

Procter & Gamble

The Procter & Gamble Company
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2651 '00 MAR -6 A9:27

March 3, 2000

Docket Management Office
5630 Fisher's Lane
Rockville, MD 20852

Dear Madam:

We wish to submit the enclosed report and cover letter entitled "FP-149 Final Report - Home Consumption Study of Olean or Triglyceride Potato Chips and Corn Chips Among Adults and Children" to the olestra docket #00F-0792 so that it is publicly available. This report was previously submitted to Mary Ditto of FDA's Office of Pre-market Approval on February 24, 1998.

In addition, this information is available in the publication listed below. We attached a copy for your convenience.

Annals of Internal Medicine 1999; 130:253-261

Please let me know if you have any questions (513-634-6808).

Thank you.

Sincerely,

THE PROCTER & GAMBLE COMPANY



Greg Allgood, Ph.D.
Associate Director
Regulatory & Clinical Development

Enclosures

00F-0792

RPT5

Gastrointestinal Symptoms in 3181 Volunteers Ingesting Snack Foods Containing Olestra or Triglycerides

A 6-Week Randomized, Placebo-Controlled Trial

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Background: Olestra is a nonabsorbable, energy-free fat substitute. Because it is not absorbed, it may cause digestive symptoms when consumed in large amounts.

Objective: To compare the frequency and impact of gastrointestinal symptoms in adults and children who freely consume snacks containing olestra or regular snacks in the home.

Design: 6-week, double-blind, randomized, parallel, placebo-controlled trial.

Setting: General community.

Participants: 3181 volunteers 2 to 89 years of age.

Intervention: Households received identical packages labeled as containing olestra corn or potato chips. These packages contained either olestra or regular chips (control).

Measurement: Gastrointestinal symptoms and their impact on daily activities were reported in a daily record.

Results: At least one gastrointestinal symptom was reported by 619 of 1620 (38.2%) persons in the olestra group and 576 of 1561 (36.9%) controls (difference, 1.3 percentage points [95% CI, -3.6 to 6.2 percentage points]; $P = 0.60$). In general, the groups did not differ significantly in the proportion of participants who reported individual gastrointestinal symptoms; however, more controls reported nausea (8.4% compared with 5.7%; difference, -2.7 percentage points [CI, -4.9 to -0.4 percentage points]; $P = 0.02$). The only difference between groups for the mean numbers of days on which symptoms were reported was that participants in the olestra group had 1 more symptom-day of more frequent bowel movements than did controls (3.7 symptom-days compared with 2.8 symptom days; difference, 0.9 symptom-days [CI, 0.1 to 1.8 symptom-days]; $P = 0.04$). The groups did not differ in the impact of symptoms on daily activities.

Conclusions: Clinically meaningful or bothersome gastrointestinal effects are not associated with unregulated consumption of olestra corn and potato chips in the home.

Olestra is an energy-free fat substitute approved by the U.S. Food and Drug Administration for use in snack foods, including potato chips, corn chips, and crackers (1). Olestra, a mixture of sucrose esters of long-chain fatty acids isolated from edible fats and oils, is neither digested nor absorbed (2, 3).

Anecdotal reports of severe diarrhea and abdominal pain associated with ingestion of olestra (4) have not been substantiated by extensive controlled testing (5-7). A recent large study, in which participants ate chips at a single sitting, showed no differences in gastrointestinal symptoms between participants who ate olestra chips and those who ate regular chips (8). We wanted to obtain data from a larger sample that freely consumed olestra snacks over a longer period. We therefore conducted a randomized, double-blind, placebo-controlled trial to evaluate the frequency of gastrointestinal symptoms and their impact on daily living in a diverse, free-living study sample consuming olestra chips over a 6-week period under market use conditions in the home environment.

Methods

The study was conducted in Phoenix, Arizona, and St. Petersburg, Florida, from 28 July 1997 to 22 September 1997. The protocol was approved by the institutional review board of Hill Top Research, Inc., Cincinnati, Ohio.

This paper is also available at <http://www.acponline.org>.

Ann Intern Med. 1999;130:253-261.

Participants

Participants were recruited by telephone from rosters of participants in previous consumer product studies or from print advertising in Phoenix and St. Petersburg. Persons 2 years of age or older were eligible for participation. For households to be eligible, at least half of their members had to have eaten corn or potato chips 4 or more times in the past month, and all eligible members had to participate. Persons were excluded if medical reasons precluded them from eating regular potato or corn chips.

At the initial visit, each household was assigned to the olestra or control group by means of a separate computer-generated randomization schedule for each of four strata (households with or without children 2 to 12 years of age at each of the two sites) (S-Plus, version 3.3, MathSoft, Inc., Seattle, Washington). Because the unit of randomization was the household, all members of the same household received the same study treatment. An adult "household contact" was designated to return to the study site each week (within a period of 7 ± 2 days) for 6 consecutive weeks.

Products

At each visit, household contacts viewed a display of 14 olestra-labeled and regular (full-fat) potato and corn chips and ordered up to 8 packages in any combination of olestra or regular packages. The olestra-labeled packages provided to households in the olestra group contained olestra (Olean, Procter & Gamble, Cincinnati, Ohio) products, but the olestra-labeled packages provided to households in the control group actually contained regular (control) chips. Households in both groups could also select regular chips in marketed packages.

The olestra products consisted of seasoned and plain olestra potato chips (WOW brand Lays and Ruffles, Frito-Lay, Dallas, Texas), corn chips (WOW brand Doritos, Frito-Lay), and potato crisps (Pringles Fat-Free brand, Procter & Gamble). The matching control products consisted of seasoned and plain regular potato chips (Lays and Ruffles, Frito-Lay), corn chips (Doritos, Frito-Lay), and potato crisps (Pringles, Procter & Gamble). All of the products were regular commercial products obtained from the manufacturers and were distributed free of charge in 5.5- to 9-ounce standard market packages.

The olestra-labeled packages containing olestra snacks were identical in appearance to the olestra-labeled packages containing regular snacks. Each package displayed the Olean logo and the following information statement: "This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some

vitamins and other nutrients. Vitamins A, D, E and K have been added."

Participants were instructed to eat the chips as they normally would. They were also told not to share the chips outside of the household and not to consume any chips other than those provided at the study site.

All study participants and personnel associated with the collection, processing, or analysis of the data were blinded to study group assignment. They were also blinded to the type of study product contained in olestra-labeled packages. Product orders were filled by staff who were specifically assigned to that duty and had no contact with the study participants. The randomization code was not available to the persons conducting the study.

Study Procedures and Data Collection

Before the study started, a screening telephone call was made to each household to determine interest in and eligibility for participation in the study. All household members who agreed to participate came to the study site for the initial visit. At this time, information collected during the screening phone call was verified, medical histories were recorded, and written informed consent was obtained from all participants or their guardians. The informed consent form explained to the participants that the olestra-labeled packages they selected might contain olestra chips or regular full-fat chips. The form also stated that "During this study, as with other changes in the diet or eating habits, some individuals may notice digestive changes or discomfort such as cramping or loose stools." Participants viewed a video instructing them how to complete the study records.

During the study, all participants indicated on a daily record how much of the olestra-labeled and regular chips they ate, in increments of one quarter of a package, and whether they had any digestive symptoms. The household contact assisted children or completed the daily records for them, as needed. Participants noted whether they experienced any of the following symptoms: heartburn or indigestion, nausea or queasiness, vomiting, gas, bloating, abdominal cramping or pain, more frequent bowel movements, or looser stool or other digestive symptoms. Participants indicated how the symptoms affected their daily activities by checking one of the following categories: 1) noticed symptoms but did not affect activities, 2) symptoms slightly affected activities, 3) missed some time at activities, or 4) missed all day at activities. Participants also noted whether they took medication or visited a physician because of their symptoms. At the end of the study, participants indicated which snacks they thought they had eaten (olestra, regular, or didn't know).

Study personnel reviewed the daily records for accuracy and completeness in the presence of the participant at each weekly visit. Although the amount of chips consumed in this study was not objectively verified, we conducted a pretrial 6-week pilot study to confirm that the data collected in the daily record would be representative of actual chip consumption. In that study, 70% of consumption estimates were within 30% of the actual weight of the chips consumed.

Statistical Analysis

The study was designed to provide at least 80% power (at an α level of 0.05) for detecting true differences between groups of 6% to 8% in the proportions of participants with symptoms, based on 500 households per test group. To account for the possible correlation of within-household information, variance estimation was done by using the sampling theory approach for ratio estimates, as described elsewhere (9, 10). Testing for treatment differences was then done by using the normal approximation method. All *P* values are two-sided and were not adjusted for multiple comparisons. Approximate 95% CIs for the difference between two proportions were constructed by using the standard large-sample normal approximation method. All statistical analyses were performed by using S-Plus software, version 3.3 (MathSoft, Inc.)

Role of the Funding Source

Data were collected by an independent contractor (Hill Top Research, Inc., Cincinnati, Ohio). Analyses were performed by the sponsor, and the results were submitted to the U.S. Food and Drug

Table 1. Demographic Characteristics of Study Participants*

Characteristic	Olestra Group	Control Group	All Participants
	(n = 1620)	(n = 1561)	(n = 3181)
	← n (%) →		
Age			
2–12 years	442 (27.3)	443 (28.4)	885 (27.8)
13–17 years	125 (7.7)	102 (6.5)	227 (7.1)
18–64 years	842 (51.9)	825 (52.9)	1667 (52.4)
65–89 years	211 (13.0)	191 (12.2)	402 (12.6)
Sex			
Male	696 (43.0)	704 (45.1)	1400 (44.0)
Female	924 (57.0)	857 (54.9)	1781 (56.0)
Ethnicity			
White	1429 (88.2)	1394 (89.3)	2823 (88.7)
African-American	71 (4.4)	81 (5.2)	152 (4.8)
Hispanic	84 (5.2)	63 (4.0)	147 (4.6)
Asian	14 (0.9)	2 (0.1)	16 (0.5)
Native American	9 (0.6)	13 (0.8)	22 (0.7)
Other	13 (0.8)	8 (0.5)	21 (0.7)
Highest level of education reached†			
High school (grade 12) or less	211 (37.5)	212 (37.4)	423 (37.4)
More than high school	353 (62.5)	355 (62.6)	707 (62.5)
Median yearly household income‡			
≤\$35 000	335 (59.5)	347 (61.3)	682 (60.4)
>\$35 000	180 (32.0)	170 (30.0)	350 (31.0)
Did not state	48 (8.5)	49 (8.7)	97 (8.6)

* Includes participants who ate olestra-labeled corn or potato chips at least once.

† Information on education was collected for the household's main wage earner only.

‡ Information was available for 563 participants in the olestra group and 566 participants in the control group.

Administration for review. The principal investigator had final authority with respect to publication of results.

Results

Disposition and Demographic Characteristics of the Study Participants

A total of 3250 volunteers—1651 persons from 579 households in the olestra group and 1599 persons from 581 households in the control group—were randomly allocated (Figure). Of these, 24 volunteers (14 in the olestra group and 10 in the control group) were excluded because they did not eat olestra-labeled chips. Of the 130 volunteers who withdrew from the study, 45 (17 in the olestra group and 28 in the control group) did so before the second visit and did not return any daily records. Therefore, 3181 volunteers, including 885 children 2 to 12 years of age and 402 elderly persons 65 to 89 years of age, were included in the analysis. Data from the 85 participants who withdrew after the second visit were included in the analysis up to the time of discontinuation.

Participants in the olestra and control groups were similar with respect to age, sex, and ethnicity ($P > 0.2$) (Table 1). They were also similar in terms

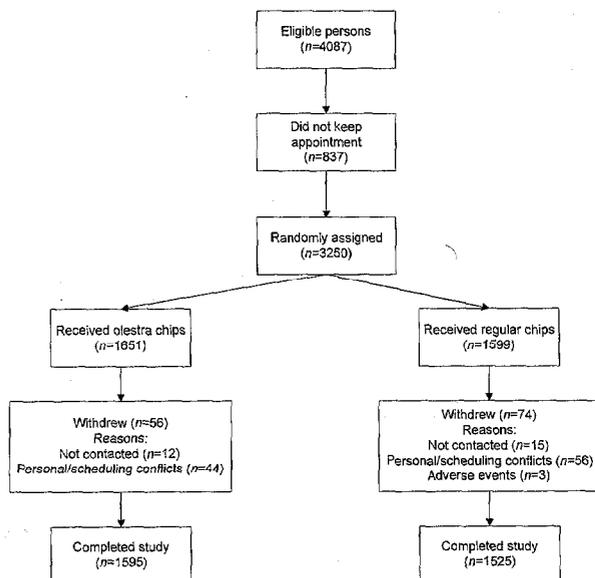


Figure. Progress of study participants during randomization and during the trial.

Table 2. Consumption of Olestra-Labeled Chips

Consumption Data	Olestra Group				Control Group			
	Participants	Eating Days*			Participants	Eating Days*		
		Median	25th, 75th Percentile	90th Percentile		Median	25th, 75th Percentile	90th Percentile
	<i>n</i>	<i>d</i>			<i>n</i>	<i>d</i>		
Overall	1620	20	12, 28	35	1561	21	14, 29	36
Men	696	18	11, 26	34	704	19	13, 27	36
Women	924	21	14, 29	35	857	22	15, 31	37
Children (2–12 years of age)	442	18	11, 24	32	443	18	12, 25	32
Teenagers (13–17 years of age)	125	15	10, 24	28	102	18	12, 23	31
Adults (18–64 years of age)	842	20	13, 28	34	825	21	15, 29	35
Seniors (65–89 years of age)	211	27	19, 35	40	191	32	21, 36	40

* Number of days on which olestra-labeled chips were eaten.

† The average amount of chips eaten per eating day is defined as the amount of chips eaten by a participant divided by his or her number of eating days.

of highest level of education reached, occupation of the main wage earner, and yearly household income.

Consumption of Study Product

During the 42-day study, participants in both groups ate olestra-labeled chips frequently (Table 2). Although consumption was slightly lower in the olestra group than in the control group, olestra chips were consumed on approximately half of the study days in a median daily amount of more than 1 ounce. In both groups, the weekly percentages of participants consuming olestra-labeled chips were consistent (82% to 91% in the olestra group and 88% to 92% in the control group) and showed no trends throughout the study. The median number of eating days and the total amount of olestra-labeled chips eaten were greatest among elderly participants. Men ate more olestra-labeled chips per eating day than women, but women tended to eat olestra-labeled chips more frequently than men and, as a result, consumed a greater median total amount. The median total amount eaten by children was about 25% less than that eaten by the group as a whole.

Symptoms

Analysis of the frequency of gastrointestinal events showed no statistically significant differences between the proportions of participants in the olestra and control groups who reported any gastrointestinal symptom (619 of 1620 [38.2%] persons in the olestra group and 576 of 1561 [36.9%] controls; difference, 1.3 percentage points [95% CI, -3.6 to 6.2 percentage points]; $P > 0.2$) (Table 3). In general, the test groups did not differ significantly in the proportion of participants reporting any of the eight individual gastrointestinal symptoms, except that a higher percentage of controls reported nausea (5.7% compared with 8.4%; difference, -2.7 percentage points [CI, -4.9 to -0.4 percentage points]; $P = 0.02$).

For participants reporting gastrointestinal symptoms, the groups did not generally differ in the number of days that symptoms were reported (symptom-days) for any gastrointestinal symptom or for any of the eight individual gastrointestinal symptoms; however, participants in the olestra group had 1 more symptom-day than controls for more frequent bowel movements (3.7 symptom-days compared with 2.8 symptom-days; difference, 0.9 symptom-days [CI, 0.1 to 1.8 symptom-days]; $P = 0.04$) (Table 3). In both groups, the median number of days on which olestra-labeled products were eaten was similar among participants who reported any gastrointestinal symptoms (20 eating days) and among those who reported no symptoms (21 eating days).

In almost all cases, symptoms were rated as having little to no effect on daily activities, and the groups did not differ in these ratings: 98.2% of the ratings in the olestra group and 97.2% of those in the control group indicated that symptoms either did not affect or only slightly affected daily activities (Table 4).

Because aggregate measures may obscure important differences in subgroups, we conducted a series of analyses to determine whether certain subgroups (children 2 to 12 years of age, teenagers 13 to 17 years of age, adults 18 to 64 years of age, elderly persons 65 to 89 years of age, and men and women) might be more likely to report effects of olestra (Table 5). When we stratified the groups by age, the groups did not differ significantly in the percentage of participants with gastrointestinal events for most gastrointestinal symptoms; the only exceptions were that more children in the control group reported other gastrointestinal symptoms (0.2% compared with 2.3%; difference, -2.1 percentage points [95% CI, -4.0 to -0.1 percentage points]; $P = 0.04$) and more adults in the olestra group reported gas (30.6% compared with 24.8%; difference, 5.8 percentage points [CI, 0.6 to 11.0 percentage points]; $P = 0.03$). Among children, the difference between

Table 2—Continued

Olestra Group			Control Group		
Average Amount of Chips Eaten Per Eating Day†			Average Amount of Chips Eaten Per Eating Day†		
Median	25th, 75th Percentile	90th Percentile	Median	25th, 75th Percentile	90th Percentile
1.30	1.01, 1.75	2.34	1.35	0.99, 1.90	2.67
1.41	1.05, 1.88	2.44	1.41	1.03, 1.98	2.79
1.24	0.97, 1.66	2.25	1.30	0.95, 1.83	2.55
1.13	0.88, 1.46	1.88	1.13	0.89, 1.54	2.18
1.37	1.00, 1.88	2.53	1.40	1.06, 1.82	2.55
1.39	1.07, 1.82	2.46	1.44	1.03, 1.99	2.87
1.38	1.07, 1.87	2.51	1.55	1.08, 2.14	2.96

the groups was mostly attributable to reported constipation. The only statistically significant difference between the test groups in terms of the number of symptom-days reported was that in the olestra group, the number of symptom-days was higher among adults for any gastrointestinal event (5.7 compared with 4.6 symptom-days; difference, 1.1 symptom-day [CI, 0.1 to 2.1 symptom-days]; $P = 0.03$) and more adults had more frequent bowel movements (4.1% compared with 2.9%; difference, 1.2 symptom-days [CI, 0.1 to 2.2 symptom-days]; $P = 0.02$).

When we stratified the test groups by sex, the percentage of men reporting nausea (3.9% compared with 7.4%; $P = 0.01$) and the mean number of symptom-days for cramping in men (1.8 compared with 2.5, $P = 0.04$) were significantly higher in the control group than the olestra group. Among women, the percentage of reported gastrointestinal symptoms did not differ significantly, but the numbers of symptom-days in the olestra group were greater for any gastrointestinal event (5.4 compared with 4.2 symptom-days; $P = 0.004$), gas (4.9 com-

pared with 3.7 symptom-days; $P = 0.009$), and more frequent bowel movements (3.9 compared with 2.9 symptom-days; $P = 0.03$). Although these differences in the numbers of symptom-days were statistically significant, they were small, consisting of only about 1 day out of a possible 42.

Of note, for all subgroups, the impact of symptoms on activities was minor; 98% to 99% of the ratings in the olestra group and 96% to 100% of those in the control group were in the "no effect" or "slight effect" categories (Table 4). In all subgroups except elderly persons, the impact of symptoms was slightly less in the olestra group than in the control group.

When participants were stratified by deciles of total olestra-labeled chips consumed, the percentage of participants in the highest decile who reported symptoms was greater in the olestra group than in the control group for more frequent bowel movements (27.9% compared with 11.7%; difference, 16.2 percentage points [CI, 5.0 to 27.4 percentage points]; $P = 0.005$) and looser stool (30.3% compared with 16.8%; difference, 13.5 percentage points

Table 3. Summary of Gastrointestinal Symptoms*

Event	Participants Who Reported GI Symptoms				Mean (\pm SE) Symptom-Days in Participants Reporting GI Symptoms			
	Olestra Group n (%)	Control Group	Difference (95% CI) percentage points	P Value	Olestra Group	Control Group	Difference (95% CI) symptom-days	P Value
Any GI event†	619 (38.2)	576 (36.9)	1.3 (-3.6 to 6.2)	>0.2	5.0 \pm 0.3	4.2 \pm 0.3	0.8 (-0.1 to 1.6)	0.07
Heartburn	139 (8.6)	131 (8.4)	0.2 (-2.2 to 2.6)	>0.2	2.6 \pm 0.3	2.4 \pm 0.3	0.1 (-0.6 to 0.9)	>0.2
Nausea	93 (5.7)	131 (8.4)	-2.7 (-4.9 to 0.4)	0.02	1.9 \pm 0.2	1.7 \pm 0.1	0.2 (-0.3 to 0.8)	>0.2
Vomiting	29 (1.8)	28 (1.8)	0.0 (-1.1 to 1.0)	>0.2	1.3 \pm 0.1	1.2 \pm 0.1	0.1 (-0.3 to 0.5)	>0.2
Gas	392 (24.2)	339 (21.7)	2.5 (-1.8 to 6.7)	>0.2	4.5 \pm 0.3	3.8 \pm 0.3	0.7 (-0.2 to 1.6)	0.12
Bloating	182 (11.2)	146 (9.4)	1.8 (-0.8 to 4.6)	0.18	3.3 \pm 0.3	2.8 \pm 0.2	0.4 (-0.3 to 1.2)	>0.2
Cramping	243 (15.0)	236 (15.1)	-0.1 (-3.3 to 3.1)	>0.2	2.4 \pm 0.2	2.5 \pm 0.2	-0.1 (-0.6 to 0.4)	>0.2
More frequent bowel movements	332 (20.5)	271 (17.4)	3.1 (-0.7 to 7.0)	0.11	3.7 \pm 0.4	2.8 \pm 0.2	0.9 (0.1 to 1.8)	0.04
Looser stool	410 (25.3)	360 (23.1)	2.2 (-2.1 to 6.6)	>0.2	3.9 \pm 0.3	3.6 \pm 0.3	0.3 (-0.6 to 1.2)	>0.2
Other GI symptoms‡	36 (2.2)	50 (3.2)	-1.0 (-2.2 to 0.3)	0.12	2.3 \pm 0.4	2.1 \pm 0.4	0.3 (-0.8 to 1.3)	>0.2

* GI = gastrointestinal.

† Includes all participants who responded "yes" to the question in the daily record.

‡ The most frequently reported other GI symptoms in the olestra and control groups, by number of participants, were constipation (15 and 17), diarrhea (8 and 7), discolored stool (5 and 2), and hard stool (3 and 2). The remainder of other GI symptoms were reported by 3 or fewer participants.

Table 4. Effect of Symptoms on Daily Activities*

Category	Participants†	Noticed Symptoms but Daily Activities Were Not Affected	Noticed Symptoms and Daily Activities Were Slightly Affected	Missed Some Time from Daily Activities	Missed All Day
All participants					
Olestra group	619	2587 (83.6)	452 (14.6)	41 (1.3)	16 (0.5)
Control group	576	2021 (82.6)	357 (14.6)	46 (1.9)	22 (0.9)
Children (2–12 years of age)					
Olestra group	133	437 (87.9)	48 (9.7)	5 (1.0)	7 (1.4)
Control group	135	389 (81.0)	74 (15.4)	9 (1.9)	8 (1.7)
Teens (13–17 years of age)					
Olestra group	42	127 (84.1)	22 (14.6)	2 (1.3)	0 (0)
Control group	40	122 (86.5)	16 (11.4)	3 (2.1)	0 (0)
Adults (18–64 years of age)					
Olestra group	376	1741 (81.9)	346 (16.3)	29 (1.4)	9 (0.4)
Control group	342	1263 (81.0)	249 (16.0)	33 (2.1)	14 (0.9)
Elderly (65–89 years of age)					
Olestra group	68	282 (87.3)	36 (11.2)	5 (1.6)	0 (0)
Control group	59	247 (92.9)	18 (6.8)	1 (0.4)	0 (0)
Men					
Olestra group	252	944 (85.1)	149 (13.4)	11 (1.0)	6 (0.5)
Control group	238	854 (82.0)	163 (15.7)	19 (1.8)	5 (0.5)
Women					
Olestra group	367	1643 (82.7)	303 (15.3)	30 (1.5)	10 (0.5)
Control group	338	1167 (83.1)	194 (13.8)	27 (1.9)	17 (1.2)
High consumers‡					
Olestra group	53	331 (83.2)	58 (14.6)	6 (1.5)	3 (0.8)
Control group	63	269 (84.6)	44 (13.8)	4 (1.3)	1 (0.3)

* Participants rated the impact of their gastrointestinal symptoms on work, school, activities, or routine.

