

Additionally, the percentage of patients with shifts to abnormal values was similar for the placebo and drug-treated patients.

In preclinical studies, high doses of orlistat were associated with increased levels of serum triglycerides; this action is presumably the result of orlistat's inhibition of lipoprotein lipase. Appropriately so, the Sponsor analyzed the triglyceride levels of 25 patients with serum levels of orlistat greater than 3ng/ml. There was no evidence that the triglyceride levels were significantly increased — when measured at the time of pharmacokinetic sampling for plasma orlistat levels.

### Fat-Soluble Vitamin and $\beta$ -carotene Levels

Review of the individual phase III studies indicated that, compared with placebo, the mean levels of vitamin E and  $\beta$ -carotene were reduced in patients receiving 120mg of orlistat. Some, but not all studies, reported lower levels of vitamin D following treatment with orlistat 120mg. The mean levels of vitamin A were not significantly affected by treatment with orlistat when compared with the changes seen in the placebo groups.

For the ISS, data were pooled and analyzed from two US studies (NM14185 and NM14161) and two non-US studies (BM14119 and BM14149). These studies were pooled separately because they had specific guidelines for vitamin supplementation. Analyzing the US and non-US studies separately seems appropriate because of the different methodologies and laboratories used in the US and the non-US studies. The following data represent two years of therapy with orlistat or placebo.

### Vitamin A

At the end of Year 2 the mean values for the change in vitamin A levels did not differ significantly between the 120mg and placebo groups. Seven subjects in the placebo and 120mg groups received vitamin supplementation because of low vitamin A levels on two consecutive measurements; these patients had vitamin A levels within the normal range at the completion of the study. The results from the non-US studies were similar to the US findings.

### Vitamin D

The mean levels of vitamin D decreased gradually during the first 72 weeks of the studies, after which time the levels increased slightly up to Week 104. At the completion of the study, the values of vitamin D were lower in both groups compared with their respective baseline values. Still, the orlistat-treated patients had a mean plasma level of vitamin D that was 6.9 mmol/L lower than the respective value in the placebo group ( $p < 0.001$ ). Similar results were obtained in the non-US studies

Approximately 13% of placebo patients and 18% of 120mg subjects with normal baseline vitamin D levels had two consecutive low values during the two years of the study.

The incidence of vitamin supplementation was 15% for the 120mg group compared with 9% for the placebo group. Approximately 70% of the subjects who received vitamin supplementation in the 120mg group had a value that was within normal limits at the last determination.

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An analysis of post-menopausal women not taking estrogen replacement was conducted to evaluate whether this population — which is at higher risk for osteoporosis — had lower vitamin D levels following treatment with orlistat. In this group of patients ( $n > 100$  per group) there did not appear to be a significantly greater reduction in mean vitamin D levels after two years of treatment when compared with placebo patients or to the overall study population. Moreover, the percentage of post-menopausal patients in the 120mg group with two consecutive low values was lower than the percentage in the

placebo patients and in the study population as a whole. Of interest, the reported dietary intake of vitamin D was approximately 135-145 IU, considerably lower than the RDA of 200 to 400 IU per day. The results of the non-US studies were similar to the US data.

### Vitamin E

In the US studies, the reduction in plasma vitamin E levels in the orlistat 120mg group compared with the change in the placebo group was significant (-1.6 umol/L,  $p=0.008$ ). However, when the vitamin E status was expressed as the ratio of vitamin E to LDL cholesterol — an appropriate adjustment given that lipid levels have a marked effect on vitamin E concentrations — no significant differences between the 120mg and placebo groups following two years of double-blind treatment. Of the subjects with normal baseline values for vitamin E, 13% of placebo and 18% of orlistat subjects had two or more consecutive low vitamin E levels during two years of treatment. Approximately 4% of 120mg subjects and 1% of placebo subjects required vitamin supplementation. One hundred percent of placebo patients and 73% of 120mg subjects had normal vitamin E levels at the completion of the study following supplementation. The results from the non-US studies were similar to the US results.

### $\beta$ -carotene

It should be pointed out that a "normal range" for  $\beta$ -carotene is not defined or widely accepted. For the purposes of these clinical studies the Sponsor derived project specific "normal" ranges for the 2 US and the two non-US studies. These project specific ranges were calculated using 2.5-97.5 percentiles for the baseline (pretreatment) values for all patients. Thus, the "normal" range for subjects in the non-US studies was 0.09-1.06 umol/L and 0.056-1.289 umol/L in the US studies.

In the US studies, the change in  $\beta$ -carotene level in the 120mg group following two years of treatment was 0.08 umol/L lower than the change in the placebo group, this difference was statistically significant ( $p<0.001$ ). Approximately 3% of placebo patients and 8% of 120mg subjects had two or more consecutive low serum values during the study, and as a result, more orlistat patients received supplementation compared with placebo patients. Of the supplemented patients, nearly 90% had  $\beta$ -carotene values within the normal range at the final laboratory determination. The results from the non-US studies did not differ substantially from the US data.

### Vitamin K

Assessment of vitamin K status was conducted by measurement of prothrombin time (PT). In both the US and non-US studies, the mean values of PT decreased slightly in the placebo and 120mg groups from baseline to Week 104. The use of PT to assess marked hypovitaminosis K is reasonable. However, when assessing subtle deficiencies in vitamin K, one has to question the validity of using PT, as some data indicate that PT remains normal with mild to moderate deficiencies of vitamin K.

