)
Geometric mean (geometric CV%)	4.55 (52.8)	0.891 (123)
$AUC_{0\text{-last}}$ (ng•h/mL)		
Mean (SD)	11.8 (7.02)	3.37 (3.90)
$AUC_{0\text{-inf}}$ (ng•h/mL)		
Mean (SD)	12.0 (7.26)	3.85 (4.00)
$t_{\frac{1}{2}}$ (hour)		
Mean (SD)	0.768 (0.153)	0.822 (0.285)

$AUC_{0\text{-last}}$, area under the plasma concentration–time curve from time zero to the last measurable concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration–time curve from time zero to infinity; C_{max}, maximum plasma concentration; Conv-O, conventional orlistat; CV%, coefficient of variation described as a percentage calculated using log-transformed standard deviation; MR-O, orlistat component of modified-release orlistat and acarbose; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to maximum plasma concentration.

between MR-OA and conventional orlistat (Conv-O) would not provide meaningful data regarding the overall effect. Therefore, a pharmacodynamic (PD) variable, specifically the amount of fat not absorbed during digestion, was used to establish bioequivalence.

In addition, the trial explores the plasma concentrations of both orlistat and acarbose. It has been shown previously that the MR-OA has similar or even lower plasma concentrations of orlistat compared with Conv-O.[3] However, the PK profiles obtained in that study were incomplete, and no PK profile for acarbose was obtained.

Methods

Ethical Aspects

Ethics approval was granted as informed via submission to the European Medicines Agency Clinical Trial Information System. All study participants signed the consent form. The trial was registered at EudraCT (2023-505671-74-00). The clinical trial was performed by the contract research organization Clinical Trial Consultants in Uppsala, Sweden.

Study Design, Part I. The first part, that is, the PD comparison, was conducted in a single-blind, crossover fashion, where the orlistat component of modified-release orlistat and acarbose (MR-O) was compared with Conv-O.

Study Design, Part II

The second part explored the PK properties of MR-OA, both alone and in comparison with Conv-O, using an open-label, fixed-sequence design.

Study Participants

Healthy male or female participants aged 20-55 years with a body mass index of either 20-27 kg/m^2 or a BMI greater than 27 kg/m^2 and normal body fat composition (10%-25% for men and 20%-30% for women) at screening, stable weight (less than 5% self-reported change during the previous 3 months preceding screening), and with self-perceived normality in defecation habits were included (Tables 1 and 2). Additional inclusion criteria were based on medical history, physical findings, vital signs, electrocardiogram, and blood chemistry values at the time of screening.

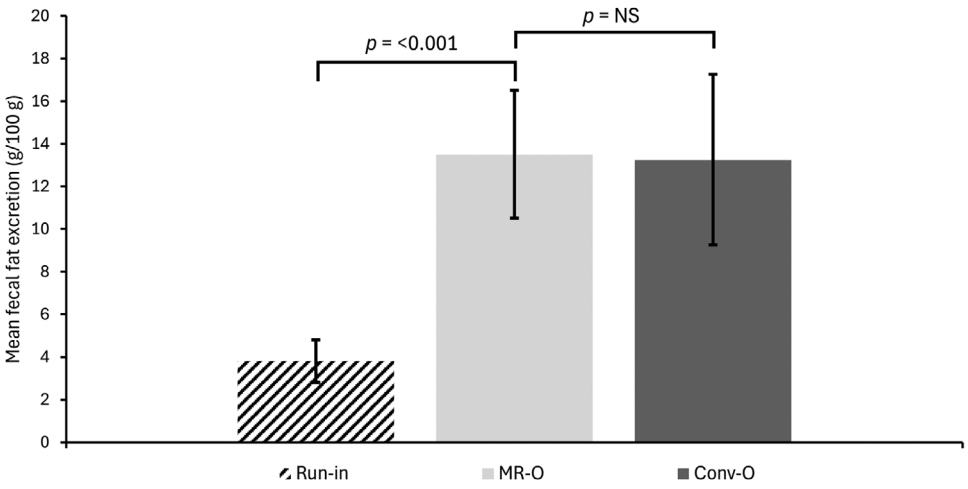

Figure 1. Part I, mean (±SD) 24-hour fecal fat excretion after a 5-day run-in period (baseline) and after treatment with MR-O or Conv-O (orlistat 120 mg) 3 times daily (n = 16). Conv-O, conventional orlistat; MR-O, orlistat component of modified-release orlistat and acarbose; NS, nonsignificant; SD, standard deviation.