† Participants who reported any gastrointestinal symptoms.

‡ Participants in the highest decile for consumption of olestra-labeled chips.

[CI, 2.1 to 25.1 percentage points]; $P = 0.02$). The numbers of symptom-days did not differ significantly between the two groups for any of the eight symptoms, and symptoms were rated as having no effect or slight effect on 97.8% and 98.4% of symptom-days in the olestra and control groups, respectively (Table 4).

Seven participants in the olestra group and 9 in the control group reported visiting a physician for gastrointestinal symptoms. Medication use for gastrointestinal symptoms, reported by 132 participants in the olestra group and 129 in the control group, was also similar between the groups, including use of antidiarrheal agents (44 and 47 participants, respectively). No participant reported leakage of oil or fecal incontinence. One woman in the control group reported a gastrointestinal adverse event (cramping) that led to withdrawal from the study. Two controls died during the study; one committed suicide and the other had a fatal cardiac event.

At the end of the study, participants indicated which type of chips they thought they had been eating. More than half of the participants (58%) stated that they did not know which kind of chip they were eating. Of the 1283 participants who guessed at the type of chips they had been eating, 612 (39%) in the olestra group correctly believed that they had received olestra snacks and 175 (12%) in the control group correctly believed that they had received regular snacks. This difference in the per-

centage of participants who guessed correctly is consistent with the fact that a much higher proportion of the participants guessed that they were eating olestra snacks. Among participants who guessed, the percentage who believed that they were eating olestra chips (79%) was almost four times the percentage who believed that they were eating regular chips (21%).

Of interest, the percentage of participants reporting gastrointestinal symptoms was significantly higher among participants who thought they had been eating olestra chips (45.3% in the olestra group and 44.4% in the control group) than among participants who thought they had been eating regular snacks (31.0% in the olestra group and 29.1% in the control group) ($P = 0.01$). For participants who said that they did not know which type of chip they had been eating, the percentage reporting gastrointestinal symptoms did not differ between the olestra (35.0%) and control (35.8%) groups.

Discussion

In this large, controlled clinical trial in free-living adults and children, we found no difference in the occurrence of clinically significant or bothersome gastrointestinal effects between participants who consumed olestra or regular snacks for 6 weeks.

The amount of olestra consumed by the partici-

pants in this study was adequate to allow assessment of olestra's gastrointestinal effects. Approximately half of the participants ate olestra snacks on more than half of the 42 study days; this rate of consumption is considerably higher than typical chip consumption in the United States (11). On the basis of dietary survey data (12), 39% of the study participants would be classified in at least the 90th percentile for U.S. snack consumers; participants in the top decile for this study, therefore, had very high consumption. If participants had experienced unpleasant symptoms and had attributed them to chip consumption, one might expect that consumption would decrease over time. In fact, consumption was consistent throughout the study in both groups. Because olestra inhibits absorption of some vitamins and other nutrients, vitamins A, D, E, and K are added to offset this effect. Thus, we would expect to see no decrease in the serum levels of these vitamins, even in participants with very high chip consumption.

In general, the test groups did not differ in the occurrence of gastrointestinal symptoms, either overall or in the subgroup analyses. Even at the upper limits of the 95% CIs for the differences between the groups in symptom frequency and symptom-days, the risks over the 42-day study would not have been meaningfully greater in the olestra group. For example, for the participants in the highest decile for chip consumption, the upper confidence limit for the difference between groups in symptom frequency indicates that the percentage of participants with more frequent bowel movements could have been 27.4% greater in the olestra group. Even if this were the case, the difference would not be clinically meaningful because almost all of the symptoms reported had little or no effect on participants' daily activities (Table 4).

Although the mean number of symptom-days for any gastrointestinal event (women and adults), gas

(women), and more frequent bowel movements (all participants, women, and adults) was significantly greater in the olestra group, these differences were not clinically significant—only about 1 day out of a possible 42—and participants did not indicate that the symptoms were bothersome. Analysis of subgroups within the overall population indicated that these differences occur more frequently in adult women.

Previous clinical experience with olestra has also shown that increases in the frequency of bowel movements, if they occur, are minor and not clinically important. In a previous study, the frequency of bowel movements increased from 1.5 per day at baseline to 1.6 per day in participants who consumed 2.5 ounces of olestra chips per day and to 2.0 per day in participants who consumed 5 ounces of olestra chips per day (13).

In our study, the incidence of diarrhea and cramping was the same in the olestra group and the control group. The labeling on both the olestra-labeled packages and the informed consent forms told participants that they may notice cramping or loose stools. Despite the availability of this information, the occurrence of cramping was not greater in the olestra group than in the control group for the group as a whole or for any of the subgroups studied. In fact, the frequency of cramping was greater in the control group than in the olestra group among men. Of note, participants who ate the highest amounts of control (regular) chips reported loose stools and more frequent bowel movements less often than participants who consumed lower amounts of control chips.

Our results are consistent with those of other studies in which participants consumed olestra snacks under ordinary snacking conditions (5–8). The results of these randomized, controlled, double-blind trials do not substantiate anecdotal reports of severe diarrhea and abdominal pain or cramping

Table 5. Participants Who Reported One or More Gastrointestinal Symptom by Age and Sex*

Category	Participants Who Reported GI Symptoms				Mean Symptom-Days (\pm SE) in Participants Who Reported GI Symptoms			
	Olestra Group	Control Group	Difference (95% CI) [†]	P Value	Olestra Group	Control Group	Difference (95% CI) [‡]	P Value
	<i>n/n (%)</i> [§]		<i>percentage points</i>		<i>symptom-days</i>			
Age								
2–12 years	133/442 (30.1)	135/443 (30.5)	-0.4 (-8.4 to 7.6)	>0.2	3.7 \pm 0.4	3.6 \pm 0.4	0.2 (-0.9 to 1.2)	>0.2
13–17 years	42/125 (33.6)	40/102 (39.2)	-5.6 (-19.1 to 7.9)	>0.2	3.6 \pm 0.6	3.5 \pm 0.8	0.1 (-1.9 to 2.1)	>0.2
18–64 years	376/842 (44.7)	342/825 (41.5)	3.2 (-2.6 to 9.0)	>0.2	5.7 \pm 0.4	4.6 \pm 0.4	1.1 (0.1 to 2.1)	0.03
65–89 years	68/211 (32.2)	59/191 (30.9)	1.3 (-8.5 to 11.2)	>0.2	4.8 \pm 0.7	4.5 \pm 0.9	0.2 (-2.0 to 2.4)	>0.2
Sex								
Male	252/696 (36.2)	238/704 (33.8)	2.4 (-3.7 to 8.5)	>0.2	4.4 \pm 0.4	4.4 \pm 0.5	0.0 (-1.2 to 1.3)	>0.2
Female	367/924 (39.7)	338/857 (39.4)	0.3 (-5.3 to 5.9)	>0.2	5.4 \pm 0.3	4.2 \pm 0.3	1.3 (0.4 to 2.1)	<0.01

* Includes all participants who responded "yes" to the question in the daily record. GI = gastrointestinal.

[†] Values are the difference between the olestra and control groups in the percentage of participants who reported symptoms.

[‡] Values are the difference between the olestra and control groups in the number of days on which participants reported symptoms.

[§] Participants in the study group/participants who reported symptoms.

associated with olestra (4); instead, they show that under ordinary snacking conditions, gastrointestinal symptoms among participants who eat snacks containing olestra are no more troublesome than those associated with consumption of regular snacks containing triglycerides. This finding is of clinical importance: Physicians who see patients experiencing significant gastrointestinal symptoms that they attribute to olestra should seek other causes for these complaints, because our data indicate that these symptoms are unlikely to be related to olestra and may instead reflect a serious condition.

Our results did not indicate that the gastrointestinal symptoms following consumption of olestra were any more bothersome than those following consumption of regular chips. The only participants who withdrew from the study because of gastrointestinal adverse events were in the control group, and in the olestra group, 98% to 99% of ratings of effects on activities indicated that symptoms had no or slight impact on activities. In addition, the use of medications and physician visits for gastrointestinal symptoms were no greater in the olestra group than in the control group, and participants consumed olestra-labeled snacks at the same rate throughout the study regardless of whether they reported any gastrointestinal effects.

Several notable features of our study deserve comment. Through the use of daily diaries, we obtained detailed information on exposure (chip consumption) and outcomes (symptoms and functional impact). Special care was taken to blind study participants and staff to the study group assignments. Recruitment of participants from households known to be regular consumers of snack foods and provision of good-tasting products free of charge helped ensure that the dose of the study products would be adequate to allow determination of their effects on gastrointestinal symptoms and daily living. The study was designed to simulate real-world circumstances: Participants chose regular or olestra snacks from product displays, as they would in the marketplace, and consumed as much or as little as they wished while in their home environment.

The study was limited in that it relied on self-reports for information on chip consumption and gastrointestinal symptoms. However, there was no incentive to misreport this information and no reason to expect differential reporting between the olestra and the control groups. In addition, adults reported the information on consumption and symptoms for young children, the only practical means of collecting these data. The conclusions reached in this study were based on consumption of olestra in snack foods only. Olestra was not otherwise present in the participants' diets. Further studies would be required to determine the effects of

olestra consumed in foods in addition to savory snacks.

An interesting finding was the association of gastrointestinal symptoms with the type of chips that participants thought they were eating. Participants who believed that they were eating olestra chips reported gastrointestinal symptoms approximately 50% more often than participants who believed that they were eating regular chips, regardless of the type of chip they were actually eating. Among participants who said that they did not know which product they were eating, the percentage of participants reporting gastrointestinal symptoms was intermediate between the percentages of participants who guessed that they were eating olestra chips and those who guessed that they were eating regular chips. These findings suggest that reporting of symptoms may have been influenced by what the participants thought they were eating. They may also help explain anecdotal reports of gastrointestinal adverse events. According to a recent national survey (14), gastrointestinal symptoms are frequent in the population; up to 40% of adults report cramping, loose stools, or gas in the previous month. Marketed Olean packages state that olestra may cause abdominal cramping and loose stools. Consumers who have read this statement or heard reports of olestra-associated gastrointestinal effects may erroneously attribute these common symptoms to olestra.

In conclusion, our study demonstrates that clinically meaningful or bothersome gastrointestinal effects are not associated with unregulated consumption of olestra corn and potato chips in the home over 6 weeks.

From University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and Procter & Gamble Co., Cincinnati, Ohio.

Note: Dr. Sandler is a consultant to Procter & Gamble Co. The terms of this arrangement are being managed by the University of North Carolina at Chapel Hill in accordance with its conflict of interest policies. Ms. Royer is an editorial consultant to Procter & Gamble.

Acknowledgments: The authors acknowledge Hill Top Research, Inc., Cincinnati, Ohio, for conducting the study.

Grant Support: By Procter & Gamble Co., Cincinnati, Ohio.

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**HOME CONSUMPTION STUDY OF OLEAN OR TRIGLYCERIDE POTATO CHIPS
AND CORN CHIPS AMONG ADULTS AND CHILDREN**

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Procter & Gamble Number FP149

Study Dates

July 28, 1997 to September 22, 1997

**FP149 Final Report - Home Consumption Study of Olean or Triglyceride
Potato Chips and Corn Chips Among Adults and Children**

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* Appendices were submitted directly to the FDA's Office of Premarket Approval and portions may be requested by way of the Freedom of Information Act.

Home Consumption Study of Olean or Triglyceride Potato Chips and Corn Chips Among Adults and Children

Summary

Anecdotal reports have suggested that consumption of olestra snacks could cause significant adverse effects, such as the immediate onset of diarrhea and cramping, which has at times been described as severe and necessitating emergency treatment. These reports have not been substantiated during extensive testing in double-blind, controlled trials conducted under strict laboratory conditions or under conditions simulating expected snacking patterns of olestra marketed products for frequent snackers. In contrast to the severe effects described in the anecdotal reports, the effects noted by subjects consuming olestra snacks during clinical testing were no more severe than those observed in test subjects consuming full-fat placebo products and were not troublesome enough to cause subjects to withdraw from the studies.

We conducted a 6-week, double-blind, randomized, controlled trial to compare the frequency, severity, and impact on daily living of common gastrointestinal (GI) experiences in adults and children consuming Olean® snacks under market use conditions with those in adults and children consuming regular triglyceride snacks, that are labeled as Olean, under similar conditions.

Methods

A total of 3,250 subjects from 1,160 households were enrolled and randomly assigned to either the Olean group or the Control group. Each participant completed an informed consent which stated that the Olean-labeled chips may or may not contain olestra and which contained the Olean label statement regarding the GI symptoms "looser stools and abdominal cramping." For each household, an adult "household contact" was identified to be the primary contact for that household during the study. Each week, the household contacts came to the site and viewed a display of a selection of packages of potato and tortilla chip products labeled as containing Olean chips (Olean-labeled products) and a similar selection of packages labeled as containing regular chips (regular-labeled products). The household contacts then selected up to eight bags and/or cans from the selection of Olean-labeled and regular-labeled packages. For the Olean group, the Olean-labeled packages contained Olean chips, but for the Control group, the Olean-labeled packages contained regular chips. For both groups, the regular-labeled packages contained regular chips. The household contact was required to return to the study site each week for 6 consecutive weeks to select new study product and to turn in their study records.

On each day of the study, each household member completed a daily record form on which was recorded the amount of Olean-labeled and regular snacks consumed and whether or not he/she had any digestive symptoms. If subjects had GI symptoms, they were to indicate whether or not they had experienced any of the eight specific symptoms

listed on the daily record form or any other GI symptoms and how the symptoms affected their daily activities. The symptom impact was assessed for each day on which a GI symptom was reported by asking participants to record the effect on their activities, using a scale ranging from "noticing but having no effect" to "missing an entire day of work/school." They were also to indicate whether or not they took any medication for the symptoms and whether or not they visited the doctor for the symptoms. At each weekly visit the household contact returned the completed daily record forms for the previous week and reviewed them with the study staff.

At the sixth (next to last) visit, household contacts received an exit questionnaire on which they were asked which product they believed was in the Olean-labeled packages (Olean, regular, don't know).

The study products consisted of regular chips and Olean chips manufactured by Frito-Lay and Pringles. The Frito-Lay product varieties consisted of Lays, Ruffles, Doritos Nacho Cheesier, and Doritos Cooler Ranch. The Pringles product varieties consisted of Original, Barbecue, and Sour Cream & Onion. The Olean-labeled products were in current test market packaging with the Olean logo on the package. All Olean-labeled packages displayed the following information statement: "This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added." The Olean-labeled packages were identical in appearance regardless of whether they contained Olean snacks or regular snacks. The regular snacks in the packages labeled as containing regular chips were also in standard market packaging.

Adverse experiences were assessed from the time subjects made their first study visit until the exit from the study. All health-related symptoms were captured either in the daily record forms and/or on an adverse experience form. Gastrointestinal events reported by the subjects on the daily record form were captured separately from adverse experiences. However, GI events from the daily record for which study participants saw a physician were also captured as adverse experiences. Non-gastrointestinal events listed under "other" in the daily record were also captured as adverse experiences.

The primary data analysis was to compare the occurrence and frequency of GI symptoms between individuals who consumed Olean-labeled Olean chips and those who consumed Olean-labeled regular chips.

Results

Subject Enrollment. Of the 3,250 subjects enrolled, 69 either did not consume Olean-labeled product or did not return after the first visit and were not evaluable (31 Olean and 38 Control). Thus, 3,181 from 1,138 households, 1,620 from 568 households in the Olean group and 1,561 from 570 households in the Control group, ate Olean-labeled chips and were evaluable for data analysis (98% of randomized). Eighty-five subjects from 42

households, 39 from 22 households in the Olean group and 46 from 20 households in the Control group, discontinued the study after the second visit. Their data were included up to discontinuation. There were three subjects who discontinued the study because of an adverse event. Two subjects, both in the Control group, were discontinued because of death, and one additional subject, also in the Control group, dropped out of the study because of a GI adverse event.

Demographics. The Olean and Control groups were similar with respect to age, sex, and race. Of the 3,181 evaluable subjects, 885 (27.8%) were children 2 to 12 years of age, 227 (7.1%) were teens 13 to 17 years of age, 1,667 (52.4%) were adults 18 to 64 years of age, and 402 (12.6%) were elderly, 65 to 89 years of age. There were slightly more females (56.0%) than males (44.0%), and 88.7% of the subjects in both study groups were Caucasian.

Product Consumption. Subjects consumed both Olean-labeled and regular products frequently, throughout the study. The median number of eating days for all study subjects who consumed Olean-labeled product was 20 and 21 for the Olean and Control groups, respectively, out of a potential 42 eating days. Subjects in the top 10% with respect to the number of eating days ate the Olean-labeled products almost every day of the study, consuming product on ≥ 35 days in the Olean group and ≥ 36 days in the Control group. The total amount eaten was also comparable between the Olean and Control groups, with a median amount of 26.0 oz in the Olean group and 28.4 oz in the control group.

Approximately one-half of all subjects in the two study groups consumed the Olean-labeled products on each day of the study. In both study groups, the percentages of subjects consuming Olean-labeled chips were consistent from week to week over the course of the study and were comparable between the two study groups, with differences generally less than 5%. The highest levels of consumption were noted among the elderly subjects, who ate product often and in larger amounts each day on average.

Gastrointestinal Symptoms. There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of subjects who reported one or more GI symptoms of any type during the study (38.2% vs. 36.9%, Olean vs. Control, $p=0.60$) (Summary Table 1). There also were no significant differences between test groups in the percentage of subjects reporting any of the eight individual GI symptoms evaluated, except that the percentage of subjects reporting nausea was greater in the Control group than in the Olean group (8.4% vs. 5.7%, Control vs. Olean, $p=0.02$).

Summary Table 1

Percentage of All Subjects Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean (n = 1620)</u>	<u>Control (n = 1561)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	38.2	36.9	0.60	1.3 (-3.6, 6.2)
Heartburn	8.6	8.4	0.88	0.2 (-2.2, 2.6)
Nausea	5.7	8.4	0.02	-2.7 (-4.9, -0.4)
Vomiting	1.8	1.8	1.00	0.0 (-1.1, 1.0)
Gas	24.2	21.7	0.25	2.5 (-1.8, 6.7)
Bloating	11.2	9.4	0.18	1.9 (-0.8, 4.6)
Cramping	15.0	15.1	0.94	-0.1 (-3.3, 3.1)
More frequent BMs	20.5	17.4	0.11	3.1 (-0.7, 7.0)
Looser stool	25.3	23.1	0.31	2.2 (-2.1, 6.6)
Other symptom	2.2	3.2	0.12	-1.0 (-2.2, 0.3)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

For those subjects reporting symptoms, there were no statistically significant differences between the test groups with respect to the mean number of symptom-days (defined as a day on which a symptom was reported) per subject for "any GI event" or for any of the individual GI symptoms, except that the number of days for which "more frequent bowel movements" was reported approximately 1 day more, out of 42 potential study days, in the Olean group than in the Control group (3.7 days vs. 2.8 days, Olean vs. Control, $p=0.04$) (Summary Table 2). This difference was small, not clinically important and could have been due to both an increased frequency in the Olean group or a decreased frequency in the Control group, or both. There was no indication of any association of cramping with Olean snack consumption.

Summary Table 2

Number of Symptom-Days^a in All Subjects Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	619	5.0 ± 0.3	576	4.2 ± 0.3	0.07	0.8 (-0.1, 1.6)
Heartburn	139	2.6 ± 0.3	131	2.4 ± 0.3	0.72	0.1 (-0.6, 0.9)
Nausea	93	1.9 ± 0.2	131	1.7 ± 0.1	0.44	0.2, (-0.3, 0.8)
Vomiting	29	1.3 ± 0.1	28	1.2 ± 0.1	0.64	0.1 (-0.3, 0.5)
Gas	392	4.5 ± 0.3	339	3.8 ± 0.3	0.12	0.7 (-0.2, 1.6)
Bloating	182	3.3 ± 0.3	146	2.8 ± 0.2	0.23	0.4 (-0.3, 1.2)
Cramping	243	2.4 ± 0.2	236	2.5 ± 0.2	0.69	-0.1 (-0.6, 0.4)
More frequent BMs	332	3.7 ± 0.4	271	2.8 ± 0.2	0.04	0.9 (0.1, 1.8)
Looser stool	410	3.9 ± 0.3	360	3.6 ± 0.3	0.46	0.3 (-0.6, 1.2)
Other symptom	36	2.3 ± 0.4	50	2.1 ± 0.4	0.64	0.3 (-0.8, 1.3)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement

- a A symptom-day was defined as a day on which the GI symptom was reported.
- b Number of subjects who reported symptom.
- c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.
- d Includes all subjects who responded "yes" to the question in the daily record form.

There was no evidence of any negative impact on daily activities associated with Olean products. Subjects in the Olean group rated symptoms as having no impact (83.6%) or slight impact (14.6%) on activities 98.2% percent of the time, while subjects in the Control group rated them as no impact (82.6%) or slight impact (14.6%) on activities 97.2% of the time. There were more days in the Control group than the Olean group on which subjects rated symptoms as having greater than a slight impact (2.8% vs. 1.8%, Control vs. Olean).

Other measures of the impact of GI symptoms were whether subjects took medication or visited a physician for symptoms. The number of subjects taking medications for symptoms was low and similar in both groups (7.0% vs. 6.9%, Olean vs. Control). Also, there was no evidence of an association of more clinically significant events with Olean, as more participants in the Control group visited a physician for their symptoms than in the Olean group (9 vs. 7, Olean vs. Control).

To evaluate whether GI symptoms were a factor in Olean snack consumption, the consumption of Olean-labeled chips was tabulated for individuals who reported GI symptoms and compared to those who did not report any GI symptoms. The median number of eating days (20 vs. 21 days) was comparable, whether or not subjects had reported a GI symptom.

If Olean chips were causing GI symptoms one might expect to see a dose-response relationship. To evaluate this, subjects were categorized both according to the number of days on which they ate Olean-labeled product (frequency of eating) and also according to the total amount of Olean-labeled product consumed during the study. There was no relationship between the reporting of any GI symptoms to the frequency of Olean product consumption. There was also no overall dose-response related to the total amount consumed. For subjects in the highest consumption category (approximately the 90th percentile), there was a greater percentage of Olean group subjects who reported the symptoms "more frequent bowel movements" or "looser stool." There was also a lower percentage of Control group subjects who reported these same symptoms in the highest consumption category, compared to the reporting rate in the lower consumption categories.