### The Incidence of Low Vitamin Levels During 2 Years of Treatment

As shown in the table below, over the course of the 2-year studies M14119, M14149, M14161, and M14185, when compared with placebo, a statistically significantly larger percentage of patients receiving 120mg of orlistat had low levels of vitamins D, E, and  $\beta$ -carotene on two or more consecutive occasions.

**Incidence of Low Vitamin Values on Two or More Consecutive Visits (Patients with normal baseline values - first and second year)**

	Placebo	120mg	P
Vitamin A	1.0%	2.2%	0.1
Vitamin D	6.6%	12.0%	0.002
Vitamin E	1.0%	5.8%	<0.0001
$\beta$ -carotene	1.7%	6.1%	0.0002

Given the tendency of orlistat to impair absorption of the fat-soluble vitamins and  $\beta$ -carotene it is not surprising that in the two US studies, 17% of the 120mg patients and 5% of the placebo patients ( $p=0.07$ ) had at least two different vitamin values that were low on two or more consecutive occasions. It is also not surprising that the individuals who developed two or more consecutive low vitamin levels had low normal baseline values for these fat-soluble nutrients.

**Time to First Occurrence of Two Consecutive Low Vitamin Levels**

Examination of curves depicting the cumulative incidence of two consecutive low vitamin levels indicates that for vitamins D, E, and  $\beta$ -carotene there is a constant rate of accumulation of individuals with low values. This being the case, screening for low vitamin levels would not be practical.

**Other Vitamin Data**

Data from three studies that are not included in the above discussion are briefly summarized below

Study BM14119B was a non-US trial comparing 120mg of orlistat to placebo for one year. Following 52 weeks of treatment the mean change from baseline in  $\beta$ -carotene was -0.11  $\mu\text{mol/L}$  in the orlistat group and 0.0  $\mu\text{mol/L}$  in the placebo group ( $p<0.001$ ). No significant differences between the two groups in the mean change from baseline in vitamins A and D or in the ratio of vitamin E/total cholesterol. A greater percentage of orlistat patients had two or more consecutive low vitamin A, D, and E values compared with the placebo subjects.

Study NM14336 was a one-year trial comparing 120mg of orlistat to placebo in patients with NIDDM. Following 52 weeks of treatment, the mean change from baseline in  $\beta$ -carotene was -0.12  $\mu\text{mol/L}$  in the orlistat group and -0.03  $\mu\text{mol/L}$  in the placebo group ( $p<0.001$ ). There were no significant differences between the two groups in the mean change from baseline in vitamins A and D or in the ratio of vitamin E/total cholesterol. However, more active-treatment subjects had two or more consecutive low vitamin D and E and  $\beta$ -carotene values during the trial (see table below).

**Incidence of Low Vitamin Values on Two or More Consecutive Visits in Patients with Normal Baseline Values**

	Placebo	120mg	P
Vitamin D	9%	22%	0.002

	Placebo	120mg	P
$\beta$ -carotene	1%	12%	0.0002

Similarly, more orlistat patients required a vitamin supplement because of low values (see table below). In most cases, the supplement appeared to increase the vitamin or  $\beta$ -carotene values to within normal limits at the time of the last determination.

#### Outcome of Vitamin Supplementation

	Placebo	120mg
<b>Vitamin D</b>		
Received Supplement	7%	17%
Last Value Low	9%	0%
<b>Vitamin E</b>		
Received Supplement	0.6%	1.3%
Last Value Low	0%	0%
<b><math>\beta</math>-carotene</b>		
Received Supplement	0%	9%
Last Value Low	0%	7%

Study NM14302 was an 18-month trial in which obese patients were instructed to maintain a hypocaloric diet for six months, after which time subjects were randomized to one of four groups: placebo, orlistat 30mg tid, orlistat 60mg tid, or orlistat 120mg tid for an additional 12 months. All patients were instructed to take a once-a-day multivitamin (Centrum) with breakfast throughout the 18-month study. At the completion of the 52-week active-treatment phase the levels of vitamins D, E, and  $\beta$ -carotene were significantly lower in the active-treatment groups compared with the placebo group. In addition, the value of vitamin E/Total cholesterol was significantly lower in the three active-treatment groups compared with the placebo group. The percentage of patients with two or more consecutive low vitamin D, E or  $\beta$ -carotene values was higher in the 120mg group than the placebo group. Very few subjects required an additional vitamin supplement during the trial. Because all of the orlistat-treated patients received a multivitamin during the trial it is not possible to accurately assess the efficacy of supplementation.

#### Subgroup Analyses of the Incidence of Low Vitamin Levels

The incidence of two consecutive low vitamin levels in patients with normal baseline values was examined in several subgroups. These groups included age (<40, >40<60, >60), gender, race (Caucasian, Black, Hispanic, and other), and BMI (<30, >30<35, >35). The US and non-US studies were pooled separately. To simplify matters only those subgroups that are significant in both the US and non-US studies will be reported. Significant placebo vs drug differences in the incidence of two consecutive low vitamin A levels during Year 1 were observed for age. This was because none of the subjects over the age of 60 years had two consecutive low vitamin A levels. For vitamins D, E, and  $\beta$ -carotene none of the

subgroup analyses were significant in both the US and non-US studies.

Thus, to summarize, orlistat does appear to interfere with the absorption of vitamins D, E, and  $\beta$ -carotene. The long-term treatment with orlistat does not appear to cause frank vitamin K deficiency. Yet, the use of PT as an indicator of vitamin K status precludes one from commenting about subclinical deficiencies of this vitamin. In this Reviewer's opinion, the vitamin data argue in favor of universal vitamin supplementation.