Study Outline

Eligible and consenting participants arrived at the research clinic for a 5-day diet run-in baseline period. Following the baseline period, participants were randomized to 1 of 2 treatment sequences (MR-O → Conv-O or Conv-O → MR-O) in a single-blind fashion (Figure 1). The treatment periods were separated by a 4- to 14-day washout. Participants were provided with main meals as well as snacks, with 30% or less of the energy content from fat. Except for water, tea, and coffee, participants were not allowed to eat anything other than the food provided. Drug products were taken orally concomitant with the 3 main daily meals (fed state); these were either 1 of the dose strengths of the test product or the reference product. Each participant was instructed to take the drug product halfway through each meal. The single-unit capsules of MR-O and Conv-O had different strengths of orlistat: 60 and 120 mg, respectively. To maintain the blinding for the participants, the investigational medicinal products were administered as follows:

- MR-O 60-mg orlistat: 2 capsules 3 times daily
- Conv-O 120-mg orlistat: 1 capsule plus placebo 1 capsule 3 times daily

The PK part of the study started after a 4- to 14-day washout. Following an overnight fast of at least 8 hours and a light standardized breakfast upon admission (approximately 2 hours before dosing), MR-OA was taken halfway through a regular standardized breakfast (5 minutes after the start of the meal, which was expected to be finished in 10 minutes) with approximately 50-200 mL of water. No food was allowed until the standardized lunch (4 hours after dosing). Water, but no other drinks, was allowed ad libitum, except for 1 hour before and after each dose administration. After another 4- to 14-day washout, the participants returned and performed the same procedures with Conv-O.

The participants received a single dose of MR-OA (2 capsules each of 60-mg orlistat and 20-mg acarbose) and a single dose of Conv-O (1 capsule of 120-mg orlistat).

Lunch, dinner, and evening meals (optional) were served approximately 4, 8, and 12 hours after dosing at each visit.

Part I

Pharmacodynamic Analysis: 24-hour Fecal Collection. The participants performed a 24-hour fecal collection for measurement of percentage of fecal fat excretion during the last day of the diet run-in baseline period, as well as during the last day of each 9-day treatment session. Samples were handed in at the clinic after each 24-hour sample period.

A separate feces collection instruction manual was provided to the participants together with all collection materials needed. After each bowel movement, the bags were stored and refrigerated (2-8°C) until delivery to the trial site. The trial site stored the collection bags frozen (−18°C or less) until shipment (on dry ice) to the analyzing laboratory (Ardena Bioanalysis B.V.).

Fecal Fat Measurement. Human feces samples were obtained for the determination of fat (measured as glyceryl trioleate [triolein]) concentrations at predetermined time points as specified in the clinical protocol.

Triolein (Sigma–Aldrich) was used for the preparation of the quality control (QC) samples. The blank matrix used for the preparation of QC samples was a pool of human feces, 500 g, collected from individual healthy

volunteers, and with an addition of 1000 g of Ultrapure Water (UPW; Veolia/Millipore). This pool was homogenized for 3 minutes with an Ultra Turrax homogenizer (IKA-Werke). Aliquots of 30-75 g were weighed, and the portions were stored at −18°C or less.

The fecal study samples were saponified by boiling the samples in a concentrated ethanolic potassium hydroxide (Merck) solution under a reflux condenser. The soaps derived from the neutral fats and the fatty acids that were originally present in the feces samples constitute the end products of this saponification reaction. By acidifying the solution, the fatty acids were liberated, and they were subsequently extracted with petroleum ether (b.p. 40-60°C; Acros Organics). In an aliquot sample of the petroleum ether layer, the fatty acids were titrated with sodium hydroxide (Merck) using thymol blue (Fluka) (2% in 50% ethanol in UPW) as an indicator. The amount of sodium hydroxide added was directly proportional to the total fat content of the sample. The exact molarity of the sodium hydroxide solution was determined using a standard solution of hydrochloric acid (0.1 M; Merck). The millimoles of sodium hydroxide used for the titration of the fat content in the study sample per 100 g of feces was calculated. The results obtained by titration of the fatty acid fraction present in the sample accounts for the amount of fat present (g triolein/g feces) in each sample. The study samples were reported as g triolein/100 g feces. Assay: analytical range: 10.0-250 mg triolein/g feces; sample amount: 15.0 g homogenate (feces:UPW [1:2] corresponding to 5.0 g of feces); matrix: human feces.