The study was specifically designed to include children (ages 2-12) and elderly (age 65+) subjects to provide information for these subgroups. There were no significant differences between the Olean and Control groups in the percentages of subjects reporting symptoms or the number of symptom-days for any GI symptoms, in either children, teens, or the elderly, even among the highest consumers for these subgroups. The overall study population was also analyzed for males and females. There were no significant differences between the two groups with respect to any GI symptoms for males. For females, while there were no significant differences in the percentages of subjects reporting symptoms, the number of symptoms-days was significantly greater (approximately 1 day more) in the Olean group for three symptoms: "any GI event", "gas" and "more frequent bowel movements". These differences were small and not clinically important. Also, there was no indication of any negative effect on subjects' activities from the impact ratings, with 98.0% of symptom-days rated as none or slight impact in the Olean group and 96.9% in the Control group.

The subgroup of adults (ages 18-64) showed similar results as the females. There was a greater percentage of subjects reporting "gas" in the Olean group (30.6% vs. 24.8%, Olean vs. Control, $p=0.03$). Also, the number of days for which subjects reported "any GI event" and "more frequent bowel movements" was significantly greater (approximately 1 day more) in the Olean group. Again, these differences were small and not clinically meaningful, and the impact ratings demonstrated no negative effects on subjects' activities.

Both the Olean and Control groups received chips in Olean-labeled packages and at the completion of the study subjects were asked which type of chips they thought were in these packages (Olean or regular). The frequency with which subjects reported GI symptoms was significantly related to the type of chips (Olean vs. regular) subjects thought were in the Olean-labeled packages. In both study groups, participants who thought that they were eating Olean chips reported GI symptoms 50% more frequently than participants who thought they were eating regular chips.

The primary strength of this study are that it is a rigorous randomized controlled trial, in a large diverse population, consuming Olean snacks frequently and in substantial quantities. Detailed information on exposure (chip consumption) and outcomes (GI symptoms) was obtained using daily diary forms. The study included a large group of children and the elderly.

While the study relied on self-report information, there is no other practical way to obtain the types of information needed to address the study objectives. Also, there was no reason to expect differential reporting in consumption or symptoms between the Olean and Control groups.

Conclusions

We conducted a large, controlled, randomized, double-blind, clinical trial of consumption of corn and potato chips in free-living adults and children. Subjects complied with protocol requirements and completed records as required. The large population of people of different ages and the duration of the trial ensured that range of snacking behaviors could occur. In order to maximize the probability of detecting differences in gastrointestinal effects, the study population was deliberately selected toward heavy consumers of snacks.

The results of the study demonstrated the following:

- 1) There was no indication of clinically significant or harmful GI effects associated with the consumption of Olean snacks in this large group of participants including children, teens and elderly subjects who frequently consumed Olean chips. Specifically there was no increase in physician visits, or use of medications for GI symptoms in the Olean group when compared to the Control group.
- 2) There was no evidence of an increase in negative or bothersome effects of GI symptoms on daily activities of the individuals in the study population as a whole or in the various subgroups (children, elderly) evaluated.
- 3) The type of chips (Olean or regular) that subjects thought they were eating from the Olean-labeled packages was significantly associated with GI symptom reporting. In both study groups, participants who thought that they eating Olean chips reported GI symptoms 50% more frequently than participants who thought they were eating regular chips.
- 4) Statistically significant, but small, differences between the Olean and Control groups in the frequency of reporting of the GI symptoms "more frequent bowel movements" and/or "looser stools" were observed in some subgroups, particularly in those consuming the highest amounts of Olean snacks. These effects were minor, not clinically important, on average being reported only 1 more day of the 42 potential study days, and were rated as having no impact or only slight impact on daily activities by the vast majority of subjects (>97%). The impact was not different than that observed in the Control group.

5) Gastrointestinal symptoms are relatively common in the general population. Consumers of Olean snacks, eating typical servings sizes of chips (1.3 oz) and consuming them as frequently as they wish, will not experience an increase in the occurrence of meaningful GI symptoms over background rates. Specifically, there was no increase in the frequency of abdominal cramping overall or in any subgroup in this study.

Final Report - Home Consumption Study of Olean or Triglyceride Potato Chips and Corn Chips Among Adults and Children

Introduction

Olestra is a non-absorbable, energy-free fat substitute that has been approved by the U.S. Food and Drug Administration for use in the preparation of savory snack foods such as potato and corn chips, extruded snacks, and crackers.¹ Olestra is prepared by esterifying sucrose with long-chain fatty acids isolated from edible fats and oils.² Because of its structure, the olestra molecule is neither digested³ nor absorbed.⁴⁻⁷ Olestra is not metabolized by colonic bacteria⁸ and passes through the gastrointestinal (GI) system unchanged.⁹ Olestra, made by the The Procter & Gamble Company, is sold to snack food manufacturers such as Frito-Lay as the branded ingredient Olean®.

Olestra has undergone extensive safety testing. The results of studies in which olestra was fed to dogs at up to 10% of the diet for 20 months,¹⁰ to rats at up to 9% of the diet for 24 months,¹¹ to mice at up to 10% of the diet for up to 24 months,¹² and to monkeys for up to 44 months¹³ have shown that olestra is not toxic or carcinogenic. Humans have safely consumed olestra in clinical studies on a daily basis for up to 16 weeks¹⁴ and on an intermittent basis for over 9 years.

Anecdotal reports have suggested that olestra is associated with immediate onset of diarrhea and cramping, some of which have been described as severe and necessitating emergency treatment.¹⁵ These reports have not been substantiated during extensive testing in double-blind, controlled trials conducted under strict laboratory conditions^{16,17} or under conditions simulating expected snacking patterns of olestra marketed products for frequent snackers.^{14,18,19} In contrast to the severe effects described in the anecdotal reports, the effects noted by subjects consuming olestra snacks during clinical testing were no more severe than those observed in test subjects consuming full-fat placebo products and were not troublesome enough to cause subjects to withdraw from the studies.

We conducted a 6-week, double-blind, randomized, controlled trial to compare the frequency and severity of GI events and their effect on daily living in individuals consuming Olean chips with those in individuals consuming regular full-fat chips. This study was especially rigorous in that subjects completed daily diaries in which they recorded the amount of chips consumed each day and responded to questions about the occurrence of specific GI events. The study was designed to provide data from males and females of a broad range of ages consuming Olean snacks under market use conditions in their home environment.

Study Objectives

1. To compare the frequency, severity, and impact on daily living of common GI symptoms in adults and children consuming Olean snacks under market use conditions with those in adults and children consuming regular snacks under similar conditions.
2. To compare the consumption patterns and product acceptance of Olean snacks consumed by adults and children under market use conditions with those of regular snacks consumed under similar conditions.

Study Design

Overall Study Design

This was a randomized (by household), double-blind, placebo-controlled, 6-week, parallel group study of Olean or regular potato and tortilla chips. The study was conducted in eligible male and female adults (ages 18 years and over), children (ages 2 to 12 years), and teenagers (ages 13 to 17 years) at two sites, one in Arizona and one in Florida. Participants consumed study products *ad libitum* in their respective homes. The study was conducted on a household basis: up to 550 households were to be enrolled into each of the two study groups (approximately one half at each study site). For each household, an adult "household contact" was identified to be the primary contact for that household during the study.

Potential subjects were recruited by Hill Top Research, Ltd. from a database of known panelists who had previously participated in studies at the sites and from print advertising about the study. A screening phone call was made to each potential household contact to determine interest and eligibility for participation in the study and to collect demographic data and information on current medications.

All eligible household members came to the study site for the initial visit. At this time, informed consent was obtained and the information collected during the screening phone call was verified. In addition, all subjects provided a medical history, and those 18 years of age or older answered questions about the occurrence of abdominal pain or discomfort and about their bowel movements and stool quality. Subjects viewed a training video to familiarize them with the study procedures and to teach them how to complete the daily records. The household contact was required to return to the study site each week for 6 consecutive weeks.

At the initial visit, households were randomly assigned to one of two study groups as described below:

The **Olean group** had the option of selecting eight bags and/or cans of product from a selection of Olean-labeled potato and tortilla chip products and a similar selection of products labeled as containing regular potato and tortilla chips. For this group, the Olean-labeled packages contained Olean chips.

The **Control group** had the option of selecting eight bags and/or cans of product from a selection of Olean-labeled potato and tortilla chip products and a similar selection of products labeled as containing regular potato and tortilla chips. For this group, all the Olean-labeled packages contained regular chips.

(For both groups, packages labeled as containing regular potato and tortilla chip products always contained regular chips.)

At each of the first six visits, the household contacts viewed a display of all of the study products available to them (Exhibit 1). The display contained packages of plain potato chips, seasoned tortilla chips, and plain and seasoned potato crisps (Pringles) either labeled as containing Olean snacks or labeled as containing regular snacks. The household contacts were to look at the display and select what they would normally select for their household by completing a product order form. Orders were filled by personnel at the study site. Household contacts could order up to eight packages of study product per week, in any combination of Olean-labeled and regular chips that they wished. Household contacts in the Olean group who ordered Olean-labeled products received Olean products in Olean packaging. In contrast, household contacts in the Control group who ordered Olean-labeled products received regular chips in the Olean packages. In both groups, household contacts who ordered products labeled as containing regular chips always received regular chips as indicated on the product label.

The household contacts were to ensure that each household member completed a daily record form on each day of the study. The household contact assisted children and/or completed the daily record for them, as needed. On the daily record form, subjects (or the household contact) recorded the amount of Olean-labeled and regular snacks they consumed, an overall rating of the snacks consumed, and whether or not they had any digestive symptoms. If they had symptoms, they were to indicate whether or not they had experienced any of the eight specific symptoms listed on the daily record form or any other digestive symptoms and how the symptoms affected their daily activities. They were also to indicate whether or not they took any medication for the symptoms and whether or not they visited the doctor for the symptoms. The household contact was responsible for returning the completed daily record forms to the study site at each weekly visit.

At each visit, the household contact scheduled a date and time to return to the site the following week to turn in records and select new study product. A comprehensive review of daily records was conducted with the household contact at each of the Visits 2 through Visit 7. Household contacts were strongly encouraged to keep weekly appointments on the same day of the week, but were permitted to vary their appointment day by 1 or 2 days, if necessary. If household contacts were unable to come to the site for a weekly visit (e.g., because of illness), they could arrange to have another adult household member substitute for them if this was deemed permissible by the study staff. At Visit 4, household contacts were asked whether or not there had been any changes in the medications or medical conditions of any of the study participants in their household.

At the sixth (next to last) visit, household contacts received a product acceptance and exit questionnaire on which they were to record product acceptance information. At the final study visit (Visit 7), the household contacts returned the product acceptance and exit questionnaires and were again asked whether or not there had been any changes in the medications or medical conditions of any of the study participants in their household.

Finally, study subjects could be asked to participate in one-on-one interviews and/or focus groups following the completion of the study. These interviews were for the purpose of collecting information regarding the product performance.

A schedule of study procedures as defined by the protocol is presented in Table 1 shown below. Appendix 2 contains a copy of the protocol.

Table 1

Activity Schedule

	Screening Call	Visit Week						
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>
Demographic information	X	X ^a						
Concurrent medications	X	X ^a			X ^b			X ^b
Informed consent		X						
Medical history		X						
Video instructions ^c		X						
Randomization		X						
Selection and distribution of study product		X	X	X	X	X	X	
Daily record forms reviewed and collected			X	X	X	X	X	X
Significant health events					X ^d			X ^d
Adverse events		←-----→						
Product acceptance and exit questionnaire								X

a Confirmation of information obtained at screening.

b Household contact was asked if there had been any change in medications for any household member other than the medications listed on the daily record form.

c Video tape gave instructions on how to complete the daily record form.

d Household contact was asked if there had been any significant change in the medical condition of any household member other than symptoms listed on the daily record form.

Test Group Assignment and Blinding

Randomization was based at the household level such that all individuals in the same household were assigned to the same test group. Households were assigned to their test group via stratified randomization. Two strata at each of the two sites were defined: households with one or more children from 2 to 12 years of age, and households with no child from 2 to 12 years of age. Separate randomization schedules (provided by the project statistician) were used within each of these four strata. Appendix 3 contains the randomization schedule.

All study personnel associated with the collection, processing, or analysis of the data were blinded to the study group assignment. These personnel included the study staff at the site, the investigator, and the sponsor's staff, including study physician, monitors, data managers, and statistician. Study participants were also blinded with respect to the study group assignment. All study personnel and study subjects were blinded with respect to the identity of the study products contained in Olean-labeled packages (i.e., whether the package contained Olean or regular snacks).

Study Sites and Investigator

The study was conducted by Hill Top Research, Ltd. of Miamiville, OH. The protocol was reviewed and approved by the Institutional Review Board of Hill Top Research, Ltd. The study was conducted in a single site in each of two cities, Scottsdale, AZ and St. Petersburg, FL.

The Principal Investigator was Robert S. Sandler, MD, MPH, a consultant to Procter & Gamble Co. The study physician was Robert K. Miday, MD, a Procter & Gamble Co. employee. Curricula vitae of key study personnel are provided in Appendix 2.

Protocol Amendments

There were no amendments to the protocol.

Study Population

Subject Selection

Potential subjects were recruited by Hill Top Research, Ltd. from a database of known panelists who had previously participated in studies at the two sites and from respondents to print advertising about the study.

The protocol specified that up to 1,100 households were to be enrolled into the study, in order that a minimum of 3,000 participants would complete the study. Up to 550 households were to be enrolled into each study group, with about half from each of the two study sites. A minimum of 600 children (ages 2 to 12 years) and 400 elderly subjects (aged 65 years or greater) were to be enrolled.

Inclusion/Exclusion Criteria

Male or female subjects were eligible to be enrolled in the study if they met the following inclusion criteria:

- at least 2 years of age at time of enrollment
- willing to consume Olean chips in the study
- willing and able to comply with all study procedures, including completion of daily records by each household member
- provided the investigator or delegate with informed consent that they had signed or that had been signed by their parent or guardian if they were minor subjects

In addition, each household was required to meet the following inclusion criteria:

- minimum household chip consumption criteria (at least one half of household members reported consuming potato or tortilla chips, on average, at least four times in previous month)
- all eligible household members met inclusion criteria for household to be enrolled (except for 2 year age minimum and allergy/intolerance to potato and corn food products as listed below)

Subjects were excluded from study entry if they met the following exclusion criteria:

- allergy/intolerance to potato and corn food products or medically precluded from consuming potato chip and corn chip products.
- security/market research conflict

Only households in which all eligible members volunteered to participate were enrolled in the study. The total participation in each household was to be at least 50% of the members.

There were no restrictions with respect to the medications subjects could take during the study.

Each household was assigned a unique four-digit number, and each subject within the household received a two-digit number. When used in conjunction with the first five characters of the protocol number and the four-digit investigator number, this sequence uniquely identified each subject in the study. This number remained with the subject throughout the study and was used in all references to the subject on this study. Once assigned, this number was not used for any other subject.

Example:	FP149	-1077	-1000	-01
	Protocol No.	Investigator No.	Household No.	Subject No.

Removal of Subjects from the Study

Households whose contacts missed more than one visit could be withdrawn from the study by the site study staff, with approval from the study sponsor and investigator.

Also, if the household failed to complete any 2 weeks of daily records, it was to be dropped from the study.

If an adverse event occurred, the subject could be withdrawn from the study at the discretion of the site physician. If a subject were withdrawn, the rest of the household could continue to participate in the study. If study product use was discontinued as a result of any other finding, the reason was to be reported to the clinical monitor and to the study physician. An updated listing of all study participants who dropped out of the study, regardless of reason, was to be forwarded to the clinical monitors on a weekly basis.

Subjects could drop out of the study at any time if they so desired.

Study Products

Study Products and Packaging

The study products consisted of regular chips and Olean chips manufactured by Frito-Lay and Pringles. The Frito-Lay product varieties consisted of Lays, Ruffles, Doritos Nacho Cheesier, and Doritos Cooler Ranch. The Pringles product varieties consisted of Original, Barbecue, and Sour Cream & Onion. For each product variety there were Olean product in Olean-labeled packages, regular product in Olean-labeled packages, and regular product in packages labeled as containing regular chips. All regular product was packaged in 6.0- to 9.0-oz current market packages (bags or cans); all Olean-labeled product was packaged in 5.5- to 7.5-oz current test market packages (bags or cans). Appendix 4 presents information about the manufacture, shipment, and disposal of the study products and lists each study product variety and package size and each Frito-Lay and Pringles product and its unique series of control and product identification numbers.

The Olean-labeled products were in current test market packaging (Frito-Lay WOW or Pringles Fat Free) with the Olean logo on the package. All Olean-labeled packages displayed the following information statement: "This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added." Olean-labeled product given to household contacts in the Olean group contained Olean snacks. Olean-labeled product given to household contacts in the Control group contained regular snacks. The Olean-labeled packages were identical in appearance regardless if they contained Olean snacks or regular snacks.

The regular snacks in the packages labeled as containing regular chips were also in standard market packaging (Pringles, Lays, Ruffles, or Doritos). The product in the packages labeled as containing regular chips that were given to household contacts in both groups contained regular snacks, as indicated on the product labeling.

Stickers were applied to each package stating that the product was test product and not for sale. The sticker also displayed a toll-free telephone number that subjects could call if they had questions or comments about the study or study products. A non-removable sticker with new bar codes that uniquely identified each product was applied over the existing UPC bar code for all products (the identification number code was not available to study personnel other than the individual responsible for tracking product inventory). The new bar codes were used to verify that households received the appropriate product and to ensure that the study personnel remained blinded to the package contents.

Selection and Consumption of Study Products

At each site visit, the household contacts were shown a display of the variety of products available to them (Exhibit 1). Household contacts in both test groups chose from among seven Olean-labeled and seven regular snacks, choosing any combination of Olean-labeled and regular chips that they wished. Household contacts were to look at the display and select the products that they normally would if they were purchasing them for their household. Each household contact could choose a maximum of eight packages per week by completing a product order form. Appendix 5 contains the case report forms and a sample product order form.

Product orders were filled by study staff specifically assigned to that duty who had no contact with the study subjects. After the household contact had completed the product order form, a staff member (product carrier) took the order form to the product distribution center, which was located in a separate part of the building from the rooms visited by the study subjects, and gave it to the staff member who would fill the order from the product inventories. This staff member matched the household number with the appropriate product and filled the order accordingly by placing the appropriate packages in a bag marked with the household number. To verify that the order had been filled correctly, a staff member scanned the household number bar code from the product order form and scanned all of the packages in the bag. After the order had been verified, the carrier delivered the bagged packages to the household contact, who had remained in another part of the building. Using these procedures, the study staff who were involved with collection, processing, or analysis of data, as well as the study subjects, remained blinded with respect to the test group assignments.

Household contacts in the Olean group who chose Olean-labeled packages received Olean-labeled packages that contained Olean snacks. Household contacts in the Control group who chose Olean-labeled packages received Olean-labeled packages that contained regular snacks. Household contacts in both test groups who chose regular snacks received packages containing regular products. Since the whole household was assigned to one of the two test groups, all members of the household received the same test products for consumption.

The household contact was instructed not to share the test chips outside of the household. They were also asked not to consume any chips other than those provided at the study site. Unused chips were not returned to the study site. Subjects were instructed to dispose of their test product at the end of the study.

Data Collection

Screening Phone Call

A screening phone call was made to each potential household contact to determine interest and eligibility for participation in the study and to collect demographic information and information on current medications. During this call, subjects provided information on household snack consumption; employment; allergy, intolerance, or a medical reason that would limit any household member from eating potato or corn food products; and willingness of household members to eat Olean snacks. For households that qualified for the study, the caller identified each person in the household that would be participating and collected information on each starting with the main wage earner and progressing from the oldest to youngest additional household members. For each person, birth date, sex, race, and current medications and dosages were recorded. For the main wage earner, the highest level of schooling reached and occupation were also recorded. The total yearly household income was noted as well if the household member chose to give that information.

Site Visits

At the initial site visit, the inclusion/exclusion criteria for the study were reviewed and adult household members checked and verified the information collected during the screening phone call. They also completed medical history forms for each household member. In addition, household members 18 years of age or older were asked questions about functional bowel symptoms. Appendix 5 contains the case report forms.

At Visits 4 and 7, household contacts were asked whether or not there had been any change in their medications or the medications of any participant in their household other than changes noted on the daily record form. In addition, they were asked whether there had been any significant change in their medical condition, or that of any participant in their household, other than the symptoms listed on the daily record form.

Daily Record

At the first six study visits, household contacts were given a daily record form to be completed by each household member each day during the study. Appendix 5 contains the case report forms and a sample daily record form. The household contact assisted children and/or completed the daily record form for them, as needed. If the household contact or individual household members went out of town (for up to one week), they were instructed to maintain their daily record forms, even if no study chips were available during that period.

On the daily record form, subjects indicated how much of the Olean chips they ate and how much of the regular chips they ate (none, less than 1/4 package, about 1/4 package,

about 1/2 package, about 3/4 package, about 1 package, more than 1 package [subjects who consumed more than one package wrote in the amount they ate by 1/4 of package]). In determining the amount of chips eaten, as a rule, subjects were to consider three handfuls to be equivalent to one quarter of a bag of chips.

The daily record form also asked, "Did you have any digestive symptoms today that you want to report?"

Subjects who had digestive symptoms were to indicate whether or not they had experienced the following symptoms:

- heartburn or indigestion
- nausea or queasiness
- vomiting
- gas
- bloating
- abdominal cramping or pain
- more frequent bowel movements
- looser stool
- other digestive symptoms. List _____

Subjects who had digestive symptoms were also to indicate how the symptoms affected their work, school, activities, or routine by choosing which of the following best described their situation:

- Noticed but did not affect my work, school, activities or routine
- Noticed and slightly affected my work, school, activities or routine
- I missed some time at my work, school, activities, or routine
- I missed all day at my work, school, activities, or routine

Subjects were asked whether or not they took any medication for their symptoms and if so, to list them, and whether or not they visited the doctor for their digestive symptoms.

Household contacts were responsible for returning the completed daily record forms on a weekly basis. At each site visit, the personnel at the site reviewed the daily record forms in the presence of the subject for accuracy and completeness. If the daily records had missing information or were incorrectly filled out, then the error was explained to the household contact and he or she was urged to be more careful. If the daily record were missing information from the questions relating to product consumption and quality, the errors were explained to the subject but no attempt was made to capture the information. If the daily record were missing information from the questions on digestive symptoms, then the study days for which this information was missing were noted and the household contacts were asked whether or not they had any digestive symptoms they wanted to report for those days. If so, the site personnel asked them on which days the symptoms

occurred and whether or not they had had any of the symptoms listed on the daily record form or any other digestive symptoms. They were also asked how the symptoms affected their activities or routine, whether or not they visited a doctor for these symptoms, and whether or not they had taken any medication for these symptoms. This information was used in the analysis of digestive symptoms along with the information recorded by the subjects in their daily record forms.

Product Acceptance and Exit Questionnaire

At Visit 6, household contacts were given a product acceptance and exit questionnaire which they were to complete and turn in at the last study visit. Appendix 5 contains the case report forms and a sample product acceptance and exit questionnaire. On the questionnaire, subjects were to rate each of the products they tried (excellent, very good, good, fair, poor) and to indicate whether the product met expectations, neither met nor did not meet expectations, or did not meet expectations. In addition, they were asked to list the things they liked and did not like about the products they tried. They were also asked to indicate which kind of chips they thought were in the Olean-labeled packages (Olean chips, regular chips, don't know).

At the final study visit, household contacts returned the completed product acceptance and exit questionnaire and the final set of daily record forms.

Following the completion of the study, some subjects were asked to participate in one-on-one interviews and/or focus groups for the purpose of providing information regarding product performance.