### Vital Signs

The baseline values for pulse, systolic and diastolic blood pressure were nearly identical for the placebo and orlistat 120mg groups. There were small, but statistically significant reductions in the mean levels of pulse, systolic, and diastolic blood pressure ( $\approx 1.5$  bpm and 1.5 mmHg) in the 120mg group compared with the placebo group after one year of treatment. Over a 2-year period, pulse, systolic, and diastolic blood pressure increased slightly ( $\approx 1-2$  mmHg) from baseline in both groups. The increase in mean levels was greater in the placebo group compared with the 120mg group, though the relative changes were minimal and not statistically significant.

### Electrocardiograms

There was no evidence that treatment with orlistat for one or two years adversely affected electrocardiographic parameters.

### Gallbladder Ultrasounds

Eight hundred and fifty-six patients treated with placebo and 1164 patients treated with 120mg had gallbladder ultrasounds at baseline and at the end of one year of double-blind treatment. Of patients with normal baseline ultrasounds, 22 (3.6%) placebo and 29 (3.6%) orlistat-treated patients developed stones; and one (0.2%) placebo and 4 (0.5%) orlistat-treated patients developed sludge ( $p=0.89$ ). Four hundred and two patients treated with placebo and 471 subjects treated with 120mg had ultrasounds at baseline and at the end of two full years of treatment. Of the patients with normal baseline ultrasounds, eight (2.8%) of the placebo subjects and 14 (3.9%) of the 120mg subjects developed stones; and three (1.0%) placebo and none of the 120mg subjects developed sludge ( $p=1.00$ ). Of some interest, in patients with a baseline ultrasound abnormality classified as "other" (ie fatty liver, polyps) abnormality, 5 (3.3%) placebo patients and 14 (6.0%) orlistat patients developed stones after one year of treatment; and none of the placebo and 2 (0.9%) of the orlistat-treated subjects developed sludge ( $p=0.17$ ).

### Renal Ultrasounds

Six hundred and seventeen patients treated with placebo and 939 patients treated with 120mg had renal ultrasounds at baseline and at the end of one year of double-blind treatment. In patients with normal baseline ultrasounds, one (0.2%) placebo patient and seven (0.8%) subjects in the 120mg group had stones visualized at the end of one year of treatment ( $p=0.12$ ). Four hundred and thirteen patients treated with placebo and 476 subjects treated with 120mg had ultrasounds at baseline and at the end of two full years of treatment. In patients with normal baseline tests, one (0.3%) placebo and five (1.1%) orlistat-treated patients had stones at the completion of the study ( $p=0.15$ ) (two of the patients in the orlistat group are included in both the one and two year computations).

### Summary of Gallbladder and Kidney Stone Data

Advancing age, female gender, obesity, and rapid weight loss all increase the risk for the development of cholesterol gallstones. It would not be unexpected, therefore, for some patients to develop cholelithiasis

following treatment with orlistat. Following two years of treatment, in patients with normal baseline ultrasounds, approximately 3% of placebo and 4% of 120mg-treated patients developed gallstones, which were presumably asymptomatic. Hence, it appears safe to say that in patients with normal ultrasonic examinations of the gallbladder, the use of orlistat for up to two years is not associated with a marked increase in the incidence of gallstones. In patients with a baseline abnormality (fatty liver, polyps, cysts, etc.) as determined by ultrasound, there was an increase in the incidence of stone + sludge formation in the group receiving orlistat compared with the incidence in the placebo group. The heterogeneity of the baseline gallbladder abnormalities makes it difficult to assess the meaningfulness of this finding. Of relevance, the incidence of symptomatic gallstone disease was 0.4% in the both the placebo and 120mg groups.

With respect to kidney stones, the ultrasound data are compatible (though not incontrovertible) with the interpretation that orlistat is associated with an increased risk for the development of ultrasound-detected renal stones. Data from study NM14161 indicate that more patients on orlistat compared with placebo had markedly elevated levels of 24-hour urinary oxalate. These data provide biological plausibility with which to link the use of orlistat with the development of nephrolithiasis. These cases of kidney stones were presumably asymptomatic; adverse event data indicate that 0.4% of placebo patients and 0.2% of orlistat 120mg patients were coded as developing renal calculi, and 0.2% of placebo and 0.1% of orlistat 120mg subjects were coded as developing renal colic during the studies. The discrepancy between the number of stones visualized by ultrasound with the number of reported cases of renal calculi and colic is not surprising given that not all stones are symptomatic. If one accepts the assumption that orlistat — when used for at least one year — increases the risk of developing asymptomatic kidney stones, the crucial question remains: does orlistat increase the risk of symptomatic nephrolithiasis? This Reviewer acknowledges that the current weight of evidence may not support a warning in the labeling. Yet, without question, the Sponsor should conduct a systematic post-approval assessment of orlistat's lithogenic potential.

### 10.3.3 Special Studies

#### Bone Metabolism

Because orlistat may influence the absorption of vitamin D and dietary calcium, the Sponsor conducted special studies of bone metabolism in subgroups of patients from protocols BM14119C and BM14149.

In study BM14119C bone mineral content and density (DEXA), serum levels of ionized Ca<sup>+</sup>, PTH, alkaline phosphatase, osteocalcin, and vitamin D, as well as urinary hydroxyproline/creatinine, and calcium/creatinine ratios were determined in 11 placebo and 16 orlistat 120mg patients at baseline and following one year of treatment. The table below provides the baseline demographic characteristics of the two groups

	Orlistat 120mg N=16	Placebo N=14
Age (yrs)	42	40+
% Female	81	93+
% Caucasian	100	100+
BMI (kg/m <sup>2</sup> )	36	35+

+ p=ns

Both groups lost approximately 9.5 kg of body weight by the end of the treatment year.