Part II

Plasma PK. Venous blood samples (approximately 4 mL) for the determination of plasma concentrations and PK characterization of OA were collected through an indwelling venous catheter or by venipuncture at the prespecified visits and time points. All participants received MR-OA at Visit 11 and Conv-O at Visit 12, as presented in Figure 1. A 12-hour PK blood sampling session was performed each day for analysis of MR-OA and Conv-O plasma concentrations. Actual time for blood PK sampling could not deviate more than ±10% from the planned time, except that the predose PK sampling before the first dose could be performed within 60 to 15 minutes before dosing.

The blood samples were collected in prelabeled dipotassium ethylenediaminetetraacetic acid tubes. The collected samples were centrifuged at 2000 g at 4 °C for 10 minutes within 60 minutes of sampling. Both blood samples and plasma were kept cold and handled on ice until frozen. The separated plasma from each blood sample was frozen at 80°C within 1 hour of centrifugation.

Plasma samples for determination of plasma concentrations of OA were analyzed by Lablytica Life Science AB, Uppsala, Sweden, by means of a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method.

Orlistat Assay. Protein precipitation was performed on the study samples using 5% acetonitrile. After centrifugation, the samples were loaded onto the ultra-high-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) system, and an aliquot of the supernatant was injected into a reversed-phase C18 analytical column (Acquity UPLC CSH Phenyl-Hexyl [50×2.1 mm, 1.7 µm], Waters). Mobile phase A was 2 mM of ammonium acetate in water and mobile phase B was acetonitrile used in a gradient elution.

Detection of the analyte was performed using multiple reaction monitoring on a UPLC-MS/MS System Xevo TQ-S (Waters). The first quadrupole was set to m/z 496.5 and the third quadrupole was set to m/z 319.4, with a cone voltage of 33 V and a collision energy of 12 eV. Ethanol was used as the needle wash for the i-Class FTN autosampler (Waters). The calibration was performed in the range of 0.050-50.0 ng/mL for orlistat in human plasma. Eight calibration samples and sets of QC samples at 3 levels were prepared by spiking known amounts of orlistat into blank matrix. The calibration and QC samples were then extracted in duplicate for each analytical run and analyzed together with the study samples.

Acarbose Assay. Protein precipitation was performed on the study samples using 20% trichloroacetic acid in water. After centrifugation, the samples were loaded onto the UPLC-MS/MS system, and an aliquot of the supernatant was injected onto a reversed phase C18 analytical column (Acquity Premier HSS T3 [50×2.1 mm, 1.8 µm], Waters). Mobile phase A was 0.1% formic acid in water, and mobile phase B was acetonitrile used in a gradient elution.

Detection of the analyte was performed using multiple reaction monitoring on a UPLC-MS/MS System Xevo TQ-D (Waters). The first quadrupole was set to m/z 646.3 and the third quadrupole was set to m/z 304.2, with a cone voltage of 44 V and a collision energy of 24 eV. Thirty percent methanol in Milli-Q water was used as the needle wash for the i-Class FTN (Waters) autosampler. The calibration was performed in the range of 5.00-5000 ng/mL for acarbose in human plasma. Eight calibration samples and sets of QC samples at 3 levels were prepared by spiking known amounts of acarbose into blank matrix. The calibration and QC samples were then extracted in duplicate for each analytical run and analyzed together with the study samples.

Pharmacokinetic Data Analysis. The PK analysis was based on the PK analysis set and performed by Clinical Trial Consultants in Uppsala, Sweden. The following noncompartmental PK parameters were assessed: area under the plasma concentration–time curve (AUC) from time zero to the last measurable concentration (AUC0–last), AUC from time zero to infinity, maximum plasma concentration (C_{max}), time to C_{max}, and half-life. PK concentrations and parameters were summarized descriptively.

Statistical Analysis. No formal sample size calculation was performed for this trial. The proposed sample size was considered sufficient to provide adequate information to meet the trial objectives based on a previous trial.[4] The aim was to have at least 16 evaluable participants in each part.

The bioequivalence between MR-O and Conv-O in terms of fecal fat excretion was assessed using analysis of covariance. A model with the logarithm of the percentage of fecal fat excretion as the dependent variable was estimated. In the model, 3 parameters were included as fixed effects: treatment, period, and treatment sequence. Participant was included as a random effect. Also, the baseline value of percentage of fecal fat excretion from the end of the run-in period at Visit 3 was included as a covariate in the model. The least-squares difference of the treatment effect was back-transformed to present the ratio of geometric means with the 90% confidence interval (CI) of percentage of fecal fat excretion for the doses of MR-O and Conv-O.