Adverse Events

Adverse experiences were assessed from the time subjects made their first study visit until the exit from the study. Subjects were instructed to report any medically related changes in their well-being to study personnel. In addition, at Visits 4 and 7, study personnel asked household contacts whether there had been any significant change in their medical condition or that of any participant in their household (other than any symptoms listed on the daily record form). Study participants were provided with a toll-free telephone number that they could call to ask questions or to report adverse health experiences. This number provided study participants with 24-hour access to the site personnel for management of adverse experiences.

All health-related symptoms were captured either in the daily record and/or on an adverse experience form. Gastrointestinal events reported by the subjects on the daily record form were captured separately from adverse experiences. However, GI adverse events for which study participants saw a physician were also captured as adverse experiences. Non-gastrointestinal events listed under "other" in response to the digestive symptoms questions in the daily record were also captured as adverse experiences.

An adverse event was defined as any undesirable health experience occurring to a subject during the clinical study, whether or not the event was considered to be related to the investigational products. Gastrointestinal events noted on the daily record forms were analyzed separately and were not additionally captured as adverse events unless the subject saw a physician as a result of the event.

For all adverse events, site personnel were to record the dates of onset and resolution of the event, as well as the source of the report (spontaneous, elicited, observed). The maximum severity of the event was rated according to the following scale:

<u>Severity</u>	<u>Description</u>
Mild	Normal activities unimpaired
Moderate	Normal activities impaired
Severe	Unable to perform normal activities
Unknown	Unknown

For moderate or severe events, a description of how activities were affected was requested. The site personnel also noted whether or not therapy was administered for the symptoms and if so, provided a description of the therapy given. Events were characterized as a single continuous event or intermittent episodes, and the clinical outcome of the event was described as resolved, resolved with sequela, not resolved, subject died, or unknown. Finally, events were characterized as serious or not serious. If the event was serious, it was noted whether the event was fatal, life threatening, cancer/neoplasm, permanent or severe disability, congenital anomaly, or hospitalization or whether intervention was required to prevent one of these outcomes or whether emergency or urgent care procedures were required.

Adverse events defined as serious and those resulting in withdrawal were immediately reportable. In the event of a serious or immediately reportable adverse event, the study site was required to notify the sponsor within 24 hours of being informed or becoming aware of the event. Medical records were requested for all serious events.

Ongoing adverse events were reviewed at each site visit. Subjects with on-going symptoms were followed until the event was resolved or until, in the opinion of the site physician, follow-up was no longer indicated. If an adverse experience occurred, the subject could be withdrawn from the study at the discretion of the site physician. The site physician reviewed all adverse events on a weekly basis.

Conduct of the Study

The study was conducted in accordance with Good Clinical Practices as contained in the U.S. Code of Federal Regulation, Title 21, Parts 50 and 56, and the Standard Operating Procedures of Hill Top Research, Ltd.

Institutional Review Board

The clinical investigation, including the protocol, the advertisement, the informed consent, and all addenda for this study, was reviewed by an Institutional Review Board in accordance with Title 21 of the Code of Federal Regulations, Parts 50 and 56. Approval by the Board was obtained on 17 June 1997, prior to initiation of the investigation. Appendix 2 contains the Institutional Review Board approval letter.

Informed Consent

Each subject provided the investigator or delegate with a signed informed consent in order to participate in this study. Appendix 2 contains a copy of the informed consent forms. The consent form complied with all applicable regulations governing protection of the subjects in the study, and was approved by the Institutional Review Board. For minors (<18 years of age), the consent was signed by a parent or legal guardian. Minors (generally ≥ 7 years of age) also signed the informed consent. Verbal assent was obtained, when possible, for those younger than 7 years of age.

The informed consent form stated the purpose of the study, described the study procedures, and explained that the Olean-labeled packages that the subjects selected may contain chips made with Olean or they may contain regular full-fat chips. The form also stated, "During this study, as with other changes in the diet or eating habits, some individuals may notice digestive changes or discomfort such as cramping or loose stools."

Study Product Accounting Procedure

Study product inventory records were kept by the site personnel. The records show the study product shipped and received, the study product dispensed to the households, and the disposition of damaged or unused study product. These records, like all other records associated with the study, were subject to inspection by FDA and Procter & Gamble Co. auditors.

Statistical Methods

Population Analyzed

All subjects were considered evaluable up to the point that data existed for that subject. Any subject who did not eat Olean-labeled chips was not included in the analysis.

Analysis of the Data

In this parallel group placebo-controlled study, randomization was based at the household level such that all individuals in the same household were in the same test group. To account for the possible correlation of within-household information, variance estimation was carried out using the sampling theory approach for ratio estimates as described by Lee²⁰ and Henderson *et al.*²¹ Testing for treatment differences was then carried out using the usual normal approximation method. [Note: This analysis replaces the permutation testing that was specified in the protocol. This analysis is more comprehensive in that it yields standard errors in addition to p-values and is equally valid given the large sample sizes (>1500/treatment group).]

Note: In the protocol, the primary response variable was defined as the “% of eating days where a GI event was reported within 2 days.” Interpretation of this variable is clear when eating days are separated in time by more than 2 days. However, in this study, most individuals ate study product on numerous days such that one GI event could fall into the time window for 1, 2, or 3 eating days. As such, the “% of eating days” variable can be calculated but cannot be clearly interpreted because each event can be associated with 2 or 3 eating days. As a result, this response variable will be presented in the analysis section but only as a secondary, supporting analysis.

Primary Analysis

The primary data analysis was to compare the occurrence and frequency of gastrointestinal symptoms between individuals who consumed Olean-labeled Olean chips and those who consumed Olean-labeled regular chips.

The primary response variable was the percentage of individuals that reported a gastrointestinal event. For those that reported a GI event, the number of symptom days was also compared between treatments. The occurrence and frequency of each of the gastrointestinal symptoms listed on the daily record form were compared separately. Multiplicity adjustment of the individual p-values has not been performed.

Secondary Analysis

The percentage of times that Olean-labeled snacks were consumed that were followed within 2 days by a gastrointestinal event was also compared between the treatment groups.

Additional exploratory analyses were also performed.

Sample Size Determination

A sample size of 500 households per treatment group was planned for this study. Assuming that at least one person per household eats Olean-labeled chips, one obtains a sample size of at least 500 at the subject level, which ensures at least 80% power (0.05 significance level) for detecting a difference in GI event frequencies of 6% to 8%, depending on background symptom frequencies. However, sensitivity for the primary analysis (based on individual eating occasions) should be even greater. For example, if households average around 18 eating occasions (three/week) and if little correlation exists among households, then an effective sample size of 9,000 occurs at the eating occasion level, which ensures 80% power for detecting (0.05 significance level) differences in GI event frequencies in the range of 1%. Hence, under modest assumptions, study sample sizes yield adequate power for detecting differences in GI event frequencies.

Results

Study Population

Subject Accountability

A total of 3,250 subjects from 1,160 households, 1,651 from 579 households in the Olean group and 1,599 from 581 households in the Control group, were randomized, filled out the study forms, and took home study product. A total of 1,732 (53.3%) of the subjects were enrolled at the Scottsdale, AZ site, and 1,518 (46.7%) were enrolled at the St. Petersburg, FL site.

Of the 3,250 subjects, 45 subjects, 17 in the Olean group and 28 in the Control group, attended the first visit and received study product but were lost to follow-up, never returning for the second visit or returning any daily record forms. In addition, 24 subjects, 14 in the Olean group and 10 in the Control group, did not eat any Olean-labeled chips during the study. Thus, a total of 3,181 subjects from 1,138 households; 1,620 from 568 households in the Olean group and 1,561 from 570 households in the Control group, ate Olean-labeled chips and were evaluable for data analysis.

Eighty-five subjects from 42 households, 39 from 22 households in the Olean group and 46 from 20 households in the Control group, discontinued the study after the second visit. Their data were included up to discontinuation. The disposition of the study subjects is shown in Exhibit 2.

Of the 45 subjects who dropped out of the study before the second visit, 4 subjects, 2 in the Olean group and 2 in the Control group, could not be contacted, and 35 subjects, 10 in the Olean group and 25 in the Control group, dropped out because of scheduling conflicts; 5 subjects, 4 in the Olean group and 1 in the Control group, dropped out for personal reasons; and 1 subject in the Olean group dropped out because he went on a salt-restricted diet.

Of the 85 subjects who withdrew from the study after the second visit, 23 subjects, 10 in the Olean group and 13 in the Control group, could not be contacted and 59 subjects, 29 in the Olean group and 30 in the Control group, withdrew for personal reasons or because of schedule conflicts. Two additional subjects, both in the Control group, were discontinued because of death, and one additional subject, also in the Control group, dropped out of the study because of a GI adverse event.

Demographic Characteristics

Demographic characteristics were well-balanced between the Olean and Control groups. Specifically, the Olean and Control groups were similar with respect to age, sex, and race (Exhibit 3). Of the 3,181 evaluable subjects, 885 (27.8%) were children 2 to 12 years of

age, 227 (7.1%) were teens 13 to 17 years of age, 1,667 (52.4%) were adults 18 to 64 years of age, and 402 (12.6%) were elderly, 65 to 89 years of age. There were slightly more females (56.0%) than males (44.0%), and almost 90% of the subjects in both study groups were Caucasian.

The demographic characteristics of the 69 subjects who were not evaluable because they did not eat Olean-labeled chips were similar to those for the population of 3,181 evaluable subjects except that the percentage of children was higher and the percentage of elderly was lower in the population of subjects who were not evaluable (Exhibit 4).

For each household, information was collected about the highest level of schooling reached by the main wage earner, the occupation of the main wage earner, and yearly household income. The test groups were comparable with respect to the highest level of education reached, the occupation of the main wage earner, and yearly household income (Exhibit 5).

Medical History

Study participants were asked about past history of a number of medical conditions. The responses to these questions show that there was a broad range of common medical conditions in the population studied and that there were no important differences between the Olean and Control groups, particularly with regard to self-reported gastrointestinal conditions (Exhibit 6).

Information about functional bowel disease was sought from all subjects in the general medical history (Exhibit 6) and from subjects 18 years of age and older in a separate questionnaire on the symptoms of irritable bowel syndrome (IBS) (Appendix 8). In the general medical history, 32 (2.0%) of the 1,620 subjects in the Olean group and 34 (2.2%) of the 1,561 subjects in the Control group self-reported that they had an irritable bowel, spastic bowel, or functional bowel problem. On the IBS history questionnaire loose or watery stools were reported by 81 (7.7%) of the 1,053 respondents in the Olean group and by 96 (9.4%) of the 1,021 respondents in the Control group, and hard or lumpy stools were reported by 96 (9.9%) of the 1,053 respondents in the Olean group and by 102 (10.0%) of the 1,022 respondents in the Control group.

Protocol Deviations

The protocol specified that household contacts were to return to the study site within 5 to 9 days of the previous visit to return daily records and choose study product. Of the 1,138 evaluable households, nine households, five in the Olean group and four in the Control group, had study visits that fell outside of the range of days specified by the protocol. None of the households missed more than one visit.

The product order forms for two households at the St. Petersburg site were inadvertently switched at the first visit. As a result, household 3348, which was randomized to the Olean group, received the control product, and household 3248, which was randomized to the Control group, received Olean product at each study visit. Consequently, the study group assignment for household 3348 was changed from Olean to Control, and the study group assignment for household 3248 was changed from Control to Olean.

Product Consumption

Consumption of Regular Product

Approximately one-half of the products selected by the household contacts were Olean-labeled products and half were regular-labeled full-fat products. Consumption of regular-labeled full-fat product was also comparable between the two groups. The median numbers of eating days for regular-labeled product were 20 and 18 in the Olean and Control groups, respectively. The numbers of days on which subjects consumed both Olean-labeled and regular-labeled product were also comparable between the two groups. The median numbers of eating days for consumption of both regular-labeled and Olean-labeled product were 5 and 6 for the Olean and Control groups, respectively (data not shown).

All Subjects Who Consumed Olean-Labeled Product

During the 6-week study, the median number of eating days for all study subjects who consumed Olean-labeled product were 20 and 21 for the Olean and Control groups, respectively (Exhibit 7). Subjects in the top 10% with respect to the number of eating days ate the Olean-labeled products almost every day of the study, consuming product on ≥ 35 days in the Olean group and ≥ 36 days in the Control group. The total amount eaten was comparable between the Olean and Control groups with slightly greater consumption in the Control group. The difference at the 90th percentile (0.33 oz), represents about 6 potato chips.

The percentages of subjects who consumed Olean-labeled chips on each day of the study show that overall consumption was consistent throughout the study (Exhibit 8), with half of all subjects in the two study groups consuming the Olean-labeled products on each day of the study. In both study groups, the percentages of subjects consuming Olean-labeled chips were consistent from week to week over the course of the study and showed no trends. The percentages of subjects who consumed Olean-labeled chips each week were comparable between the two study groups, with differences generally less than 5%.

Males and Females

The median number of eating days in males was 18 and 19 in the Olean and Control groups, respectively (Exhibit 9), and the median number of eating days in females was 21

and 22 in the Olean and Control groups, respectively (Exhibit 10). Male and female subjects in the top 10% with respect to the number of eating days ate the Olean-labeled products almost every day of the study, with males consuming product on ≥ 34 days in the Olean group and ≥ 36 days in the Control group, and females consuming product on ≥ 35 days in the Olean group and ≥ 37 days in the Control group. For both sexes, the total amount eaten was comparable between the Olean and Control groups, with slightly greater consumption by the Control group. The total cumulative amount eaten by females over the entire study was slightly greater than that by males. Although females consumed on average fewer ounces of chips per eating day, they ate product on more eating days.

Adults 18 to 64 Years of Age

Half of the study subjects were adults 18 to 64 years of age. During the 6-week study, the median number of eating days for adults was the same as for the overall population, with adults consuming Olean-labeled product 20 and 21 days for the Olean and Control groups, respectively (Exhibit 11). Adult subjects in the top 10% with respect to the number of eating days ate the Olean-labeled products almost every day of the study, consuming product on ≥ 34 days in the Olean group and ≥ 35 days in the Control group. The total amount eaten was comparable between the Olean and Control groups with slightly greater consumption in the Control group, with the Control group eating a total of 2.5 oz more over the course of the study.

Children 2 to 12 Years of Age

As a group, the 885 children 2 to 12 years of age in this study ate product often; the median number of eating days was 18 in both the Olean and Control groups (Exhibit 12). The total amount of Olean-labeled product eaten in children was comparable in the Olean and Control groups with overall consumption of Olean product about 30% lower in children than that in the adult population in the study. Children in the top 10% with respect to the number of eating days ate the Olean-labeled products on most days, consuming product on ≥ 32 days in both study groups.

Teenagers 13 to 17 Years of Age

Consumption by teenagers 13 to 17 years of age was slightly lower than that in the overall population. While the average amount eaten per day by the teens was very similar to the amount eaten per day by the adult population in the study, the median number of eating days for teens was lower with 15 and 18 days in the Olean and Control groups, respectively (Exhibit 13). Teenagers in the top 10% with respect to the number of eating days ate the Olean-labeled products on most days, consuming product on ≥ 28 days in the Olean group and ≥ 31 days in the Control group.

Elderly Subjects 65 to 89 Years of Age

The median number of eating days for elderly subjects 65 to 89 years of age were 27 and 32 in the Olean and Control groups, respectively (Exhibit 14). It was of interest in this study that subjects in this age range had the highest levels of consumption. While the average amount eaten each day by elderly subjects was similar to that eaten by the younger adult population (18 to 64 years of age), they ate product more often than any other group in the study. The elderly subjects in the top 10% ate ≥ 2.51 oz on each eating day in the Olean group and ≥ 2.96 oz on each eating day in the Control group. In the heaviest consumers (90th percentile), cumulative consumption during the study was 101 oz in the Control group compared to 72 oz in the Olean group.

Gastrointestinal Symptoms

All Subjects Who Consumed Olean-Labeled Product

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of subjects who reported one or more GI symptoms of any type during the study (38.2% vs. 36.9%, Olean vs. Control, $p=0.60$) (Exhibit 15). There also were no significant differences between test groups in the percentage of subjects reporting any of the eight individual GI symptoms evaluated, except that the percentage of subjects reporting nausea was greater in the Control group than in the Olean group (8.4% vs. 5.7%, Control vs. Olean, $p=0.02$).

For subjects who reported GI symptoms, the number of days on which GI symptoms were reported was evaluated. A symptom-day is defined as a day on which at least one symptom was reported. Analyses of the mean number of symptom-days also showed no statistically significant differences between the two test groups for "any GI event" or for any of the individual GI symptoms, except that the number of symptom-days for which more frequent bowel movements was reported was approximately 1 day more in the Olean group than in the Control group (3.7 days vs. 2.8 days, Olean vs. Control, $p=0.04$) (Exhibit 16).

For the subjects who reported symptoms, the impact of those symptom(s) on their daily activities was rated each day according to one of four categories (Exhibit 17). In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities. Symptoms were rated as having no or slight impact on activities on 98.2% of symptom-days by subjects in the Olean group and on 97.2% of symptom-days by subjects in the Control group (Exhibit 17). Also, the percentage of symptom-days on which subjects rated their symptoms as having a greater impact (categories 3 and 4) was slightly higher in the Control group than in the Olean group (2.8% vs. 1.8%, Control vs. Olean).

Male Subjects

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of male subjects who reported one or more GI symptoms of any type during the study (36.2% vs. 33.8%, Olean vs. Control, $p=0.44$) (Exhibit 18). There also were no significant differences between test groups in the percentage of subjects reporting any of the eight individual GI symptoms evaluated, except that the percentage of subjects reporting nausea was greater in the Control group than the Olean group (7.4% vs. 3.9%, Control vs. Olean, $p=0.01$).

Analyses of the mean number of symptom-days also showed no statistically significant differences between the two test groups for "any GI event" or for any of the individual GI symptoms, except that the number of symptom-days for cramping was greater in the Control group than in the Olean group (2.5 days vs. 1.8 days, Control vs. Olean, $p=0.04$) (Exhibit 19).

In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities (Exhibit 20). Symptoms were rated as having no or slight impact on activities on 98.5% of symptom-days by subjects in the Olean group and 97.7% in the Control group (Exhibit 20). Also, the percentage of symptom-days on which subjects rated their symptoms as having a greater impact (categories 3 and 4) was slightly higher in the Control group than in the Olean group (2.3% vs. 1.5%, Control vs. Olean).

Female Subjects

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of female subjects who reported one or more GI symptoms of any type during the study (39.7% vs. 39.4%, Olean vs. Control, $p=0.92$) (Exhibit 21). There also were no significant differences between test groups in the percentage of subjects reporting any of the eight individual GI symptoms evaluated ($p \geq 0.15$).

Analyses of the mean number of symptom-days showed that the groups differed significantly with respect to the mean number of symptom-days for any GI event (5.4 days vs. 4.2 days, Olean vs. Control, $p < 0.01$), gas (4.9 days vs. 3.7 days, Olean vs. Control, $p=0.01$), and the number of days for which more frequent bowel movements was reported (3.9 days vs. 2.9 days, Olean vs. Control, $p=0.03$) (Exhibit 22). Although these differences were statistically significant, they were small, not clinically important, consisting of only about 1 day more of reporting.

In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities (Exhibit 23). Symptoms were rated as having no or slight impact on activities

on 98.0% of symptom-days by subjects in the Olean group and on 96.9% of symptom days by subjects in the Control group (Exhibit 23). Also, the percentage of symptom-days on which subjects rated their symptoms as having a greater impact (categories 3 and 4) was slightly higher in the Control group than in the Olean group (3.1 % vs. 2.0%, Control vs. Olean).

Adults 18 to 64 Years of Age

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of adult subjects who reported one or more GI symptoms of any type during the study (44.7% vs. 41.5%, Olean vs. Control, $p=0.28$) (Exhibit 24). There also were no significant differences between test groups in the percentage of subjects reporting any of the eight individual GI symptoms evaluated, except that the percentage of subjects reporting gas was greater in the Olean group than in the Control group (30.6% vs. 24.8%, Olean vs. Control, $p=0.03$).

For adult subjects who reported GI symptoms, the number of days on which GI symptoms were reported was evaluated. Analyses of the mean number of symptom-days showed significant differences between the two test groups for "any GI event" and for more frequent bowel movements. During the six weeks of the study, these symptoms were reported on average one day more in the Olean group than in the Control group (5.7 days vs. 4.6 days, Olean vs. Control for "any GI event," $p=0.03$ and 4.1 days vs. 2.9 days, Olean vs. Control, for reporting of more frequent bowel movements, $p=0.02$), (Exhibit 25).

In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities. Symptoms were rated as having no or slight impact on activities on 98.2% of symptom-days by subjects in the Olean group and on 97.0% of symptom-days by subjects in the Control group (Exhibit 26). Also, the percentage of symptom-days on which subjects rated their symptoms as having a greater impact (categories 3 and 4) was slightly higher in the Control group than in the Olean group (3.0% vs. 1.8%, Control vs. Olean).

Children 2 to 12 Years of Age

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of children 2 to 12 years of age who reported one or more GI symptoms of any type during the study (30.1% vs. 30.5%, Olean vs. Control, $p=0.93$) (Exhibit 27). There also were no significant differences between test groups in the percentage of subjects reporting any of the eight individual GI symptoms evaluated, except that the percentage of subjects reporting "other symptom" was greater in the Control group than in the Olean group (2.3% vs. 0.2%, Control vs. Olean, $p=0.04$). Most of the symptoms listed as "other symptoms" were constipation.

Analyses of the mean number of symptom-days also showed no statistically significant differences between the two test groups for "any GI event" or for any of the individual GI symptoms ($p \geq 0.22$) (Exhibit 28).

In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities (Exhibit 29). Symptoms were rated as having no or slight impact on activities on 97.6% of symptom-days by subjects in the Olean group and on 96.4% of symptom-days by subjects in the Control group (Exhibit 29). Also, the percentage of symptom-days on which subjects rated their symptoms as having a greater impact (categories 3 and 4) was slightly higher in the Control group than in the Olean group (3.6% vs. 2.4%, Control vs. Olean).

Teenage Subjects 13 to 17 Years of Age

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of teenage subjects 13 to 17 years of age who reported one or more GI symptoms of any type during the study (33.6% vs. 39.2%, Olean vs. Control, $p=0.42$) or with respect to any of the eight individual GI symptoms evaluated ($p \geq 0.06$) (Exhibit 30).

Analyses of the mean number of symptom-days also showed no statistically significant differences between the two test groups for "any GI event" or for any of the individual GI symptoms ($p \geq 0.06$) (Exhibit 31).

In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities (Exhibit 32). Symptoms were rated as having no or slight impact on activities on 98.7% of symptom-days by subjects in the Olean group and on 97.9% of symptom-days by subjects in the Control group (Exhibit 32). Also, the percentage of symptom-days on which subjects rated their symptoms as having a greater impact (categories 3 and 4) was slightly higher in the Control group than in the Olean group (2.1% vs. 1.3%, Control vs. Olean).

Elderly Subjects 65 to 89 Years of Age

There was no statistically significant difference between the Olean and Control groups with respect to the overall percentage of elderly subjects 65 to 89 years of age who reported one or more GI symptoms of any type during the study (32.2% vs. 30.9%, Olean vs. Control, $p=0.79$) (Exhibit 33) or with respect to any of the eight individual GI symptoms evaluated ($p \geq 0.12$).

Analyses of the mean number of symptom-days also showed no statistically significant differences between the two test groups for "any GI event" or for any of the individual GI symptoms ($p \geq 0.13$) (Exhibit 34).