The changes (means) in the markers of bone metabolism after 1 year of treatment are shown in the following table.

	Orlistat			Placebo			
	Baseline	Year 1	p†	Baseline	Year 1	p†	P‡
s-Ca (mmol/L)	1.2	1.2	0.01	1.2	1.2	0.2	0.3
s-PTH (pmol/L)	2.3	3.2	<0.02	2.3	3.5	0.1	0.7
s-Alk Phos (U/L)	115	125	0.01	108	117	0.06	0.2
25(OH)D2+D3 (nmol/L)	68	50	<0.001	73	54	<0.001	0.9
1,25(OH)2D3 (pmol/L)	140	111	0.02	103	94	0.1	0.7
s-osteocalcin (ug/L)	3.6	3.7	0.7	3.3	4.0	0.2	0.6
u-OHpr/Creat (L)	12	20	0.001	11	13	0.7	0.02
u-Ca/Creat (L)	223	387	0.003	218	253	0.9	0.2

†with-in group p value, ‡between group p value

Following one year of treatment, the plasma levels of osteocalcin, PTH, and alkaline phosphatase increased in both groups; the differences between the groups were not statistically significant. The serum levels of 25(OH)D2 + D3 and 1,25(OH)2D3 decreased following one year of treatment in both groups; the differences between groups were also not statistically significant. Serum levels of ionized calcium increased in the orlistat group and did not change significantly in the placebo group; the difference in change between the two groups was not significant. The ratios of urinary OHpr/creatinine and Ca/creatinine were significantly increased in the orlistat group at the end of one year of treatment. Only the difference between groups in the ratio of OHpr to creatinine was statistically significant, however.

There were no statistically significant changes in bone mineral content or density as measured for the whole body, the lumbar spine, and the forearm in the orlistat or placebo groups after one year of treatment as shown in the following table.

**BMD and BMC at Baseline and After One Year of Treatment**

	Placebo		Orlistat		P-value‡
	Baseline	Year 1	Baseline	Year 1	
<b>BMC</b>					
Total (kg)	2.97	2.93	3.01	2.98	0.3
Lumbar Spine (g)	54.7	55.1	56.3	57.2	0.2
Forearm (g)	3.92	3.74	3.91	3.82	0.7
<b>BMD (g/cm<sup>3</sup>)</b>					
Total	1.09	1.12	1.10	1.10	0.6
Lumbar Spine	1.18	1.19	1.13	1.13	0.1
Forearm	0.51	0.49	0.49	0.48	0.5

In study BM14149 bone mineral content and density were assessed at baseline and following one year of treatment in 17 placebo, 20 60mg, and 18 120mg patients, and in 15 placebo, 19 60mg, and 18 120mg subjects after two years of treatment. There was a higher percentage of males in the 120mg group (22%) compared to the 60mg group (15%) and the placebo group (6%). The ages of the subjects (43 years), their BMIs (32 kg/m<sup>2</sup>) were similar for the three groups and all the subjects were Caucasian. The baseline BMDs were 1.21, 1.23, and 1.24 g/cm<sup>2</sup> in the placebo, 60mg and 120mg groups, respectively (p=ns). There were essentially no changes in BMD or BMC after one or two years of treatment in any of the groups. differences in the changes from baseline in BMC or BMD between the placebo and orlistat groups after one and two years of treatment.

### Discussion

If one assumes that orlistat decreases the absorption of dietary calcium and vitamin D to a clinically significant extent, the expected physiological responses would include increased secretion of PTH with a resultant increase in renally synthesized 1,25(OH)<sub>2</sub>D<sub>3</sub> and decreased excretion of calcium by the kidney. If sustained long-term, one could expect an increase in bone turnover with increased levels of bone markers. Ultimately a decrease in bone mineral density might ensue.

In study BM14119C, the levels of urinary hydroxyproline/creatinine increased in the orlistat group to a greater extent than in the placebo group. The sponsor claims that the urinary creatinine levels decreased by almost 50% in the orlistat group after one year of treatment, which in part, contributed to the increased ratio of hydroxyproline/creatinine at Year 1. This may be true. The changes in serum calcium, PTH, alk phos, vitamin D, and oseteocalcin and urinary calcium levels did not significantly differ between groups after one year of treatment. In addition, in studies BM14119C and BM14149, there were no significant changes in BMD or BMC after one or two years of treatment with orlistat.

The totality of the data related to bone metabolism may be interpreted to indicate that the use of 120mg tid of orlistat for up to two years in Caucasian women of whom most are premenopausal, does not lead to dramatic and clinically significant alterations in bone metabolism. Yet this Reviewer hesitates to make any definitive statements about orlistat's effect on bone simply because relatively few patients were studied using DEXA and the sensitive bone marker, N-teleopeptide, was not used. The fact that osteoporosis is not a major problem in obese women should be taken into consideration before the Sponsor is requested to perform additional bone assessment studies. In addition, if there is evidence from the mineral balance study that calcium absorption is reduced to a significant extent by orlistat, this too will influence the need for additional study.

### Effect of Orlistat on Mineral Balance, Serum and Urinary Electrolytes, Osteocalcin, Hydroxyproline, and Fecal Fat and Biliary Acids - ND14458

**Background:** The use of orlistat results in fat malabsorption; steatorrhea may increase the excretion of calcium and magnesium. Orlistat also increases the concentration of free fatty acids in the intestine. When dietary calcium binds to free fatty acids, oxalate is left unbound and can be absorbed and eventually excreted in increased amounts by the kidney.