The null hypothesis was that MR-O and Conv-O are nonequivalent, and the alternative hypothesis was that MR-O and Conv-O are equivalent in terms of percentage of fecal fat excretion.

The relative bioavailability of MR-OA versus Conv-O (orlistat) in terms of $AUC_{0\text{-last}}$ and C_{max} was evaluated by using log-transformed $AUC_{0\text{-last}}$ and C_{max}, respectively, in a paired 2-sample t-test. The difference between MR-OA and the comparator Conv-O was back-transformed to the original scale to present test/reference treatment least-square mean ratios with the corresponding 90% CI. The point estimate of the ratio and CI provided an exploratory assessment of relative bioavailability.

All descriptive summaries and statistical analyses were performed using SAS Version 9.4 (SAS Institute).[5] The PK parameters were calculated by noncompartmental analysis using the software Phoenix WinNonlin Version 8.3 (Certara).[6]

Results

Twenty healthy volunteers were randomized in Part I of the trial. Eighteen of these participants completed Part I, and 17 continued in Part II. Of the 3 participants who did not enter Part II, 2 withdrew consent during Part I, and 1 withdrew consent after completion of Part I. One participant was replaced by another (selected from 2 additional screened candidates) who completed only Part II, resulting in a total of 18 participants finishing Part II (Figure S1).

In Part I, 3 participants were excluded: 2 due to incomplete fecal collections and 1 due to a major deviation in food intake. Of the remaining 17 participants, 1 had aberrant data, leaving data from 16 participants for the result calculations in Part I.

Of all the participants included, 17 were White individuals, and 3 were of Asian heritage. Baseline characteristics are presented in Table S1.

The mean relative and absolute fat content of the diet were the same during baseline and the 2 crossover periods (Table 1).

Pharmacodynamic Results, Part I

The mean fecal fat percentage at baseline was 3.80% (standard deviation [SD], 1.83) and increased to 13.5% (SD, 3.84) for MR-O and 13.3% (SD, 4.81) for Conv-O (Figure 1 and Table 1). Using analysis of covariance, the ratio of geometric means for MR-O/Conv-O was 1.03 (or 103%), with 90% CIs ranging from 0.91 to 1.16.

Pharmacokinetic Results, Part II

Orlistat plasma concentrations were low after both treatments (Table 2). The exposure of orlistat, in terms of both C_{max} and AUC, was consistently higher after administration of MR-OA than after administration of Conv-O (Figure 2). The interindividual variation in orlistat plasma concentrations was high after administration of both drugs.

Acarbose plasma concentration was below the lower limit of quantification of 5 ng/mL for all but 1 sample (5.15 ng/mL at time point 3.3 hours after dosing), so no PK calculations were performed.

Safety Results

Nine days of treatment with MR-O and Conv-O, respectively, as well as single-dose treatment with MR-OA and Conv-O, were safe and well tolerated as assessed by reported adverse events (AEs). A majority of the AEs (43/47) were assessed as mild in intensity, and the remaining 4 AEs were moderate (Tables S2 and S3). Flatulence was the most common AE associated with all treatments (Table S4).

Discussion

This study demonstrated that MR-O and Conv-O were bioequivalent in terms of percentage of fecal fat excretion at steady state for orlistat. Additionally, both orlistat and acarbose showed low systemic exposure, further confirming their safety profiles.