In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities (Exhibit 35). Symptoms were rated as having no or slight impact on activities on 98.5% of symptom-days by subjects in the Olean group and on 99.7% of symptom-days by subjects in the Control group (Exhibit 35).

Other GI Events

In addition to the eight specific GI symptoms listed on the daily records, there was a ninth category that allowed subjects to write in any other GI symptom that they wanted to report that day. The symptoms reported in this category are all summarized as "other GI symptoms," presented by number of subjects reporting the symptom and number of reports in Exhibit 36. The most frequently reported symptoms, by number of subjects, were constipation (15 Olean vs. 17 Control), diarrhea (8 Olean vs. 7 Control), discolored stool (5 Olean vs. 2 Control), and stool hardness (3 Olean vs. 2 Control). The remainder of the symptoms were reported by a total of three or fewer subjects. In the diarrhea category, 21 reports were made by eight subjects in the Olean group, and 10 reports were made by seven subjects in the Control group. The difference between the groups with respect to the number of reports of diarrhea was due in large part to one subject (No. 1030-02) who reported diarrhea a total of seven times on her daily records. A narrative for this subject is included in Appendix 9. There was no apparent difference in the two test groups in the number of subjects who reported individual GI symptoms that were included in the "other GI symptoms" category.

There were no reports of leakage of oil or fecal incontinence.

High-Level Consumers of Olean-Labeled Snacks

To determine if GI symptoms were reported by a greater percentage of subjects consuming high levels of olestra, the occurrence of GI symptoms was analyzed taking into account both the number of days on which Olean-labeled products were eaten and the total amount of Olean-labeled products consumed.

To compare the GI symptoms of the subjects who ate Olean-labeled products most often with the GI symptoms of all other subjects in the study, all subjects were categorized according to the number of days on which they ate Olean-labeled product (1-7 days, 8-14 days, 15-21 days, etc.). The percentage of subjects reporting GI symptoms was plotted for each category (Exhibit 37).

In the figure, the horizontal lines on each graph represent the overall mean percentage of Olean subjects (solid line) and Control subjects (broken line) who reported GI symptoms, as provided in Exhibit 14. The 90th percentile were those subjects who ate Olean-labeled products on more than 35 days of the study.

The percent of subjects in the Olean group who reported at least one GI symptom anytime during the study was not related to the number of days Olean-labeled products were consumed (Exhibit 37, "Any GI"). The same result was true for each of the individual symptoms recorded (Exhibit 37). There was no dose-responsive increase in frequency of symptom reporting as the number of days on which Olean products were consumed. For the Control group, it was noted that the percentage of subjects who reported the symptoms "Any GI", Gas, Looser Stools, or More Freq BMs was lower at the highest levels of consumption of Olean-labeled products (Exhibit 37).

There were five instances (Heartburn, Nausea, Gas, Other) where statistically significant differences were noted between the percent of subjects reporting individual symptoms in the Olean and Control groups, (as indicated on the figure by asterisks). These differences were sporadic and there was no pattern related to increasing days of consumption.

To compare GI symptom reporting in the subjects who ate the most Olean-labeled products with the GI symptom reporting of all other subjects in the study, all subjects were categorized according to their total consumption by 10 oz increments, except for the highest consuming group which included all those subjects who consumed at or above 70 oz of product during the course of the study. The 90th percentile for the Olean group included those subjects who consumed 59.4 oz or more during the entire study and those who consumed 70.0 oz or more in the Control group. The percentage of subjects reporting GI symptoms was plotted for each category Exhibit 38. In this way, the percent of subjects in the Olean group reporting GI symptoms among those in the highest consuming categories with respect to total consumption can be readily compared to the Control group, and to those subjects in the Olean group who consumed less product. Again, the horizontal lines on each graph represent the overall percentage of Olean subjects (solid line) and Control subjects (broken line) who reported GI symptoms, as provided in Exhibit 14.

The percent of subject who reported at least one GI symptom anytime during the study was not related to the amount of Olean-labeled consumed. This was the case for both the Olean and Control groups (Exhibit 38, Any GI)

There was no dose-responsive increase in frequency of symptom reporting with the number of days on which Olean products were consumed. There were five instances (Exhibit 38, Gas, More Freq BMs, and Looser Stools) where there were statistically significant differences between the percent of subjects reporting individual symptoms in the Olean and Control groups. While the percentage of subjects was slightly higher at two total dose increments (30 - 40 oz and 70 - 250 oz) in the Olean group, the percentage of subjects who reported these symptoms in the Control group was lower at these total dose increments compared to those subjects in the same group who ate lower total doses.

To understand whether the higher incidence of symptoms reported by the subjects consuming the largest doses of Olean-labeled products had any impact on these subjects,

we evaluated the impact of GI symptoms on the daily activities of the individuals who ate a total of 65 or more ounces (90th percentile overall) of Olean-labeled chips (Exhibit 39). In both test groups, symptoms were generally rated as having a very minor impact, and there was no apparent difference between test groups in the impact of symptoms on activities (Exhibit 39). Symptoms were rated as having no or slight impact on activities for 97.8% of the symptoms in the Olean group and 98.4% of the symptoms in the Control group. Thus, although there was a greater proportion of subjects in the Olean group reporting more frequent bowel movements and looser stools at the highest dose levels, these symptoms had little or no impact on the subjects' daily activities.

The relationship between total dose and frequency of symptom reporting was examined for the subsets of children and elderly. The percent of children who reported at least one GI symptom anytime during the study was not related to the total amount of Olean-product consumed over the course of the study. This was the case for both the Olean and Control groups (Exhibits 40, Any GI). Likewise there was no relationship between the frequency of reporting of any individual symptom by the children and the total amount of Olean-labeled product consumed (Exhibits 40).

For the elderly, there were no statistically significant differences in reporting of GI symptoms at any amount of Olean-labeled product eaten, but there was a pattern of fewer reports of looser stools and fewer reports of more frequent bowel movements with increasing consumption of product in the Control group (Exhibits 41, Any GI, More Freq BMs, Looser Stools).

Consumption of Olean by Subjects who Did and Did Not Report GI Symptoms

The consumption of Olean-labeled chips was tabulated for individuals reporting or not reporting any GI symptoms during the study (Exhibit 42), by test group, in order to evaluate the overall relationship between consumption and GI symptoms. The median number of eating days (20-21) was similar for Olean and Control subjects whether or not they reported a GI symptom. Also, the total amount of chips eaten during the study (25.2-28.5 oz) was comparable in subjects whether or not a GI symptom was reported.

Association Between What Product People Thought They Were Eating and GI Symptom Reporting

At the end of the study, subjects were asked which kind of chips they thought were in the Olean-labeled packages (Olean, regular, don't know). Of the 3,053 subjects who responded to this question, over half of the subjects (54.3% in the Olean group and 61.8% in Control) responded that they did not know whether they were eating Olean or regular snacks (Exhibit 43). For subjects who thought they could tell which product they were consuming, the majority of subjects thought they were in the active study group, i.e. eating Olean, with 86% of those in the Olean group believing they were eating Olean and 69% of those in the Control group believing they were eating Olean.

In both groups, the percentage of subjects reporting GI symptoms was significantly greater in subjects who believed they were eating Olean chips compared to subjects who thought they were eating regular full-fat chips (45.3% vs. 31.0% in the Olean group and 44.4% vs. 29.1% in the Control group, Exhibit 43). The percentage of subjects reporting GI symptoms among subjects who responded that they did not know which product they were eating was 35.0% in the Olean group and 35.8% in the Control group; these percentages are significantly less than those among subjects who believed they were eating Olean chips ($p=0.01$) but similar to those in subjects who believed they were eating regular chips ($p=0.13$).

In contrast, the percentage of subjects reporting GI symptoms was not different between Olean and Control groups regardless of which product they believed they were consuming or if they indicated they did not know.

Concomitant Medications

The medications that subjects reported that they took for their GI symptoms are presented in Exhibit 44. Antacids were the most commonly taken medication, taken by 53 subjects in the Olean group, who reported on 111 days that they had taken them, and by 52 subjects in the Control group, who reported on 123 days that they had taken them. The study groups were similar with respect to the numbers of subjects who took individual medications for their GI symptoms and the number of days that they reported doing so across all medication classifications except for antidiarrheals, antiflatulents, and H₂-receptor antagonists.

Antidiarrheals were taken by fewer subjects in the Olean group than in the Control group. Forty-four subjects in the Olean group reported on 70 days that they had taken antidiarrheals, and 47 subjects in the Control group reported on 91 days that they had taken antidiarrheals.

Antiflatulents were taken by 8 subjects in the Olean group, who reported on 35 days that they had taken them, and by none of the subjects in the Control group. Of the 8 subjects in the Olean group who took antiflatulents, one subject (No. 3127-01) reported on 23 days that she had taken Phazyme (simethicone).

H₂-antagonists were taken by 17 subjects in the Olean groups, who reported on 39 days that they had taken them, and by 12 subjects in the Control group, who reported on 17 days that they had taken them. Of the 17 subjects in the Olean group who took H₂-receptor antagonists, 3 from one household (Nos. 2058-01, 2058-02, and 2058-03) reported on 9, 6, and 1 days, respectively, that they had taken Tagamet. Another subject (No. 3008-01), from a different household, reported on 5 days that she had taken Tagamet.

Adverse Gastrointestinal Events

Gastrointestinal (GI) symptoms were captured on the daily record forms completed by all subjects. These symptoms were not captured separately as adverse events unless the subject visited a physician for the GI symptom. The GI symptoms associated with a physician visit (GI adverse events) are presented by number of subjects reporting a symptom and by number of reports in Exhibit 45. Seven subjects in the Olean group reported a total of 10 GI adverse events, and nine subjects in the Control group reported a total of 27 GI adverse events. There is no apparent pattern of reports in either test group and no apparent relationship to Olean consumption. The most frequently reported symptoms, by number of subjects reporting, were nausea (1 Olean vs. 5 Control), diarrhea (1 Olean vs. 4 Control) and vomiting (1 Olean vs. 4 Control). Case narratives for each of the subjects with GI adverse events are presented in Appendix 9. Only one subject (No. 3328-01 in the Control group), a 54-year-old female, reported a GI adverse event associated with study withdrawal. This subject called her physician because of severe abdominal cramping and withdrew from the study on the advice of her physician.

Eight subjects, five in the Olean group and three in the Control group, had serious adverse events (adverse events that resulted in hospitalization or death) (Exhibit 46). Only one of these events was GI related. Subject 1236-01 (Olean group), a 59-year-old male, had pre-existing cholelithiasis with incidental gallbladder cancer found at cholecystectomy. This adverse event did not appear to be study related. There were two deaths, both in the Control group. Subject 3178-02, a 71-year-old male with a preexisting history of heart failure and cardiomyopathy and Subject 4160-04, an 18-year-old male, committed suicide. The remaining five subjects with serious adverse events all had events that appear to have been related to pre-existing conditions and not study related. Narratives for all subjects with serious adverse events are presented in Appendix 9.

When all adverse events reported in the study, including the GI adverse events, serious adverse events (discussed above), and all other adverse events, were tabulated (Exhibit 47), a total of 47 subjects in the Olean group reported 74 adverse events and 50 subjects in the Control group reported 86 adverse events. The adverse events are distributed across a wide range of common medical conditions and there is no apparent pattern of types of reports or of numbers of reports in either test group. The most frequently reported symptoms, by numbers of subjects reporting, were sinus congestion (2 Olean vs. 6 Control), otitis media (5 Olean vs. 2 Control), sore throat (3 Olean vs. 4 Control), and headache (2 Olean vs. 2 Control). There is no indication that there is an association between Olean and the occurrence of adverse events.

Secondary Analysis

When the study was designed we proposed to examine GI effects within a 2-day window of Olean-labeled chip eating. Although we anticipated higher than average consumption, it was not expected that most subjects would eat chips on more than half of study days.

This made the 2-day analysis window uninterpretable due to the frequent double and triple counting of GI events that were associated with a single consumption. Also, since consumption was so frequent, those individuals eating most often contribute the most to the 2-day window analysis. The results from the 2-day analysis are consistent with the other analyses presented, particularly the highest consuming group, with reports of more frequent bowel movements and looser stools showing significant differences from the Control group. These results are summarized in Appendix 10.

Discussion

The objectives of this study were: 1) To determine and compare the frequency of common GI symptoms in a free-living population including children and elderly, consuming corn and potato chip snacks made with olestra or triglyceride, 2) To assess the impact, if any, of these symptoms on the daily lives of the subjects. A key element of the study design was that the Control group (the placebo leg) received regular triglyceride chips labeled as containing olestra while the Olean group received chips prepared with olestra and labeled accordingly. This direct comparison of olestra and triglyceride products in a blinded, tightly controlled fashion provides data useful in interpreting anecdotal reports of GI effects associated with olestra snacks in the marketplace.

In several controlled clinical studies submitted to the Food Additive Petition (FAP 7A 3997) subjects were required to consume olestra each day and GI symptoms were monitored. Although there was an increase in the frequency of mild to moderate, non-serious GI symptoms when subjects consumed olestra each day for extended periods (16, 17, 22), the contrived nature of those testing conditions limits their utility for predicting what will be the effect, if any, when snacks made with olestra are available in the marketplace. Importantly, there was never any indication from controlled clinical testing that consumption of olestra would have any harmful or clinically significant impact on consumers health or well-being.

Design of the Study

In order for the current study to address the potential real-life consequences of consuming olestra snacks under *ad libitum*, free-living conditions (as little or as many snacks as desired within a self-selected diet) several design features had to be carefully managed. First and foremost there had to be adequate consumption of the test products to ensure that the full range of possible consumption in the market place was well represented in the study. Several steps were taken to ensure that there would be adequate consumption:

- 1) Only households who stated that they were willing to eat products made with olestra and would provide these products to their family members were eligible for participation.
- 2) Households had to be regular savory snack eaters.
- 3) Marketed products with high taste acceptance were provided free of charge, attractively displayed and conveniently supplied at the study sites on a weekly basis.
- 4) Product was promoted at the study site using print and video advertising.
- 5) Study personnel were trained to respond to questions that might arise from any negative national media coverage of Olean snacks.

Consumption of Olean-labeled Product

The consumption results were considerably higher than the snack consumption anticipated when these products are purchased in the marketplace. In the current study, the Olean products had almost a 50% share of all chip selections. By comparison, after several years of successful marketing of Baked Lay's™ by Frito-Lay, Baked Lay's reduced fat chips have about an 8% share of the chips market compared to the over 40% market share for Lay's and Ruffles (23).

Relative to how often consumers are likely to eat snacks, there are two types of published data available that define average snacking: menu census data, such as that compiled by the Market Research Corporation of America (MRCA, Des Plaines, IL) and information published by the snack manufacturers themselves. A 14-day MRCA menu census among 4,741 consumers showed that the 50th and 90th percentile for snack consumption frequency was 3 and 8 days respectively, in a 14-day period (or 9 and 24 days out of 42 days) (24). During the current six week study, the 50th and 90th percentile consumption frequencies in the Olean group were 20 and 35 days, respectively.

In the January 1992 issue of *Snack World* (25), the authoritative publication of the Snack Manufacturers Association, Wuerthner and Rickard wrote the Consumer Snacking Behavior Report. They noted that the "heavy snacking households" on average purchased over 5 pounds of tortilla chips and 8 pounds of potato chips each year (or 0.6 pounds of tortilla chips and 1 pound of potato chips in a six week period). In the present study, over 90% of households would be classified as "heavy snackers" using this criterion. These data clearly support that the study design provided high levels of snacking

Power of the Study

An important feature of the study design was to ensure that we had adequate size to detect differences in symptom reporting. The fact that the study was sensitive enough to detect differences between test groups is indicated by the narrow width of the confidence intervals for GI symptom differences. The confidence intervals show that a difference of approximately 5% in the two test groups for the overall percentage of subjects reporting any GI symptom, or a difference of approximately one symptom-day in the overall mean symptom-days for any GI event could have been detected as statistically significant.

For the subgroups of children and the elderly, the confidence intervals for GI symptom differences again show sufficient sensitivity to detect meaningful differences between the study groups. Differences of approximately 8% and 10% for the percent of subjects reporting any GI events, or differences of approximately one day or two days in the overall mean symptom-days for any GI event, for the children and elderly, respectively, could have been detected as statistically significant.

Reporting of Gastrointestinal Symptoms

The percent of subjects who reported nausea was higher in the Control group than in the Olean group ($p=0.02$). There were no other significant differences between the proportions of subjects in the Olean and Control groups who reported at least one GI symptom of any type or any of the eight individual symptoms during the six-week trial.

For participants reporting symptoms, the mean number of days on which GI symptoms were reported (symptom-days), a potentially more sensitive measure than simple

proportions, was also analyzed. There were no significant differences between the Olean and Control groups overall with respect to the number of symptom-days for overall GI symptoms or for seven of the eight individual symptoms recorded. Specifically, there were no differences in GI symptom reporting for children, teenagers or elderly consuming Olean snacks vs. Control snacks.

The number of symptom-days for which more frequent bowel movements was reported was greater by one day in the Olean group than in the Control group. The difference between the groups in the mean number of days on which increased bowel movements were reported (3.7 days vs. 2.8 days out of 42 days, Olean vs. Control, $p=0.04$), while statistically significant, is a minor difference. The Olean, and Olean-labeled regular triglyceride chips, had opposite effects on stool frequency. Therefore, this small difference between groups, could have been due to more frequent bowel movements in the Olean group, less frequent bowel movements in the Control group, or both. Analysis of subgroups within the overall population indicated that this small difference was found within the adults, and primarily within adult females.

Previous clinical experience with olestra has demonstrated that increases in bowel movement frequency, if they occur at all, are minor and not of clinical importance. In two studies, in which the subjects were housed at the study site and all stools were collected, olestra was fed on a daily basis at doses of 8 to 40 g/day. Mean bowel movement frequency either was found not to change when subjects ate as much as 32 g of olestra each day for 14 consecutive days (26), or was found to increase from a baseline level of 1.5 bowel movements/day to 1.6 bowel movements/day when the subjects consumed 2.5 oz of olestra chips (20 g of olestra) per day for 6 consecutive days and to 2.0 bowel movements/day when the subjects consumed 5 oz of olestra chips (40 g of olestra) per day for 6 days (22).

Reporting of GI Symptoms by Subjects with High Consumption

In previous 8-week clinical studies in which olestra foods were consumed with all meals of a fixed dietary regimen, a dose-response increase in GI symptoms was observed (16, 17). The current study was conducted to determine if olestra snacks, consumed *ad libitum* as part of a self-selected diet were associated with an increase in GI symptoms.

If Olean chips were producing GI effects in this study, one might expect to see a dose-response association. Higher consumption would logically be expected to produce more symptoms. In this study, total dose was analyzed by two factors, how much and how often the subjects ate the snacks. In this study there was no consistent dose-response in either overall GI effects (Any GI) or for individual GI symptoms when examined by either consumption amount or number of eating days. This was also true for children and elderly. These results demonstrate that olestra snacks, consumed *ad libitum*, do not demonstrate a dose-responsive increase in GI symptoms.

In this study, subjects at the 90th percentile of consumption consumed 64 oz or more ounces Olean-labeled snacks over the 6 weeks. Even the very highest consumers, those eating more than 100 oz (with maximum consumption at 250 oz) did well in the study and did not demonstrate any unusual pattern of symptom reporting.

Although there was no consistent increase with intake in the percentage of subjects who reported GI symptoms, those subjects with the highest consumption, the 90th percentile group, did report a different number of days for more frequent bowel movements and looser stools. The percentage of subjects in the 90th percentile of Olean group who reported these symptoms was greater than the percent of subjects with lower consumption, and the inverse was true for the subjects who were among the 90th percentile consumers in the Control group. They reported fewer days for these symptoms.

The lower frequency of GI symptoms among high-dose consumers in the Control group may reflect an effect of full-fat chip consumption in these subjects, suggesting that the Control group is not a "no effect" group at this level of consumption, relative to lower levels of consumption or baseline. Experience in conducting trials with comparison groups eating large amounts of regular triglyceride potato chips has lead us to conclude that the reduced bowel movement frequency among heavy snack consumers is most likely not a chance finding. Subjects with a high intake of regular chips are ingesting a substantial proportion of their daily caloric requirement as low residue snacks to the exclusion of other foods which would supply bulk. The reduced amount of residue in such a diet is likely to decrease stool bulk and therefore stool frequency while also leading to firmer stools. This effect was noted in the recently completed Stool Composition and Consistency Study (22). In that study, subjects in the placebo group who were eating products made with conventional fat had measurable decreases in the number of mean daily bowel movements from a baseline average of 1.6 bowel movements/day to 1.1 bowel movement/day. Any stool bulk reducing effect of eating large amounts of regular triglyceride would tend to exaggerate any potential treatment effect associated with Olean if direct comparisons are made between the high-level consumers in the Olean and Control groups.

Assessment of Impact of GI Symptoms

Perhaps the most important aspect of this study was the careful assessment of the impact of GI symptoms, if any, on the day-to-day activities for a large group of consumers of all ages frequently eating snacks made with Olean. There are indirect measures of impact such as whether subjects continued to eat product if they were reporting GI symptoms and whether subjects choose to drop from the study. If subjects were experiencing significant effects from the Olean chips, one might expect that consumption would decrease over time. There was no such decrease noted; consumption of chips was consistently high throughout the study and was equivalent in subjects reporting and those not reporting GI symptoms. There was only one person who dropped from the study because of severe abdominal cramping, and this person was in the Control group.

A more direct assessment of impact was accomplished by requesting that subjects record the impact of the symptom on their activities of daily living, using a scale ranging from "noticing but having no effect" to "missing an entire day of work/school" for each day on which a GI symptom was reported. We found no evidence of an association between consumption of snack products made with Olean and any negative impact on the daily activities of the study participants. More than 80% of the impact ratings reported by the subjects in both test groups indicated that their GI symptoms had no effect at all, and an additional 15% indicated that the effect was slight. Only on a very few symptom-days did subjects report that the symptoms affected them more than slightly (1.8 % vs. 2.8%, Olean vs. Control), and there were more of these in the Control group.

There were no findings to suggest that young children or the elderly experienced any unusual or different effects than the adults in the study. The experience of these two subgroups of interest was not different between the Olean and Control groups for any of the GI symptoms assessed. The same was also true when the highest consuming subjects (90th percentile) in these two subgroups were examined.

Other measures of the impact of GI symptoms on activities were also recorded including whether the subjects took any medication for symptoms or visited a physician for symptoms. The number of subjects taking medications for GI symptoms was low and similar in both groups (7.0% Olean group and 6.9% Control group), with no indication of an Olean-associated difference. There were no important differences in the number of people taking medications by any category of medication, including antidiarrheals, which were taken more frequently by subjects in the Control group. Overall the frequency of medication use was comparable to that observed in the recent study by Innovative Medical Research (27). In their survey of 2,500 adults, they found that 20% of adults had taken medication for GI symptoms within the previous month.

Importantly, there was no evidence of clinically significant events associated with olestra, with more people in the Control group visiting their physician for a GI event compared to the Olean group (9 vs. 7, Control vs. Olean). There also was no indication of any serious study-related events, with 5 serious events reported in the Olean group compared with 3 in the Control group, which included 2 deaths. There was one hospitalization related to a GI condition (cholelithiasis, gallbladder cancer), which was clearly a pre-existing condition.