Some epidemiological data suggest that a high-fat diet increases the risk for cancer of the prostate, colon, and breast. One purported mechanism that may account for the association between dietary fat and colon

cancer is an increased delivery of secondary bile acids and free fatty acids to the colonic mucosa. In animal models, some bile acids and fatty acids increase colonic mucosal cell proliferation.

**Objective:** The primary objectives of this study were to evaluate the effects of four weeks of treatment with orlistat 120mg tid on:

- Mineral balance (calcium, phosphate, magnesium, iron, copper, and zinc) and electrolyte concentrations (sodium, potassium, magnesium, calcium, phosphate, oxalate, uric acid, bicarbonate) in the urine and serum.
- Markers of bone formation (osteocalcin and hydroxyproline)
- Composition of fecal fat and fecal biliary acids (cholic and chenodeoxycholic, deoxycholic, lithocholic, and urosdeoxycholic)

**Methods:** This was a 4-week, single-center, randomized, placebo-controlled study of 11 female and 11 male, obese patients. Subjects were instructed to consume a 1500 kcal/day diet, containing approximately 30% of calories as fat, 50% as carbohydrate, 20% protein, and a maximum of 300mg cholesterol per day. The diet was designed to cause a 0.25 to 0.50 kg per week weight loss. Baseline assessments were conducted during days -5 to -1 and post-treatment assessments were conducted during days 24 to 28. Mineral balance was to be calculated as Dietary mineral intake - (urinary mineral excretion + fecal mineral excretion).

**Results:** Six female and five male patients were randomized to the orlistat group. One patient withdrew prematurely. The placebo group contained five female and six male patients. One patient withdrew prematurely. The groups were well matched for baseline demographic characteristics, except race; there were eight and four Black patients in the placebo and orlistat groups, respectively. The ages of the patients ranged from 20 to 42 years and the average BMI was 34 kg/m<sup>2</sup>. The mean weight loss in the orlistat group was 6.1 kg and 6.6 kg in the placebo group. For unexplained reasons the data obtained from the use of sitostanol as a fecal marker was highly variable and considered unreliable by the Sponsor. As a result, only group means for dietary intake, fecal excretion, and urinary excretion are provided.

**Total Fat, Free Fatty Acids, and Total Bile Acids in Fecal Material:** The concentrations of total fat and free fatty acids in the stool increased significantly in the orlistat group when compared with baseline values and to the changes in the placebo group. Contrarily, the levels of total bile acids decreased significantly in the orlistat group relative to baseline and placebo values. The decrease in the concentration of the individual bile acids was greater in the orlistat compared with the placebo group; the reduction in lithocholic acid was statistically significant. The concentration of neutral fecal fats decreased significantly in the orlistat group when compared with baseline and to the change in the placebo group.

**Minerals and Electrolytes:** In the orlistat group there were statistically significant reductions from baseline in the following minerals: fecal copper, urinary magnesium, and fecal and urinary phosphorus. Reductions of a magnitude observed in the orlistat group were seen in the placebo group for urinary magnesium and urinary phosphorus. There were no statistically significant differences between the two groups in the changes in any of the other mineral concentrations. In addition, there were no clinically significant changes in the serum electrolytes in the orlistat or placebo groups. Urinary levels of oxalate increased in the orlistat group but the change was not statistically significant. Other changes in urinary

electrolyte concentrations did not appear to be of clinical relevance.

**Serum Osteocalcin and 24-Hour Urine Hydroxyproline:** There were no statistically significant changes noted in the levels of serum osteocalcin or urinary hydroxyproline in the orlistat group.

**Conclusions:** In this small study of 22 obese patients, treatment with orlistat 120mg tid resulted in significant increases in fecal content of total fat and free fatty acids. In addition, the level of fecal bile acids was significantly reduced following treatment with orlistat for 28 days. Valid conclusion about the effect of orlistat on mineral balance cannot be made because of methodological limitations associated with the fecal marker sitostanol. The Sponsor is conducting an additional mineral balance study and the results of this study should be submitted near the end of April 1997.

**Effect of Orlistat 120mg tid on Colonic Mucosa Cell Turnover - NP15138 (See consult from Dr. Gallo Torres, Medical Officer from the Division of Gastrointestinal and Coagulation Drug Products)**

**Background:** High levels of dietary fat have been associated with an increased risk for colon cancer in some observational studies. A potential mechanism that may explain this association invokes the proliferative effects of free fatty acids on colonic mucosa cells. Some investigators believe that risk for malignant transformation of colonic mucosa cells can be assessed by measuring biomarkers of cell proliferation such as bromodeoxyuridine (BrdU), proliferating cell nuclear antigen labeling index (PCNA), and whole crypt mitotic count value (WCMC). One pharmacodynamic effect of orlistat is to increase fecal fatty acid content. Thus, this study investigated the changes in biomarkers of cell proliferation following six weeks of treatment with orlistat 120mg tid.

**Objectives:** The primary objectives of this study were to evaluate the effects of six weeks of treatment with orlistat 120mg tid on:

- total fat, free fatty acid, and bile acid content in fecal material and fecal water
- colonic mucosal cell turnover from biopsy samples

**Methods:** This was a single-center, randomized, placebo-controlled, double-blind study conducted in 24 obese male and female patients. Subjects were instructed to consume a standardized diet consisting of 30% of calories as fat, 50% as carbohydrate, 20% as protein, and a maximum of 300 mg of cholesterol per day. The percentage of calories as fat, carbohydrate, and protein was measured by chemical analysis. Stool samples for total fat, free fatty acid and bile acid, and pH were collected at daily intervals from day -7 to day -1 and from day 36 to 42. Colonic biopsies were obtained from the rectum approximately 8-10 cm from the anus on day -7 and day 43. Analysis of samples for BrdU and PCNA were conducted at MD Anderson Cancer Center and WCMC was conducted at the Denver Veterans Affairs Medical Center.