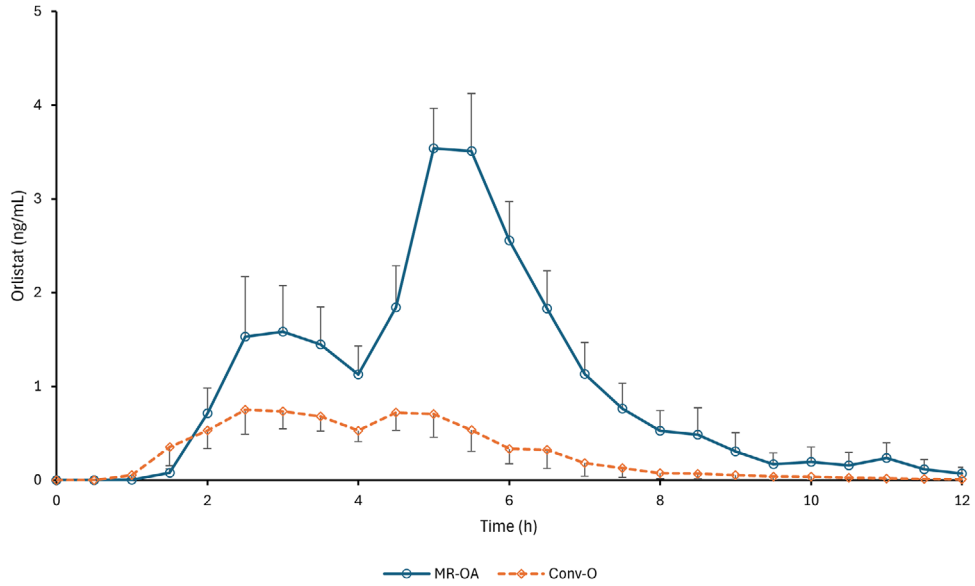

Figure 2. Part II, mean (±SE) orlistat plasma concentrations over time (linear-linear) (n = 18). Solid line and circle points: MR-OA, dashed line and diamond points: Conv-O. Conv-O, conventional orlistat; MR-OA, modified-release orlistat and acarbose; SE, standard error.

The levels of fat excreted in the feces observed in this study are similar to those reported in other studies, both at baseline and following orlistat treatment.[7,8] The amount of fat excreted serves as a quantitative measure of the total inhibition of dietary fat absorption.[7] Orlistat in its conventional form affects lipid metabolism in both the stomach and the intestine, where the latter is the main target for orlistat, as digestion of dietary fat is mainly influenced by the pancreatic lipase.[9] However, in the stomach, orlistat's inhibition of fat digestion seems sufficient to decrease fatty acid release in the duodenum and subsequently lower cholecystokinin secretion.[10] This decrease in cholecystokinin has then been shown to increase appetite.[11,12] When orlistat enters the duodenum, the bile "activates" it, enhancing its ability to inhibit lipases more effectively. In a previous study, it was shown that the MR pattern used in MR-OA had a favorable effect on appetite compared with Conv-O,[13] possibly an effect of the modified release of orlistat. Altering the release of orlistat to mainly target the pancreatic lipase and avoid inhibiting gastric lipase seems to have the same overall lipase inhibition, as the same amount of dietary fat was unabsorbed in MR-O compared with Conv-O.

As expected, the systemic uptake was generally low, with a geometric mean plasma concentration of orlistat <5 ng/mL in participants receiving both the MR-OA and conventional orlistat, consistent with prior studies.[14–16] However, both C_{max} and AUC were higher after administering MR-OA compared with Conv-O, which contrasts with findings from an earlier trial where the reverse was observed.[13] The previous trial involved standardized breakfast and lunch with both formulations, whereas the current study administered a single dose with breakfast, preceded by a light meal. This adjustment aimed to enhance orlistat absorption, addressing the lower concentrations seen in the previous study. This difference in meal timing and composition may have influenced the absorption of orlistat differently between MR-OA and Conv-O, contributing to the higher interindividual variability in plasma concentrations observed with MR-OA. The study populations also varied: The previous trial included only men with obesity, while the current trial involved primarily healthy women and some men. The high interindividual variability may have affected time to C_{max}, which was unexpectedly similar for both formulations. Given the low plasma concentration, factors beyond the release pattern likely had a greater impact on the overall plasma profile.

In agreement with previous studies using conventional acarbose,[17] acarbose plasma concentrations were virtually undetectable, indicating that the MR-OA formulation does not alter acarbose absorption. Moreover, acarbose plasma concentration is inherently difficult to measure due to the absence of ionizable functional groups in the molecule.

The strengths of this study were the use of a strict protocol for the PD part of the study, where diet was controlled, and that the participants were monitored daily. There were no differences in dietary intake across the various treatment periods. Although the sample size was small, the results suggest that a larger sample size would not have significantly impacted the findings, as

the fecal fat excretion values for both MR-OA and Conv-O overlap and are substantially higher than the baseline run-in values. The exploratory PK part was less standardized, and although the half-life of both orlistat and acarbose are short, a more rigorous standardization might have decreased the variability.

Conclusions

Bioequivalence was demonstrated between the MR-O and Conv-O dosage forms of orlistat, indicating that the overall lipase inhibition from a 120-mg dose of orlistat is not significantly influenced by the site of action within the gastrointestinal tract. Additionally, in the MR-OA, both orlistat and acarbose exhibited low systemic exposure, further confirming their favorable safety profiles.

Conflicts of Interest

The authors declare the following competing financial interests: S.G., A.F., G.A., A.S., and U.H. have equity interests in Empros Pharma A.B. and have acted as employees or consultants for the company. H.L. and S.K. are employed at Clinical Trial Consultants AB but declare no conflict of interest.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.