Perspective Relative to the Olean Marketplace Experience

The results of this study provide additional insight into anecdotal reports that the snack manufacturers (Frito-Lay and The Procter & Gamble Company) have received from the marketplace. Consistent with research conducted by Innovative Medical Research (IMR, Baltimore, MD), a substantial proportion of subjects in the Control group reported GI symptoms during the 6-week study, with 36.9% reporting one or more common digestive symptom. This figure is quite comparable to the results from IMR's national survey of

digestive complaints. In the IMR survey, 40.1% of adult respondents reported cramping, loose stools, or gas during the month prior to the survey (27). The data from the Control group and from the national survey demonstrate that a number of digestive complaints are very prevalent. The high background rates of GI symptom reporting in the community provides a context in which to interpret spontaneous reports of adverse effects after eating olestra-containing foods. Given the common occurrence of GI symptoms in the population, and the lack of evidence for a cause and effect between Olean consumption and GI symptoms in controlled trials, many of the reports in the current study may simply be coincidence unrelated to eating snacks of any type.

Olean products, including those dispensed in this study, carry an information label which states that the product may cause cramping and loose stools. In clinical tests submitted in the olestra Food Additive Petition, where there was mandatory daily consumption of olestra at doses at or above 20 g/day consumed on consecutive days has been associated in some studies with an increase in the proportion of subjects reporting mild to moderate abdominal cramping. These were studies in which the entire diet has been fixed (16, 17). In others studies where the participants self-selected their diet (14, 19, 28), cramping was not reported at a greater rate among olestra consumers. Recently completed studies have demonstrated that cramping is not more likely to be observed in subjects consuming olestra, even among consumers who identified themselves as intolerant of olestra (29), and does not occur within hours of consumption of up to 13 oz of olestra chips in a single *ad libitum* eating occasion (18, 22).

In the current study, subjects in the Olean group did not report more abdominal cramping than subjects in the Control group. This was true for the study population overall and for children, teenagers, adults and elderly as well as the subjects who consumed the highest levels of olestra. The results of this study support the conclusion that cramping is not associated with consumption of olestra containing snack foods under free-living conditions.

There were minor differences noted in the frequency of reporting of looser stool and more frequent bowel movements. These differences were not shown to be dose-related although the largest differences from the Control group were seen in those subjects consuming products most often. The impact of these two symptoms was shown to be minor with the vast majority of subjects reporting symptoms categorizing them as having no or little impact. In addition to the daily list of symptoms, subjects could write in any additional symptoms each day that they wanted to report. Terms like diarrhea, loose stools and laxative effect were rarely written in by study subjects and were volunteered by comparable numbers of subjects from both groups. Regardless of the term subjects used to describe changes in stool character, controlled studies have demonstrated that daily consumption of olestra is not associated with any meaningful increase in stool water or adverse alterations of stool electrolytes (22).

Effect of Labeling on Reporting of GI Symptoms

Subjects who selected Olean-labeled product actually received either Olean or Control (triglyceride) product depending on their group assignment. All subject signed an informed consent which indicated the products might or might not contain olestra, and at the end of the study they were asked which product they believed they had been consuming. This design allowed for an assessment of whether consumers who believed the Olean-labeled product was Olean reported different levels of GI symptoms than those who believed the Olean-labeled product was regular full-fat chips, or who didn't know.

An important observation was made that GI symptom reporting appeared to be more highly dependent on what the subjects believed they were eating than what products the subjects were actually eating. Consumers who believed they were eating Olean chips were 50% more likely to report GI symptoms than those who believed they were eating regular chips (Exhibit 43). In contrast, there was no difference in symptom reporting between the Olean and Control groups in subjects who believed they were eating Olean chips. This finding may well illustrate the so-called "nocebo" or negative placebo effect of the product's label and/or the media reports that the product will cause GI symptoms.

Strengths and Limitations of the Study

There are a number of strengths of the present study. The most notable is the fact that we conducted a rigorous, randomized, controlled clinical trial in a large population to evaluate the potential health effects of olestra snacks when eaten frequently and in substantial quantities. We obtained detailed information on exposure (chip consumption) and outcomes (symptoms and impact) using daily diary forms. Great care was taken to blind subjects and staff to test group. The study population included a large group of children and the elderly to be certain that product was tested in a broad population. Importantly the study had a very high completion rate and very low rate of missing data.

There are obvious limitations to a study of this size and complexity. We relied on self-report for information on chip consumption and symptoms. However, there was no incentive for subjects to report eating chips when they did not, and we would not expect differential reporting in consumption or symptoms between the olestra and the Control group. An adult reported information on digestive experiences from young children. Although this information may not be completely accurate, this is the only practical way to collect the data. The subjects in this study were paid volunteers and it is possible that they are not truly representative of the population at large. On the other hand, they were specially selected because of a pattern of heavier chip consumption. In that regard, their experience may be particularly reassuring when assessing what is likely to be the experience of the majority of consumers, who will generally eat at lower levels of consumption.

Conclusions

We conducted a large, controlled, randomized, double-blind, clinical trial of consumption of corn and potato chips in free-living adults and children. Subjects complied with protocol requirements and completed records as required. The large population of people of different ages and the duration of the trial ensured that range of snacking behaviors could occur. In order to maximize the probability of detecting differences in gastrointestinal effects, the study population was deliberately selected toward heavy consumers of snacks.

The results of the study demonstrated the following:

- 1) There was no indication of clinically significant or harmful GI effects associated with the consumption of Olean snacks in this large group of participants including children, teens and elderly subjects who frequently consumed Olean chips. Specifically there was no increase in physician visits, or use of medications for GI symptoms in the Olean group when compared to the Control group.
- 2) There was no evidence of an increase in negative or bothersome effects of GI symptoms on daily activities of the individuals in the study population as a whole or in the various subgroups (children, elderly) evaluated.
- 3) The type of chips (Olean or regular) that subjects thought they were eating from the Olean-labeled packages was significantly associated with GI symptom reporting. In both study groups, participants who thought that they eating Olean chips reported GI symptoms 50% more frequently than participants who thought they were eating regular chips.
- 4) Statistically significant, but small, differences between the Olean and Control groups in the frequency of reporting of the GI symptoms "more frequent bowel movements" and/or "looser stools" were observed in some subgroups, particularly in those consuming the highest amounts of Olean snacks. These effects were minor, not clinically important, on average being reported only 1 more day of the 42 potential study days, and were rated as having no impact or only slight impact on daily activities by the vast majority of subjects (>97%). The impact was not different than that observed in the Control group.
- 5) Gastrointestinal symptoms are relatively common in the general population. Consumers of Olean snacks, eating typical servings sizes of chips (1.3 oz) and consuming them as frequently as they wish, will not experience an increase in the occurrence of meaningful GI symptoms over background rates. Specifically, there was no increase in the frequency of abdominal cramping overall or in any subgroup in this study.

Signatures

Robert Miday, M.D.
RK Miday, MD, Project Physician

2/24/98
Date

Robert Sandler
RS Sandler, MD, MPH, Principal Investigator

2/24/98
Date

TG Filloon
TG Filloon, PhD, Study Statistician

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Date

HB Wiseman / alk
HB Wiseman, Clinical Monitor

2/24/98
Date

LJ Bishop
LJ Bishop, Data Manager

2/24/98
Date

Exhibits



Exhibit 2

Disposition of Subjects Who Were Randomized Into the Study

<u>Disposition</u>	<u>Olean</u>		<u>Control</u>		<u>Total</u>	
	<u>Subjects</u>	<u>Households</u>	<u>Subjects</u>	<u>Households</u>	<u>Subjects</u>	<u>Households</u>
Randomized ^a	1651	579	1599	581	3250	1160
Did not eat Olean-labeled product	14	-	10	-	24	-
Dropped out before second visit	17	10	28	11	45	21
Dropped out after second visit	39	22	46	20	85	42
Evaluable ^b	1620	568 ^c	1561	570 ^c	3181	1138 ^c

^a Came to study site for first visit, filled out forms, and took chips home.

^b Ate Olean-labeled chips during the study.

^c Households in which at least one subject ate Olean-labeled product at least once.

Exhibit 3

Demographic Characteristics of Evaluable Subjects^a

Characteristic	Number (%) of Subjects		
	Olean (n = 1620)	Control (n = 1561)	Total (n = 3181)
Age (years)			
2 - 12	442 (27.3)	443 (28.4)	885 (27.8)
13 - 17	125 (7.7)	102 (6.5)	227 (7.1)
18 - 64	842 (51.9)	825 (52.9)	1667 (52.4)
65 - 89	211 (13.0)	191 (12.2)	402 (12.6)
Sex			
Male	696 (43.0)	704 (45.1)	1400 (44.0)
Female	924 (57.0)	857 (54.9)	1781 (56.0)
Race			
Caucasian	1429 (88.2)	1394 (89.3)	2823 (88.7)
African American	71 (4.4)	81 (5.2)	152 (4.8)
Hispanic	84 (5.2)	63 (4.0)	147 (4.6)
Asian	14 (0.9)	2 (0.1)	16 (0.5)
Native American	9 (0.6)	13 (0.8)	22 (0.7)
Other	13 (0.8)	8 (0.5)	21 (0.7)

^a Evaluable subjects were those who ate Olean-labeled chips at least once.

Exhibit 4

Demographic Characteristics of Subjects Who Were Not Evaluable^a

Characteristic	Number (%) of Subjects		
	Olean (n = 31)	Control (n = 38)	Total (n = 69)
Age (years)			
2 - 12	9 (20.0)	15 (39.5)	24 (34.8)
13 - 17	2 (6.5)	3 (7.9)	5 (7.2)
18 - 64	19 (61.3)	17 (44.7)	36 (52.1)
65 - 89	1 (3.2)	3 (7.9)	4 (5.8)
Sex			
Male	17 (54.8)	20 (52.6)	37 (53.6)
Female	14 (45.2)	18 (47.4)	32 (46.4)
Race			
Caucasian	29 (93.5)	33 (86.8)	62 (89.9)
African American	2 (6.5)	4 (10.5)	6 (8.7)
Other	0 (0.0)	1 (2.6)	1 (1.4)

^a Evaluable subjects were those who ate Olean-labeled chips at least once.

Exhibit 5

Education, Employment, and Income for Households of Evaluable Subjects^{a,b}

Characteristic	Number (%) of Households		
	Olean (n = 563)	Control (n = 567 ^c)	Total (n = 1130 ^d)
Highest level of education reached			
Grade school	5 (0.9)	5 (0.9)	10 (0.9)
Attended high school	116 (20.6)	115 (20.3)	231 (20.4)
Graduated from high school	90 (16.0)	92 (16.2)	182 (16.1)
Attended college	188 (33.4)	193 (34.0)	381 (33.7)
Graduated from college	111 (19.7)	111 (19.6)	222 (19.6)
Graduate studies	53 (9.4)	51 (9.0)	104 (9.2)
Occupation of main wage earner			
Farmer, farm worker	1 (0.2)	1 (0.2)	2 (0.2)
Service worker or laborer	86 (15.3)	75 (13.2)	161 (14.2)
Crafts worker, factory worker, mechanic	71 (12.6)	74 (13.1)	145 (12.8)
Clerical worker, salesperson, technician	123 (21.8)	135 (23.8)	258 (22.8)
Professional, administrator, executive	112 (19.9)	103 (18.2)	215 (19.0)
Other	170 (30.2)	179 (31.6)	349 (30.9)
Yearly household income^{c, d}			
\$16,999 and under	102 (18.1)	102 (18.0)	204 (18.1)
\$17,000 - \$25,000	114 (20.2)	141 (24.9)	255 (22.6)
\$25,001 - \$35,000	119 (21.1)	104 (18.4)	223 (19.8)
\$35,001 - \$45,000	86 (15.3)	87 (15.4)	173 (15.3)
\$45,001 - \$55,000	46 (8.2)	38 (6.7)	84 (7.4)
>\$55,000	48 (8.5)	45 (8.0)	93 (8.2)
Refused	48 (8.5)	49 (8.7)	97 (8.6)

^a Information on education and occupation was collected for household's main wage earner only.

^b Evaluable subjects were those who ate Olean-labeled chips at least once.

^c n = 566 for yearly household income for Control group.

^d n = 1129 for yearly household income for total subjects.

Exhibit 6

General Medical History for Population of Evaluable Subjects

Condition	Number (%) of Subjects		
	Olean (n = 1620)	Control (n = 1561)	Total (n = 3181)
Heart condition (e.g., heart attack, angina, congestive heart failure)	66 (4.1)	52 (3.3)	118 (3.7)
Lung condition (e.g., emphysema, chronic bronchitis, asthma)	100 (6.2)	114 (7.3)	214 (6.7)
High blood pressure, hypertension	135 (8.3)	141 (9.0)	276 (8.7)
High cholesterol or triglyceride level	109 (6.7)	102 (6.5)	211 (6.6)
Migraines or other chronic headaches	79 (4.9)	49 (3.1)	128 (4.0)
Diabetes or glucose intolerance	54 (3.3)	46 (2.9)	100 (3.1)
Hormonal condition (e.g., thyroid or adrenal problem)	56 (3.5)	45 (2.9)	101 (3.2)
Cancer other than non-melanoma skin cancer	40 (2.5)	28 (1.8)	68 (2.1)
Gallbladder disease	34 (2.1)	30 (1.9)	64 (2.0)
Liver disease (including hepatitis)	30 (1.9)	15 (1.0)	45 (1.4)
Stomach ulcer, peptic ulcer, or duodenal ulcer	37 (2.3)	35 (2.2)	72 (2.3)
Heartburn, reflux, or hiatal hernia	89 (5.5)	79 (5.1)	168 (5.3)
Irritable bowel, spastic bowel, or functional bowel problem	32 (2.0)	34 (2.2)	66 (2.1)
Crohn's disease or ulcerative colitis	7 (0.4)	6 (0.4)	13 (0.4)
Lactose intolerance	43 (2.7)	39 (2.5)	82 (2.6)
Neurologic condition (including stroke, Parkinson's)	23 (1.4)	15 (1.0)	38 (1.2)
Arthritis	119 (7.4)	117 (7.5)	236 (7.4)
Psychiatric condition (including depression, anxiety)	57 (3.5)	40 (2.6)	97 (3.0)
Currently pregnant	8 (0.9) ^a	7 (0.8) ^b	15 (0.8) ^c
Currently lactating	10 (1.1) ^a	5 (0.6) ^b	15 (0.8) ^c

^a n = 924 (number of females).

^b n = 857 (number of females).

^c n = 1781 (number of females).

Exhibit 7

Consumption of Olean-Labeled Product by All Subjects

<u>Consumption Data</u>	<u>Olean (n = 1620)</u>			<u>Control (n = 1561)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	20	12 - 28	35	21	14 - 29	36
Total amount eaten (oz)	26.0	14.6 - 39.8	59.4	28.4	16.3 - 44.7	70.0
Average amount eaten per eating day (oz) ^b	1.30	1.01 - 1.75	2.34	1.35	0.99 - 1.90	2.67

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Daily Consumption of Olean-labeled Chips

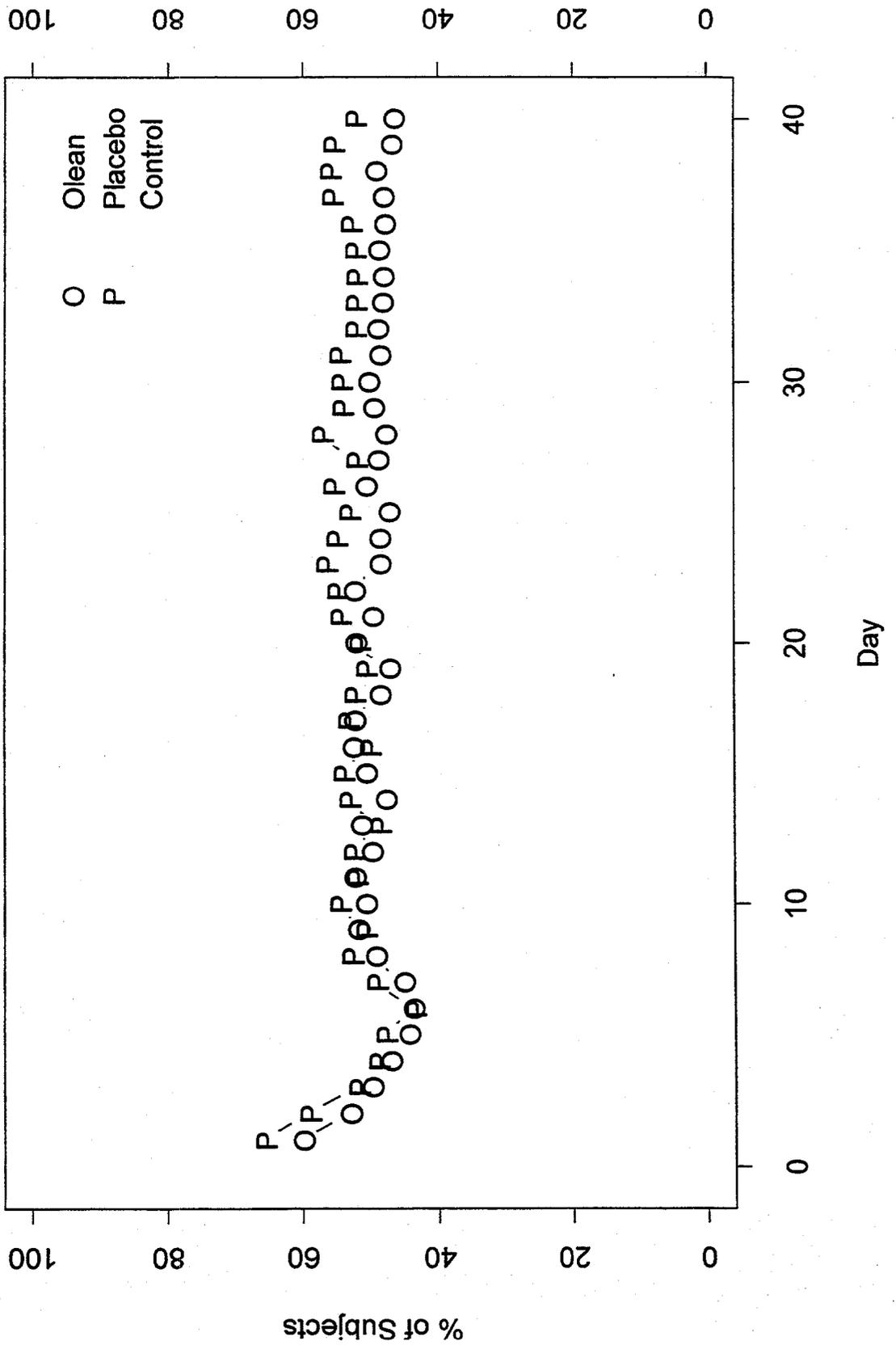


Exhibit 9

Consumption of Olean-Labeled Product by All Male Subjects

<u>Consumption Data</u>	<u>Olean (n = 696)</u>			<u>Control (n = 704)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	18	11 - 26	34	19	13 - 27	36
Total amount eaten (oz)	25.2	13.8 - 39.8	57.7	27.6	16.3 - 41.5	66.7
Average amount eaten per eating day (oz) ^b	1.41	1.05 - 1.88	2.44	1.41	1.03 - 1.98	2.79

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Exhibit 10

Consumption of Olean-Labeled Product by All Female Subjects

<u>Consumption Data</u>	<u>Olean (n = 924)</u>			<u>Control (n = 857)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	21	14 - 29	35	22	15 - 31	37
Total amount eaten (oz)	26.8	15.4 - 39.8	59.4	29.2	16.2 - 48.0	73.2
Average amount eaten per eating day (oz) ^b	1.24	0.97 - 1.66	2.25	1.30	0.95 - 1.83	2.55

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Exhibit 11

Consumption of Olean-Labeled Product by Adults 18 to 64 Years of Age

<u>Consumption Data</u>	<u>Olean (n = 842)</u>			<u>Control (n = 825)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	20	13 - 28	34	21	15 - 29	35
Total amount eaten (oz)	27.6	15.5 - 42.3	61.0	30.1	18.6 - 48.0	72.4
Average amount eaten per eating day (oz) ^b	1.39	1.07 - 1.82	2.46	1.44	1.03 - 1.99	2.87

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Exhibit 12

Consumption of Olean-Labeled Product by Children 2 to 12 Years of Age

<u>Consumption Data</u>	<u>Olean (n = 442)</u>			<u>Control (n = 443)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	18	11 - 24	32	18	12 - 25	32
Total amount eaten (oz)	19.5	11.4 - 30.6	41.4	21.1	13.8 - 32.5	48.0
Average amount eaten per eating day (oz) ^b	1.13	0.88 - 1.46	1.88	1.13	0.89 - 1.54	2.18

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Exhibit 13

Consumption of Olean-Labeled Product by Teens 13 to 17 Years of Age

<u>Consumption Data</u>	<u>Olean (n = 125)</u>			<u>Control (n = 102)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	15	10 - 24	28	18	12 - 23	31
Total amount eaten (oz)	22.7	13.0 - 33.3	51.1	24.8	15.4 - 35.0	56.8
Average amount eaten per eating day (oz) ^b	1.37	1.00 - 1.88	2.53	1.40	1.06 - 1.82	2.55

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Exhibit 14

Consumption of Olean-Labeled Product by Elderly Subjects 65 to 89 Years of Age

<u>Consumption Data</u>	<u>Olean (n = 211)</u>			<u>Control (n = 191)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	27	19 - 35	40	32	21 - 36	40
Total amount eaten (oz)	37.4	25.6 - 55.3	71.6	42.3	27.2 - 69.6	100.8
Average amount eaten per eating day (oz) ^b	1.38	1.07 - 1.87	2.51	1.55	1.08 - 2.14	2.96

n = number of subjects

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day is defined as the amount eaten by that subject, divided by their number of eating days.

Exhibit 15

Percentage of All Subjects Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean (n = 1620)</u>	<u>Control (n = 1561)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	38.2	36.9	0.60	1.3 (-3.6, 6.2)
Heartburn	8.6	8.4	0.88	0.2 (-2.2, 2.6)
Nausea	5.7	8.4	0.02	-2.7 (-4.9, -0.4)
Vomiting	1.8	1.8	1.00	0.0 (-1.1, 1.0)
Gas	24.2	21.7	0.25	2.5 (-1.8, 6.7)
Bloating	11.2	9.4	0.18	1.9 (-0.8, 4.6)
Cramping	15.0	15.1	0.94	-0.1 (-3.3, 3.1)
More frequent BMs	20.5	17.4	0.11	3.1 (-0.7, 7.0)
Looser stool	25.3	23.1	0.31	2.2 (-2.1, 6.6)
Other symptom	2.2	3.2	0.12	-1.0 (-2.2, 0.3)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 16

Number of Symptom-Days^a in All Subjects Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	619	5.0 ± 0.3	576	4.2 ± 0.3	0.07	0.8 (-0.1, 1.6)
Heartburn	139	2.6 ± 0.3	131	2.4 ± 0.3	0.72	0.1 (-0.6, 0.9)
Nausea	93	1.9 ± 0.2	131	1.7 ± 0.1	0.44	0.2, (-0.3, 0.8)
Vomiting	29	1.3 ± 0.1	28	1.2 ± 0.1	0.64	0.1 (-0.3, 0.5)
Gas	392	4.5 ± 0.3	339	3.8 ± 0.3	0.12	0.7 (-0.2, 1.6)
Bloating	182	3.3 ± 0.3	146	2.8 ± 0.2	0.23	0.4 (-0.3, 1.2)
Cramping	243	2.4 ± 0.2	236	2.5 ± 0.2	0.69	-0.1 (-0.6, 0.4)
More frequent BMs	332	3.7 ± 0.4	271	2.8 ± 0.2	0.04	0.9 (0.1, 1.8)
Looser stool	410	3.9 ± 0.3	360	3.6 ± 0.3	0.46	0.3 (-0.6, 1.2)
Other symptom	36	2.3 ± 0.4	50	2.1 ± 0.4	0.64	0.3 (-0.8, 1.3)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 17

Impact of GI Symptoms on Daily Activities for All Subjects

<u>Impact^a</u>	<u>No. of Symptom-Days</u>		<u>% of All Symptom-days</u>	
	<u>Olean (n=619)^b</u>		<u>Control (=576)^b</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Noticed but did not affect	2587	83.6	2021	82.6
Noticed and slightly affected	452	14.6	357	14.6
Missed some time	41	1.3	46	1.9
Missed all day	16	0.5	22	0.9

GI = gastrointestinal.