**Results:** Twelve patients (6 M and 6 F) were randomized to placebo and 12 patients were randomized to orlistat (6 M and 6 F). Ten orlistat and 12 placebo patients were available for pharmacodynamics. The groups were well matched for baseline demographic variables. The mean age was 41 years, the average BMI was 33 kg/m<sup>2</sup>, and approximately 90% of the subjects were Caucasian.

**Total Fat, Free Fatty Acids, Total Bile Acids, Calcium, Fecal Weight, and pH:** The fecal levels of total fat and free fatty acids increased significantly in the orlistat group relative to baseline and to the change

in the placebo group. The levels of total bile acid decreased significantly more in the orlistat group compared with the placebo group. The concentrations of deoxycholic and lithocholic acid accounted for most of the reduction in total bile acid in the orlistat group. The levels of calcium did not change in either group.

**Biomarkers of Cell Proliferation:** The baseline values for biomarkers were not significantly different in the two groups. WCMC increased by 0.6 in the placebo group and decreased by 0.04 in the orlistat group ( $p=ns$ ); BrdU decreased by 0.5 and 4.0 in the placebo and orlistat groups, respectively ( $p=ns$ ); and PCNA increased by 3.4 and 2.3 in the placebo and orlistat groups, respectively ( $p=ns$ ). The correlation coefficients between the changes in fecal fat and FFA content with the changes in PCNA and BrdU ranged from 0.4 to 0.6 in the orlistat group and -0.2 to 0.1 in the placebo group (all ns).

**Conclusions:** Although none of the correlations between fecal fat and FFA content with the changes in markers of proliferation were statistically significant, the absolute values in the orlistat group are suggestive of a meaningful relationship. Statistical significance would be difficult to achieve in a sample of only 10 subjects. These data do suggest that there is a direct correlation between increased levels of fecal total fat and FFA with increased activity of the biomarkers for proliferation in the orlistat group, but not in the placebo group. However, as pointed out in Dr. Hugo Gallo Torres's consult, there is good reason to question the predictive value of colonic cell proliferation in models of carcinogenesis. Above all else, the data from this study are not worrisome enough to prevent marketing of the drug. An appropriate post-marketing surveillance study (details of which are discussed in Dr. Gallo Torres's consult) should be conducted to gain a more meaningful assessment of orlistat's effect on colonic cell physiology.

#### **10.3.4 Drug - Demographic Interactions**

See page 75 for an account of subgroup analyses for GI-related adverse events.

#### **10.3.5 Drug - Disease Interactions**

No studies in patients with liver or kidney disease were done.

#### **10.3.6 Drug - Drug Interactions**

See biopharm review

The Sponsor conducted drug-drug interaction studies of orlistat with atenolol, captopril, furosemide, nifedipine (IR and SR), digoxin, oral contraceptives, phenytoin, warfarin, alcohol, glyburide, pravastatin, vitamins A and E, and beta-carotene. Orlistat, taken three times a day significantly increased the  $C_{max}$  and AUC of pravastatin, and reduced the  $C_{max}$  and AUC of vitamin E and beta-carotene. The studies of atenolol, captopril, furosemide, and IR nifedipine were conducted with 50mg tid of orlistat and did not reveal significant drug-drug interactions.

#### **10.3.7 Withdrawal Phenomena/Abuse Potential**

The Sponsor claims that no effects on behavior or signs indicative of an effect on the central nervous system were observed in single dose oral (maximum dose 5000mg/kg) and IV (100mg/kg) studies of

orlistat in mice and rats. Similar results were obtained in dogs. No studies in humans that specifically addressed abuse potential or withdrawal phenomena were conducted with orlistat. However, as with any weight-loss agent, there is potential for abuse by certain populations (i.e., anorexia nervosa, bulimia). A warning to this effect should appear in the labeling.

#### **10.3.8 Overdose**

There is no human experience of accidental overdose with orlistat. In humans, single doses of 800mg and multiple doses of 400mg tid of orlistat were not associated with adverse events other than gastrointestinal. The local effects of orlistat in the gastrointestinal tract should abate within 48-72 hours.