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 18

Percentage of All Male Subjects Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean</u> <u>(n = 696)</u>	<u>Control</u> <u>(n = 704)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	36.2	33.8	0.44	2.4 (-3.7, 8.5)
Heartburn	6.9	7.2	0.82	-0.3 (-3.4, 2.7)
Nausea	3.9	7.4	0.01	-3.5 (-6.3, -0.8)
Vomiting	1.7	1.6	0.83	0.2 (-1.3, 1.6)
Gas	21.8	19.2	0.33	2.7 (-2.7, 8.0)
Bloating	7.8	5.4	0.11	2.4 (-0.5, 5.3)
Cramping	11.6	11.4	0.88	0.3 (-3.4, 4.0)
More frequent BMs	19.3	16.2	0.21	3.1 (-1.8, 7.9)
Looser stool	24.0	22.0	0.48	2.0 (-3.6, 7.5)
Other symptom	1.3	2.0	0.33	-0.7 (-2.1, 0.7)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 19

Mean Number of Symptom-days^a in All Male Subjects Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	252	4.4 ± 0.4	238	4.4 ± 0.5	0.97	0.0 (-1.2, 1.3)
Heartburn	48	2.6 ± 0.4	51	2.4 ± 0.4	0.79	0.2 (-0.9, 1.3)
Nausea	27	1.3 ± 0.1	52	1.5 ± 0.1	0.39	-0.1 (-0.4, 0.2)
Vomiting	12	1.2 ± 0.2	11	1.1 ± 0.1	0.46	0.2 (-0.3, 0.6)
Gas	152	3.9 ± 0.4	135	4.0 ± 0.6	0.85	-0.1 (-1.5, 1.3)
Bloating	54	2.5 ± 0.4	38	2.5 ± 0.5	0.95	0.0 (-1.2, 1.3)
Cramping	81	1.8 ± 0.2	80	2.5 ± 0.3	0.04	-0.7 (-1.3, 0.0)
More frequent BMs	134	3.4 ± 0.6	114	2.6 ± 0.2	0.19	0.8 (-0.4, 2.1)
Looser stool	167	3.7 ± 0.5	155	3.9 ± 0.5	0.75	-0.2 (-1.6, 1.2)
Other symptom	9	1.4 ± 0.2	14	1.6 ± 0.3	0.69	-0.1 (-0.7, 0.5)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 20

Impact of GI Symptoms on Daily Activities for All Male Subjects

<u>Impact^a</u>	<u>No. of Symptom-days</u>		<u>% of All Symptom-days</u>	
	<u>Olean n=252^b</u>		<u>Control n=238^b</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Noticed but did not affect	944	85.1	854	82.0
Noticed and slightly affected	149	13.4	163	15.7
Missed some time	11	1.0	19	1.8
Missed all day	6	0.5	5	0.5

GI = gastrointestinal.

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 21

Percentage of All Female Subjects Who Reported GI Symptoms

<u>GI Symptoms</u>	Olean (n = 924)	Control (n = 857)	P-Value	<u>Difference (95% CI)^a</u>
Any GI event ^b	39.7	39.4	0.92	0.3 (-5.3, 5.9)
Heartburn	9.8	9.3	0.74	0.5 (-2.5, 3.5)
Nausea	7.1	9.2	0.15	-2.1 (-4.9, 0.7)
Vomiting	1.8	2.0	0.83	-0.1 (-1.5, 1.2)
Gas	26.0	23.8	0.38	2.2 (-2.7, 7.0)
Bloating	13.9	12.6	0.49	1.3 (-2.3, 4.8)
Cramping	17.5	18.2	0.74	-0.7 (-4.7, 3.3)
More frequent BMs	21.4	18.3	0.16	3.1 (-1.2, 7.5)
Looser stool	26.3	23.9	0.34	2.4 (-2.5, 7.2)
Other symptom	2.9	4.2	0.15	-1.3 (-3.0, 0.5)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 22

Mean Number of Symptom-Days^a in All Female Subjects Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	367	5.4 ± 0.3	338	4.2 ± 0.3	<0.01	1.3 (0.4, 2.1)
Heartburn	91	2.5 ± 0.3	80	2.4 ± 0.3	0.70	0.1 (-0.7, 1.0)
Nausea	66	2.1 ± 0.3	79	1.8 ± 0.2	0.43	0.3 (-0.5, 1.1)
Vomiting	17	1.4 ± 0.2	17	1.3 ± 0.2	0.86	0.1 (-0.6, 0.7)
Gas	240	4.9 ± 0.4	204	3.7 ± 0.3	0.01	1.2 (0.3, 2.1)
Bloating	128	3.6 ± 0.4	108	3.0 ± 0.3	0.16	0.6 (-0.3, 1.5)
Cramping	162	2.7 ± 0.3	156	2.5 ± 0.2	0.62	0.2 (-0.5, 0.8)
More frequent BMs	198	3.9 ± 0.4	157	2.9 ± 0.2	0.03	1.0 (0.1, 1.8)
Looser stool	243	4.1 ± 0.3	205	3.3 ± 0.3	0.09	0.8 (-0.1, 1.6)
Other symptom	27	2.6 ± 0.5	36	2.3 ± 0.4	0.61	0.4 (-1.0, 1.7)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 23

Impact of GI Symptoms on Daily Activities for All Female Subjects

<u>Impact^a</u>	<u>No. of Symptom-Days</u>		<u>% of All Symptom-days</u>	
	<u>Olean n=367^b</u>		<u>Control n=338^b</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Noticed but did not affect	1643	82.7	1167	83.1
Noticed and slightly affected	303	15.3	194	13.8
Missed some time	30	1.5	27	1.9
Missed all day	10	0.5	17	1.2

GI = gastrointestinal

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 24

Percentage of Evaluable Adults 18 to 64 Years of Age Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean (n = 842)</u>	<u>Control (n = 825)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	44.7	41.5	0.28	3.2 (-2.6, 9.0)
Heartburn	12.1	12.0	0.95	0.1 (-3.5, 3.7)
Nausea	7.1	9.6	0.11	-2.4 (-5.4, 0.5)
Vomiting	1.3	1.8	0.40	-0.5 (-1.7, 0.7)
Gas	30.6	24.8	0.03	5.8 (0.6, 11.0)
Bloating	15.6	13.1	0.20	2.5 (-1.3, 6.2)
Cramping	18.9	18.3	0.79	0.6 (-3.7, 4.8)
More frequent BMs	24.3	20.1	0.08	4.2 (-0.5, 9.0)
Looser stool	29.1	27.4	0.52	1.7 (-3.4, 6.9)
Other symptom	3.0	3.6	0.45	-0.7 (-2.4, 1.1)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 25

Number of Symptom-days^a in Adults 18 to 64 Years of Age Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	376	5.7 ± 0.4	342	4.6 ± 0.4	0.03	1.1 (0.1, 2.1)
Heartburn	102	2.7 ± 0.3	99	2.3 ± 0.3	0.38	0.4 (-0.5, 1.3)
Nausea	60	1.8 ± 0.2	79	1.6 ± 0.1	0.58	0.1 (-0.3, 0.6)
Vomiting	11	1.3 ± 0.2	15	1.0 ± 0.1	0.19	0.3 (-0.1, 0.7)
Gas	258	4.9 ± 0.4	205	4.2 ± 0.4	0.21	0.7 (-0.4, 1.7)
Bloating	131	3.4 ± 0.3	108	3.0 ± 0.3	0.37	0.4 (-0.5, 1.2)
Cramping	159	2.4 ± 0.2	151	2.7 ± 0.2	0.42	-0.3 (-0.9, 0.4)
More frequent BMs	205	4.1 ± 0.5	166	2.9 ± 0.2	0.02	1.2 (0.1, 2.2)
Looser stool	245	4.3 ± 0.4	226	3.8 ± 0.4	0.32	0.6 (-0.5, 1.7)
Other symptom	25	2.0 ± 0.3	30	1.9 ± 0.3	0.89	0.1 (-0.8, 0.9)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 26

Impact of GI Symptoms on Daily Activities for Adults 18 to 64 Years of Age

<u>Impact^a</u>	<u>No. of Symptom-Days</u>		<u>% of All Symptom-days</u>	
	<u>Olean n=376^b</u>		<u>Control n=342^b</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Noticed but did not affect	1741	81.9	1263	81.0
Noticed and slightly affected	346	16.3	249	16.0
Missed some time	29	1.4	33	2.1
Missed all day	9	0.4	14	0.9

GI = gastrointestinal.

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 27

Percentage of Children 2 to 12 Years of Age Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean (n = 442)</u>	<u>Control (n = 443)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	30.1	30.5	0.93	-0.4 (-8.4, 7.6)
Heartburn	3.6	2.7	0.53	0.9 (-1.9, 3.7)
Nausea	4.8	8.1	0.09	-3.4 (-7.2, 0.5)
Vomiting	3.2	2.5	0.59	0.7 (-1.8, 3.2)
Gas	15.4	17.2	0.59	-1.8 (-8.3, 4.7)
Bloating	4.5	3.4	0.53	1.1 (-2.4, 4.7)
Cramping	10.0	12.6	0.31	-2.7 (-7.9, 2.5)
More frequent BMs	16.1	12.9	0.31	3.2 (-3.0, 9.4)
Looser stool	21.9	18.3	0.31	3.7 (-3.4, 10.7)
Other symptom	0.2	2.3	0.04	-2.0 (-4.0, -0.1)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 28

Number of Symptom-days^a in Children 2 to 12 Years of Age Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	133	3.7 ± 0.4	135	3.6 ± 0.4	0.74	0.2 (-0.9, 1.2)
Heartburn	16	1.3 ± 0.2	12	1.9 ± 0.5	0.22	-0.6 (-1.6, 0.4)
Nausea	21	1.8 ± 0.5	36	1.8 ± 0.3	0.98	0.0 (-1.1, 1.2)
Vomiting	14	1.1 ± 0.1	11	1.5 ± 0.4	0.33	-0.4 (-1.2, 0.4)
Gas	68	3.3 ± 0.5	76	2.7 ± 0.3	0.28	0.6 (-0.5, 1.7)
Bloating	20	1.8 ± 0.4	15	1.6 ± 0.2	0.62	0.2 (-0.6, 1.0)
Cramping	44	2.0 ± 0.3	56	2.2 ± 0.4	0.51	-0.3 (-1.2, 0.6)
More frequent BMs	71	2.6 ± 0.5	57	2.8 ± 0.3	0.76	-0.2 (-1.3, 1.0)
Looser stool	97	3.1 ± 0.4	81	3.2 ± 0.4	0.75	-0.2 (-1.4, 1.0)
Other symptom	1	1.0 ± 0.0	10	2.1 ± 1.1	0.31	-1.1 (3.2, 1.0)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 29

Impact of GI Symptoms on Daily Activities for Children 2 to 12 Years of Age

<u>Impact^a</u>	<u>No. of Symptom-days</u>		<u>% of All Symptom-days</u>	
	<u>Olean n=133^b</u>		<u>Control n=135^b</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Noticed but did not affect	437	87.9	389	81.0
Noticed and slightly affected	48	9.7	74	15.4
Missed some time	5	1.0	9	1.9
Missed all day	7	1.4	8	1.7

GI = gastrointestinal.

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 30

Percentage of Teens 13 to 17 Years of Age Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean</u> <u>(n = 125)</u>	<u>Control</u> <u>(n = 102)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	33.6	39.2	0.42	-5.6 (-19.1, 7.9)
Heartburn	8.8	2.9	0.06	5.9 (-0.3, 12.1)
Nausea	2.4	8.8	0.06	-6.4 (-13.2, 0.4)
Vomiting	0.8	1.0	0.89	-0.2 (-2.7, 2.3)
Gas	20.8	22.5	0.77	-1.7 (-13.5, 10.0)
Bloating	4.8	5.9	0.72	-1.1 (-7.0, 4.8)
Cramping	12.8	11.8	0.81	1.0 (-7.6, 9.7)
More frequent BMs	14.4	16.7	0.68	-2.3 (-13.1, 8.5)
Looser stool	22.4	20.6	0.76	1.8 (-10.0, 13.7)
Other symptom	3.2	1.0	0.24	2.2 (-1.5, 5.9)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 31

Number of Symptom-days^a in Teens 13 to 17 Years of Age Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	42	3.6 ± 0.6	40	3.5 ± 0.8	0.94	0.1 (-19, 2.1)
Heartburn	11	3.4 ± 1.0	3	1.0 ± 1.7	0.22	2.4 (-1.5, 6.2)
Nausea	3	2.3 ± 1.3	9	2.1 ± 1.0	0.90	0.2 (-3.1, 3.5)
Vomiting	1	2.0 ± 0.0	1	1.0 ± 0.0	--	1.0 --
Gas	26	3.1 ± 0.7	23	3.9 ± 1.3	0.59	-0.8 (-3.7, 2.1)
Bloating	6	5.3 ± 1.9	6	2.0 ± 1.5	0.18	3.3 (-1.5, 8.2)
Cramping	16	2.3 ± 0.5	12	1.8 ± 0.4	0.45	0.5 (-0.8, 1.7)
More frequent BMs	18	3.1 ± 0.5	17	1.8 ± 0.5	0.06	1.3 (-0.1, 2.6)
Looser stool	28	2.9 ± 0.6	21	2.1 ± 0.4	0.29	0.7 (-0.6, 2.0)
Other symptom	4	3.8 ± 1.9	1	2.0 ± 0.0	0.35	1.8 (-1.9, 5.4)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 32

Impact of GI Symptoms on Daily Activities for Teens 13 to 17 Years of Age

<u>Impact^a</u>	<u>No. of Symptom-days</u>		<u>% of All Symptom-days</u>	
	<u>Olean n=42^b</u>		<u>Control n=40^b</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Noticed but did not affect	127	84.1	122	86.5
Noticed and slightly affected	22	14.6	16	11.4
Missed some time	2	1.3	3	2.1
Missed all day	0	0	0	0

GI = gastrointestinal.

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 33

Percentage of Elderly Subjects 65 to 89 Years of Age Who Reported GI Symptoms

<u>GI Symptoms</u>	<u>Olean (n = 211)</u>	<u>Control (n = 191)</u>	<u>P-Value</u>	<u>Difference (95% CI)^a</u>
Any GI event ^b	32.2	30.9	0.79	1.3 (-8.5, 11.2)
Heartburn	4.7	8.9	0.12	-4.2 (-9.4, 1.1)
Nausea	4.3	3.7	0.77	0.6 (-3.5, 4.7)
Vomiting	1.4	0.5	0.36	0.9 (-1.0, 2.8)
Gas	19.0	18.3	0.88	0.6 (-7.7, 9.0)
Bloating	11.8	8.9	0.38	2.9 (-3.7, 9.6)
Cramping	11.4	8.9	0.45	2.5 (-4.0, 8.9)
More frequent BMs	18.0	16.2	0.66	1.8 (-6.2, 9.8)
Looser stool	19.0	16.8	0.60	2.2 (-6.0, 10.4)
Other symptom	2.8	4.7	0.33	-1.9 (-5.6, 1.9)

CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^b Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 34

Number of Symptom-days^a in Elderly Subjects 65 to 89 Years of Age Who Reported GI Symptoms

GI Symptoms	Olean		Control		P-Value	Difference (95% CI) ^c
	n ^b	Mean ± SEM	n ^b	Mean ± SEM		
Any GI event ^d	68	4.8 ± 0.7	59	4.5 ± 0.9	0.84	0.2 (-2.0, 2.4)
Heartburn	10	1.7 ± 0.3	17	3.4 ± 1.2	0.18	-1.7 (-4.2, 0.8)
Nausea	9	2.9 ± 0.8	7	1.3 ± 0.7	0.13	1.6 (-0.5, 3.7)
Vomiting	3	2.0 ± 1.0	1	1.0 ± 0.0	0.32	1.0 (-1.0, 3.0)
Gas	40	4.9 ± 0.9	35	3.7 ± 1.2	0.44	1.2 (-1.7, 4.1)
Bloating	25	3.4 ± 1.1	17	3.1 ± 0.9	0.85	0.3 (-2.6, 3.1)
Cramping	24	3.1 ± 1.1	17	2.3 ± 0.5	0.51	0.8 (-1.6, 3.1)
More frequent BMs	38	3.9 ± 1.0	31	2.5 ± 0.5	0.22	1.4 (-0.8, 3.7)
Looser stool	40	4.4 ± 0.9	32	4.1 ± 1.1	0.87	0.2 (-2.7, 3.2)
Other symptom	6	3.2 ± 1.8	9	2.7 ± 1.0	0.81	0.5 (-3.5, 4.5)

SEM = standard error of the mean; CI = confidence intervals; GI = gastrointestinal; BM = bowel movement.

^a A symptom-day was defined as a day on which the GI symptom was reported.

^b Number of subjects who reported symptom.

^c Values are the difference (95% CI) in the percentage of subjects reporting symptoms between the Olean and Control groups.

^d Includes all subjects who responded "yes" to the question in the daily record form.

Exhibit 35

Impact of GI Symptoms on Daily Activities for Elderly Subjects 65 to 89 Years of Age

<u>Impact^a</u>	<u>No. of Symptom-days</u>		<u>% of All Symptom-days</u>	
	<u>Olean n=68^b</u>		<u>Control n=59^b</u>	
	<u>No.^b</u>	<u>Percent</u>	<u>No.^b</u>	<u>Percent</u>
Noticed but did not affect	282	87.3	247	92.9
Noticed and slightly affected	36	11.2	18	6.8
Missed some time	5	1.6	1	0.4
Missed all day	0	0	0	0

GI = gastrointestinal.

^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

^b Subjects who reported any GI symptoms.

Exhibit 36

Other GI Symptoms from Daily Record

<u>Reported Term</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Abdominal pain	0	0	2	2	2	2
Aftertaste	0	0	3	4	3	4
Anorexia	0	0	2	4	2	4
Bowel Movement Urgency	1	1	0	0	1	1
Constipation	15	27	17	40	32	67
Constriction Throat	1	2	0	0	1	2
Diarrhea	8	21	7	10	15	31
Discoloration Stool	5	7	2	3	7	10
Discomfort Abdomen	0	0	2	2	2	2
Dizziness	1	4	0	0	1	4
Dyspepsia	1	2	0	0	1	2
Dyspnea	0	0	1	0	1	2
Eructation	1	1	2	6	3	7
Fullness Abdominal	0	0	1	2	1	2
Gastritis	0	0	1	1	1	1
Headache	1	4	1	1	2	5
Irregularity Heartbeat	1	2	0	0	1	2
Irritation Local Throat	0	0	1	1	1	1
Laxative Effect	0	0	1	2	1	2
Pain Gas	0	0	1	2	1	2
Pain Rectal	0	0	1	1	1	1
Queasy	1	2	0	0	1	2
Rash	0	0	1	1	1	1
Reflux Gastroesophageal	0	0	1	1	1	1
Stomach Ache	0	0	1	1	1	1
Stool Black	0	0	1	2	1	2

Exhibit 36 - (cont'd)

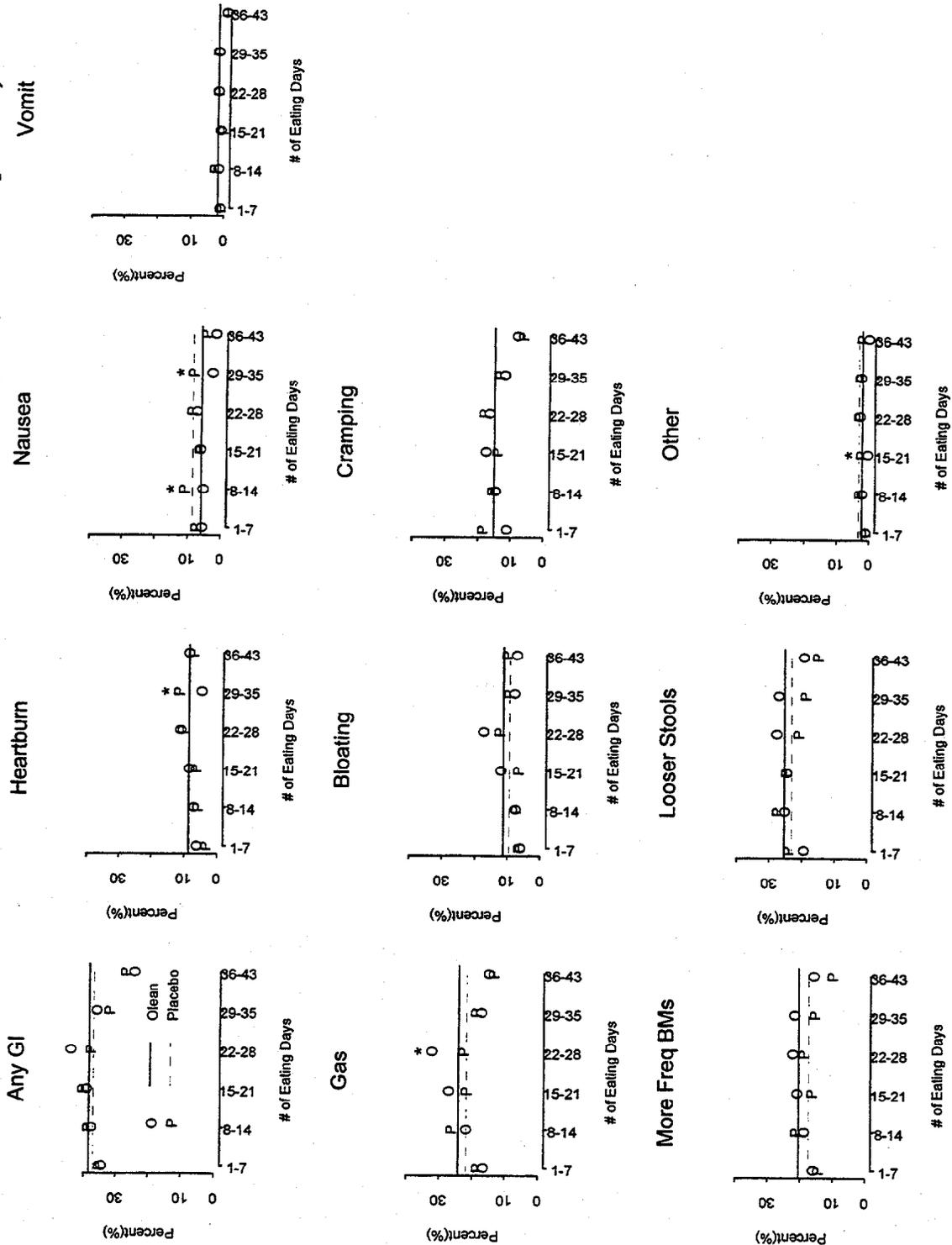
Other GI symptoms from Daily Record

<u>Reported Term</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Stool Frequency Decreased	1	5	2	2	3	7
Stool Frequency Increased	1	5	0	0	1	5
Stool Hardness	3	3	2	2	5	5
Stool Soft	0	0	1	1	1	1
Stools Abnormal	1	1	0	0	1	1
Stools Loose	1	1	0	0	1	1
Taste Loss	0	0	1	1	1	1
Taste Perversion	0	0	1	10	1	10
Thirst	0	0	1	1	1	1
Tongue Disorder	0	0	1	1	1	1
Upset Stomach	0	0	3	5	3	5
Weakness Generalized	0	0	1	1	1	1
Weight Loss	0	0	1	3	1	3
Total^a	36	88	50	114	86	202

GI = gastrointestinal.

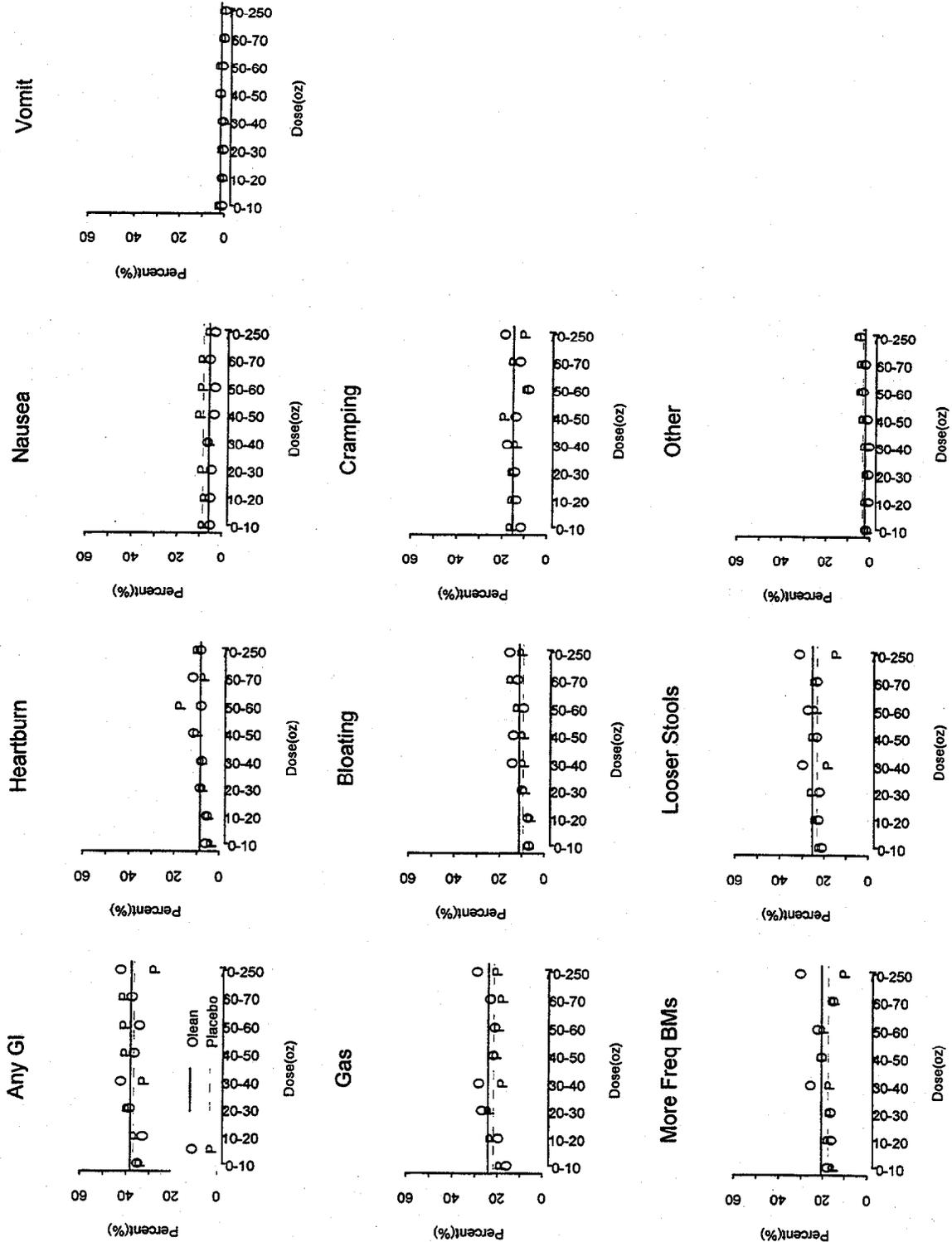
^a Subjects could report more than one "other" GI symptom.

Incidence of GI Symptoms vs Eating Days (All Subjects)



* denotes stat. sig. different from Placebo (p ≤ 0.05)

Incidence of GI Symptoms vs Dose (All Subjects)



* denotes stat. sig. different from Placebo (p ≤ 0.05)

Exhibit 39

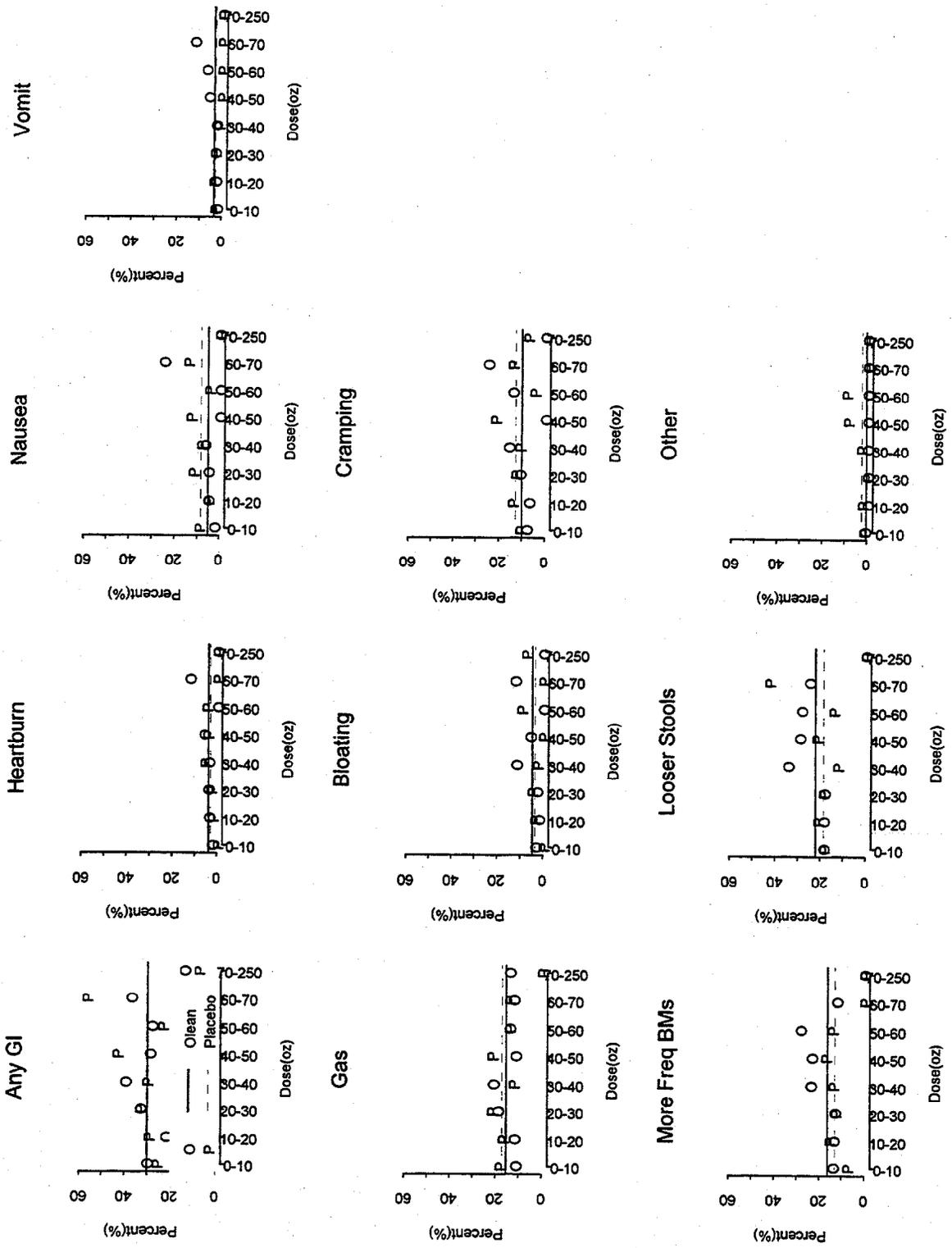
Impact of GI Symptoms on Daily Activities for Subjects
Who Ate a Total of 65 or More Ounces of Olean-Labeled Chips

<u>Impact^a</u>	<u>No. of Symptom-days (% of All Symptom-days)</u>	
	<u>Olean n=53</u>	<u>Control n=63</u>
Noticed but did not affect	331 (83.2)	269 (84.6)
Noticed and slightly affected	58 (14.6)	44 (13.8)
Missed some time	6 (1.5)	4 (1.3)
Missed all day	3 (0.8)	1 (0.3)

GI = gastrointestinal.

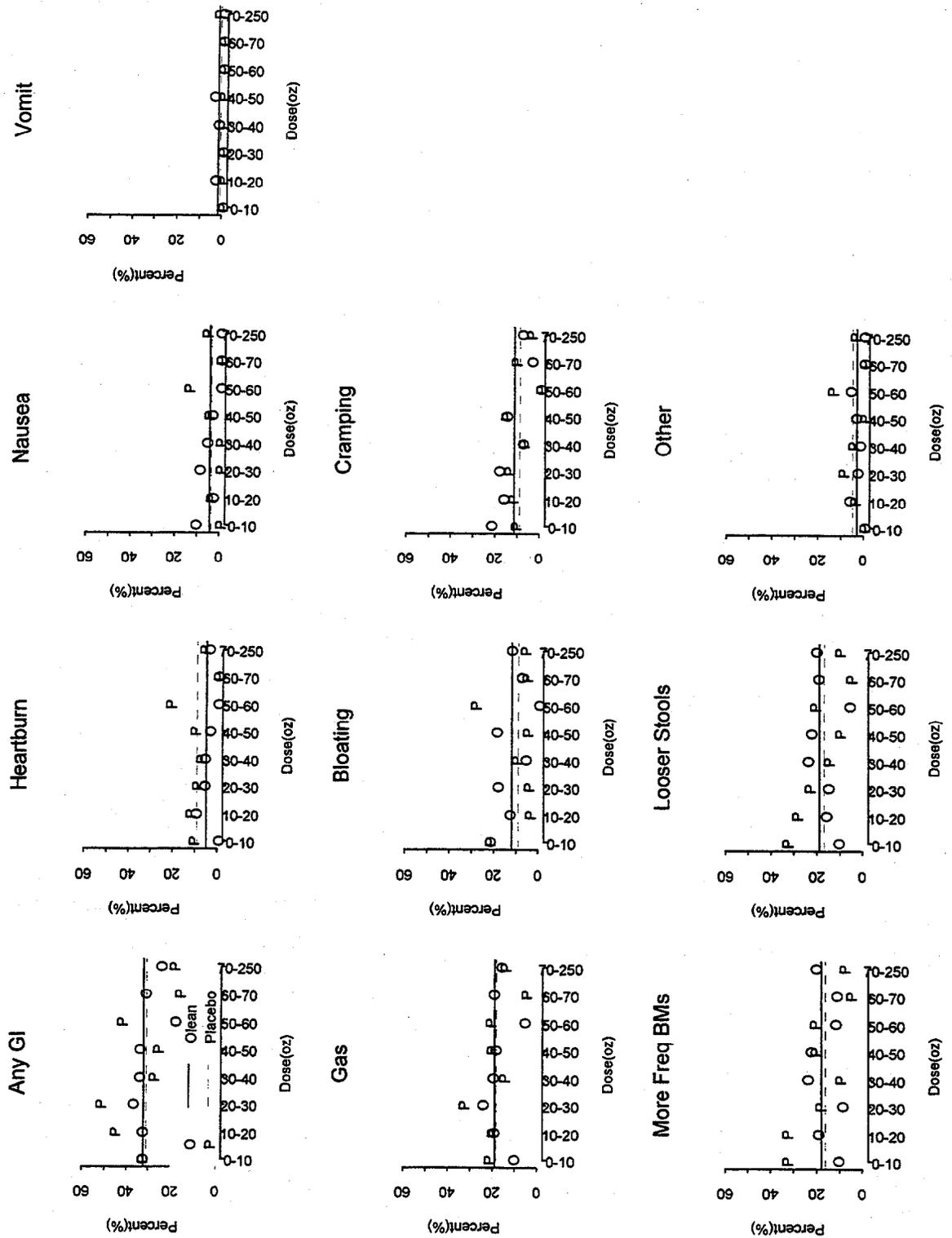
^a Subjects rated the impact of their GI symptoms on their work, school, activities, or routine.

Incidence of GI Symptoms vs Dose (Kids 2-12)



* denotes stat. sig. different from Placebo (p ≤ 0.05)

Incidence of GI Symptoms vs Dose (Seniors 65-89)



* denotes stat. sig. different from Placebo (p ≤ 0.05)

Exhibit 42

Consumption By Subjects Who Did or Did Not Report GI Symptom

Did Not Report GI Symptom

<u>Consumption Data</u>	<u>Olean (n = 1001)</u>			<u>Control (n = 985)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	20	12 - 28	36	21	14 - 44.7	38
Total amount eaten (oz)	25.2	14.6 - 39.8	58.6	28.5	16.2 - 44.7	75.3
Average amount eaten per eating day (oz) ^b	1.25	.97 - 1.70	2.32	1.29	0.95 - 1.92	2.67

Did Report GI Symptom

<u>Consumption Data</u>	<u>Olean (n = 619)</u>			<u>Control (n = 576)</u>		
	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>	<u>Median</u>	<u>25th-75th Percentile</u>	<u>90th Percentile</u>
Number of eating days ^a	20	12 - 26	33	20	14 - 27	35
Total amount eaten (oz)	26.8	16.2 - 39.8	60.9	27.2	17.1 - 43.1	65.2
Average amount eaten per eating day (oz) ^b	1.39	1.08 - 1.83	2.37	1.42	1.04 - 1.88	2.59

GI = gastrointestinal.

n = number of subjects.

^a Number of days on which Olean-labeled product was eaten.

^b For each subject, average amount eaten per eating day, is defined as the total amount eaten by that subject, divided by their number of eating days.

Exhibit 43

How subjects responded to question about which product they thought was in the Olean-labeled packages^a

	<u>Believe they were eating Olean-chips</u>		<u>Believed they were eating Regular chips</u>		<u>Didn't know which product they were eating</u>	
	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>	<u>No.</u>	<u>Percent</u>
Olean group (n = 1557)	612	39.3	100	6.4	845	54.3
Control group (n = 1496)	396	26.5	175	11.7	925	61.8

^a 3053 subjects responded to this question on the exit questionnaire

Percentage of Subjects Who Reported One or More GI Symptoms^a by Which Product (Olean or Regular) They Thought was in the Olean-labeled Packages

<u>How subjects responded to question about which product they thought was in the Olean-labeled packages</u>	<u>Olean (n = 1571) Percent</u>	<u>Control (n = 1504) Percent</u>
Believed they were eating Olean chips	45.3 ^{1,3}	44.4 ^{2,4}
Believed they were eating Regular chips	31.0 ¹	29.1 ²
Did not know which product they were eating	35.0 ³	35.8 ⁴

GI = gastrointestinal.

^a Includes all subjects who responded "yes" to the question in the daily record form.

1, 2, 3, 4 Figures with same superscript are statistically different at p=0.01.

Exhibit 44

Number of Subjects Who Took Medications for Their GI Symptoms
and the Number of Days on Which the Subjects Reported Taking the Medications

<u>Medication Classification</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Analgesics	4	6	7	8	11	14
Antacids	53	111	52	123	105	234
Antibiotics	1	2	2	5	3	7
Antidiarrheals	44	70	47	91	91	161
Antiemetics	0	0	2	2	2	2
Antiflatulents	8	35	0	0	8	35
Cough and cold preparations	0	0	1	1	1	1
GI anticholinergics	1	1	1	1	2	2
GI antispasmodics	1	1	1	2	2	3
H ₂ receptor antagonists	17	39	12	17	29	56
Laxatives	3	4	4	4	7	8
Total ^a	132	269	129	254	261	523

GI = gastrointestinal.

^a Subjects could take more than one medication.

Exhibit 45

GI Adverse Events by Reported Term

<u>GI Adverse Event</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Abdominal Pain	2	2	1	1	3	3
Anorexia	1	1	0	0	1	1
Borborygmus	0	0	1	1	1	1
Cholelithiasis	2	2	0	0	2	2
Colon Irritable	0	0	1	1	1	1
Cramp Abdomen	0	0	2	2	2	2
Diarrhea	1	1	4	4	5	5
Diverticulitis	1	1	0	0	1	1
Flatulence	0	0	1	1	1	1
Gastroenteritis	0	0	2	2	2	2
Hernia Hiatal	0	0	1	1	1	1
Nausea	1	1	5	5	6	6
Pain Gallbladder	1	1	0	0	1	1
Stool Frequency Increased	0	0	1	2	1	2
Stool Loose	0	0	1	2	1	2
Upset Stomach	0	0	1	1	1	1
Vomiting	1	1	4	4	5	5
Total ^a	7	10	9	27	16	37

GI = gastrointestinal.

^a Subjects could report more than one GI Adverse Event.

Exhibit 46

Serious Adverse Events By Reported Term

<u>Adverse Event</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Abdominal Pain	1	1	0	0	1	1
Bladder Neoplasm	1	1	0	0	1	1
Cardiomyopathy	0	0	1	1	1	1
Chest Pain	1	1	1	1	2	2
Cholelithiasis	1	1	0	0	1	1
Congestive Heart Failure	1	1	0	0	1	1
Coronary Artery Disease	1	1	0	0	1	1
Death	0	0	2	2	2	2
Disorder Urethral	1	1	0	0	1	1
Dizziness	0	0	1	1	1	1
Faintness	1	1	0	0	1	1
Heart Failure	0	0	1	1	1	1
Irregularity Heartbeat	1	1	0	0	1	1
Kidney Calculus	1	1	0	0	1	1
Kidney Failure	1	1	0	0	1	1
Urinary Tract Infection	1	1	0	0	1	1
Ventricular Tachycardia	1	1	0	0	1	1
Total ^a	5	13	3	6	8	19

GI = gastrointestinal.

^a Subjects could report more than one Adverse Event.

Exhibit 47

All Adverse Events Reported In The Study By Reported Term

<u>Reported Term</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Abdominal Pain	2	2	1	1	3	3
Ache	1	1	0	0	1	1
Aggravation Reaction	0	0	1	1	1	1
Anorexia	1	1	0	0	1	1
Anxiety	1	1	0	0	1	1
Back Pain	1	1	0	0	1	1
Basal Cell Carcinoma	2	2	0	0	2	2
Bladder Neoplasm	1	1	0	0	1	1
Blood in Urine	1	1	0	0	1	1
Borborygmus	0	0	1	1	1	1
Bronchitis	1	1	1	1	2	2
Bronchospasm Aggravated	0	0	1	1	1	1
Cardiomyopathy	0	0	1	1	1	1
Cataract	0	0	1	1	1	1
Chest Pain	1	1	3	3	4	4
Chills	0	0	1	1	1	1
Cholelithiasis	2	2	0	0	2	2
Cicatrix Skin	1	1	0	0	1	1
Colon Irritable	0	0	1	1	1	1
Common Cold	0	0	1	1	1	1
Congestion Sinus	2	2	6	6	8	8
Congestive Heart Failure	1	1	0	0	1	1
Conjunctivitis	0	0	2	2	2	2
Constriction Throat	1	1	0	0	1	1
Coronary Artery Disease	1	1	0	0	1	1
Coughing	1	1	0	0	1	1
Cramp Abdomen	0	0	2	2	2	2
Cyst Ovary	1	1	0	0	1	1
Death	0	0	2	2	2	2
Depression	1	1	0	0	1	1
Depression Aggravated	1	1	0	0	1	1

Exhibit 47 - (cont'd)

All Adverse Events Reported In The Study By Reported Term

<u>Reported Term</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Diarrhea	1	1	4	4	5	5
Disorder Urethral	1	1	0	0	1	1
Diverticulitis	1	1	0	0	1	1
Dizziness	1	1	2	2	3	3
Dyspnea	1	1	2	2	3	3
Earache	0	0	1	1	1	1
Faintness	1	1	0	0	1	1
Feeling Detached	0	0	1	1	1	1
Fever	1	1	2	2	3	3
Flatulence	0	0	1	1	1	1
Furunculosis	0	0	1	1	1	1
Gastroenteritis	0	0	2	2	2	2
Headache	2	2	2	2	4	4
Heart Failure	0	0	1	1	1	1
Hernia Hiatal	0	0	1	1	1	1
Herpetic Lesion Oral	1	1	0	0	1	1
Infection Bladder	1	1	0	0	1	1
Infection Eye	1	1	0	0	1	1
Infection Respiratory	1	1	0	0	1	1
Infection Upper Respiratory	1	1	2	2	3	3
Injury Accidental	3	4	1	1	4	5
Injury Accidental (Musculoskeletal)	0	0	1	1	1	1
Injury Accidental (Skin)	2	2	1	1	3	3
Irregularity Heartbeat	1	1	0	0	1	1
Irritation Local Throat	0	0	1	1	1	1
Kidney Calculus	1	1	0	0	1	1
Kidney Failure	1	1	0	0	1	1
Kidney Pain	0	0	1	1	1	1
Lupus Erythematosus Syndrome Aggravated	1	1	0	0	1	1

Exhibit 47 - (cont'd)
All Adverse Events Reported In The Study By Reported Term

<u>Reported Term</u>	<u>Olean (n = 1620)</u>		<u>Control (n = 1561)</u>		<u>Total (n = 3181)</u>	
	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>	<u>Number of Subjects</u>	<u>Number of Reports</u>
Migraine	0	0	1	1	1	1
Nausea	1	1	5	5	6	6
Neck Pain	0	0	1	1	1	1
Neoplasm Vaginal Benign	0	0	1	1	1	1
Neuritis Sciatic	1	1	0	0	1	1
Numbness	0	0	1	1	1	1
Otitis Media	5	5	2	2	7	7
Pain Gallbladder	1	1	0	0	1	1
Pain Muscle	0	0	1	1	1	1
Pain Shoulder	1	1	0	0	1	1
Palsy Bells	1	1	0	0	1	1
Pruritus	0	0	1	1	1	1
Rash	3	3	1	1	4	4
Sinusitis	0	0	1	1	1	1
Smell Perversion	1	1	0	0	1	1
Stool Frequency Increased	0	0	1	2	1	2
Stools Loose	0	0	1	2	1	2
Sweat Night	0	0	1	1	1	1
Swelling	0	0	1	1	1	1
Syndrome Carpal Tunnel	0	0	1	1	1	1
Tachycardia	1	1	0	0	1	1
Tendon Disorder	0	0	1	1	1	1
Throat Sore	3	3	4	5	7	8
Upset Stomach	0	0	1	1	1	1
Urinary Tract Infection	3	3	0	0	3	3
Urination Difficulty	1	1	0	0	1	1
Vascular Headache	0	0	1	1	1	1
Ventricular Tachycardia	1	1	0	0	1	1
Vomiting	1	1	4	4	5	5
Water Retention	1	1	0	0	1	1
Weight Loss	1	1	0	0	1	1
Total ^a	47	74	50	86	97	160

^a Subjects could report more than one Adverse Event.