#### **10.3.9 Human Reproduction Data**

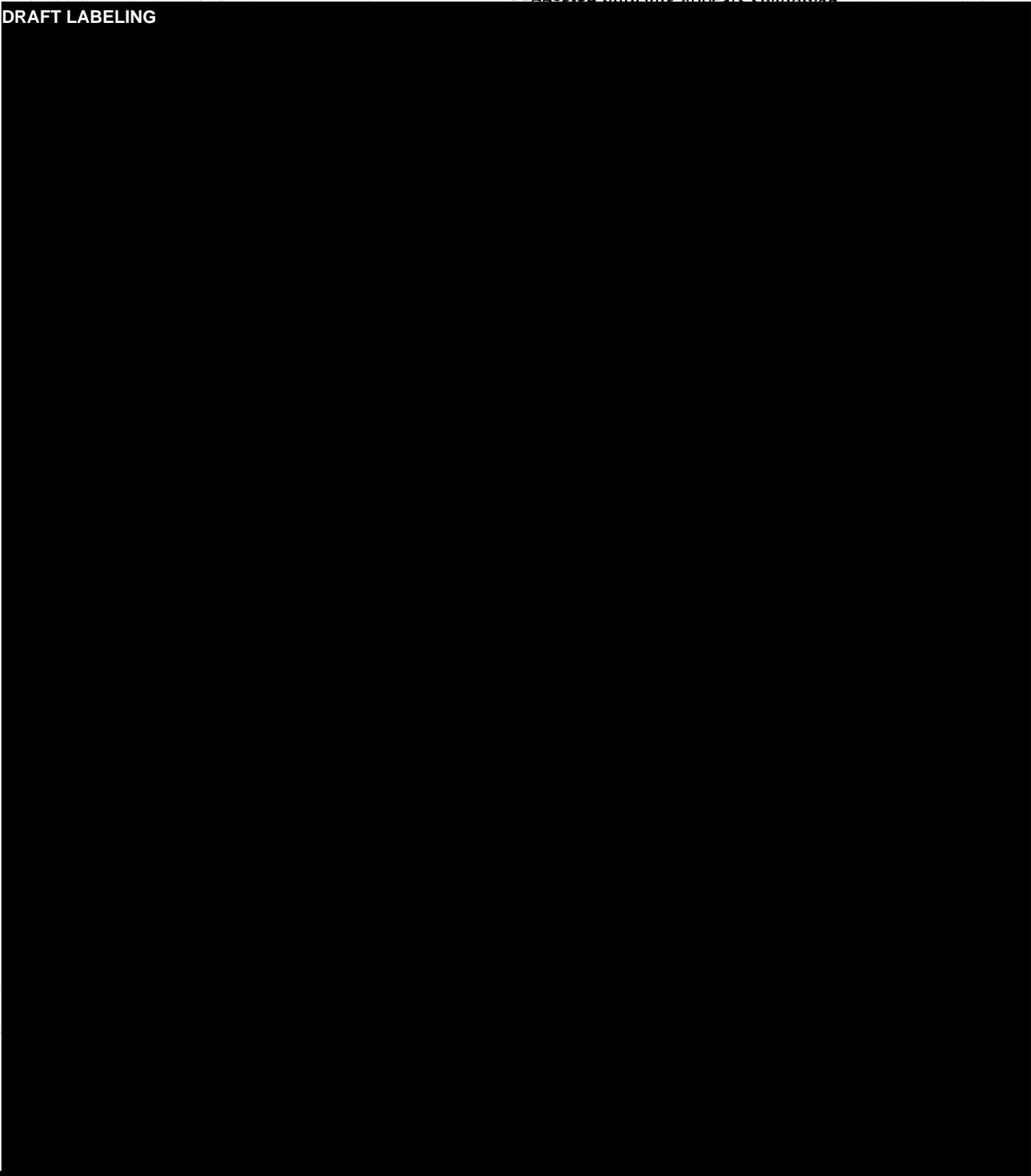
There was a total of 51/4188 pregnancies in the Phase III studies. Twenty-one of the pregnancies were in the placebo group and 30 in the orlistat group. One patient in the orlistat group delivered an infant with "bowed legs." According to the Sponsor, the infant's pediatrician felt the condition was due to gestational positioning. The mother's vitamin D level during the study was slightly above the normal level.

APPEARS THIS WAY ON ORIGINAL

## 11 Labeling Review

In the following review I have used ~~strike out~~ to indicate letters, words, or sentences that I do not feel are appropriate, and I offer my rationale in bold *italics*. Suggested phrasing appears shaded.

DRAFT LABELING

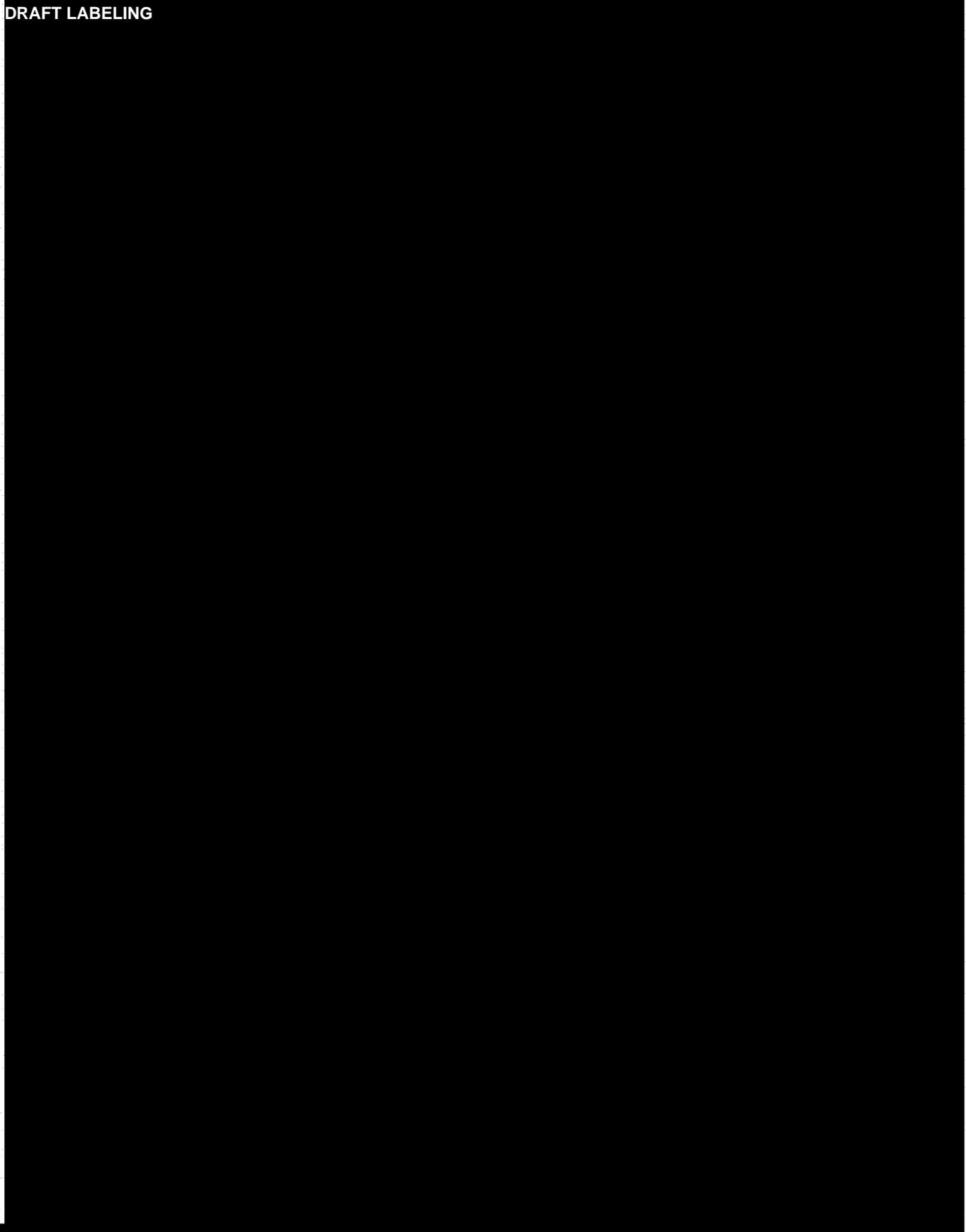


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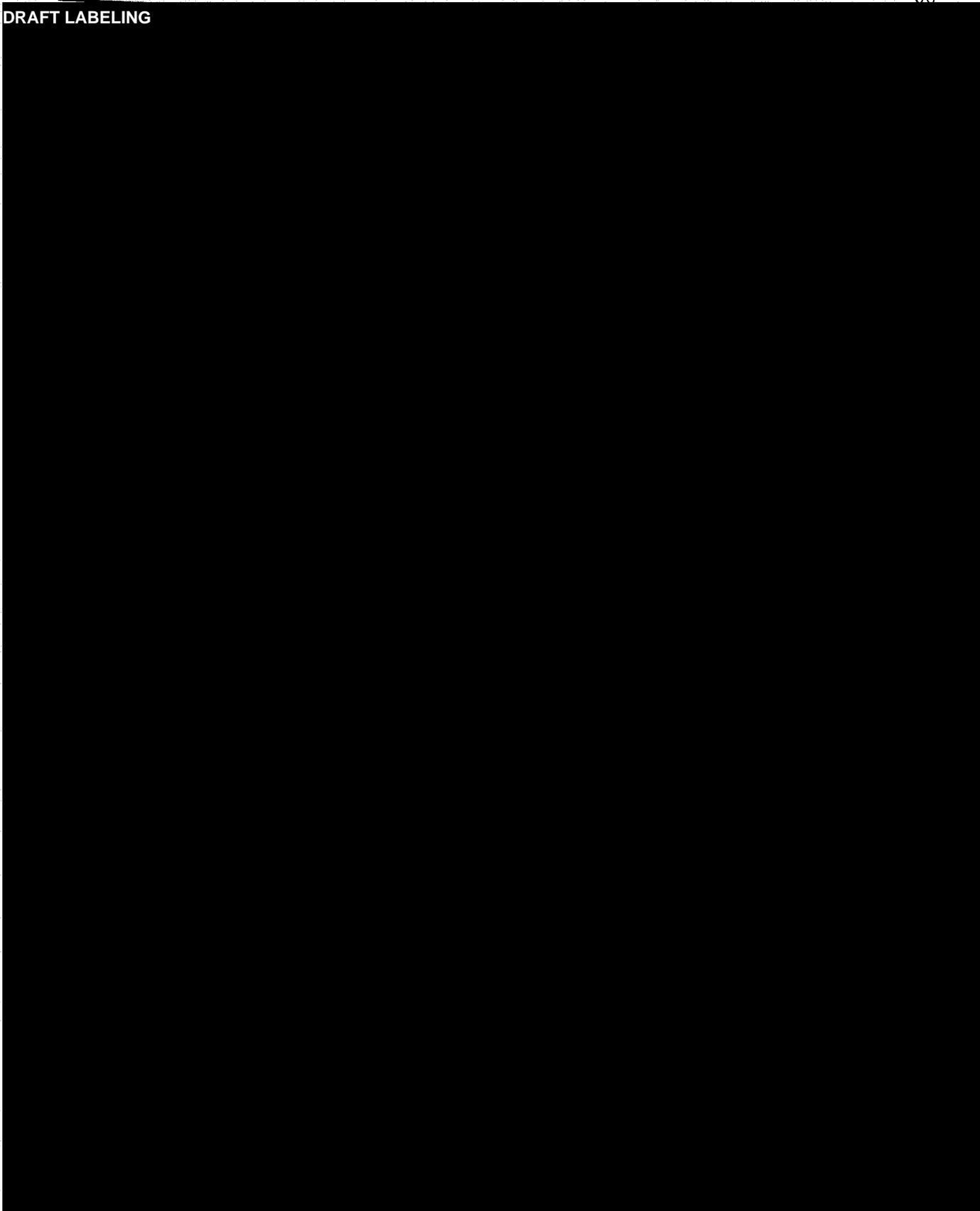
83

DRAFT LABELING

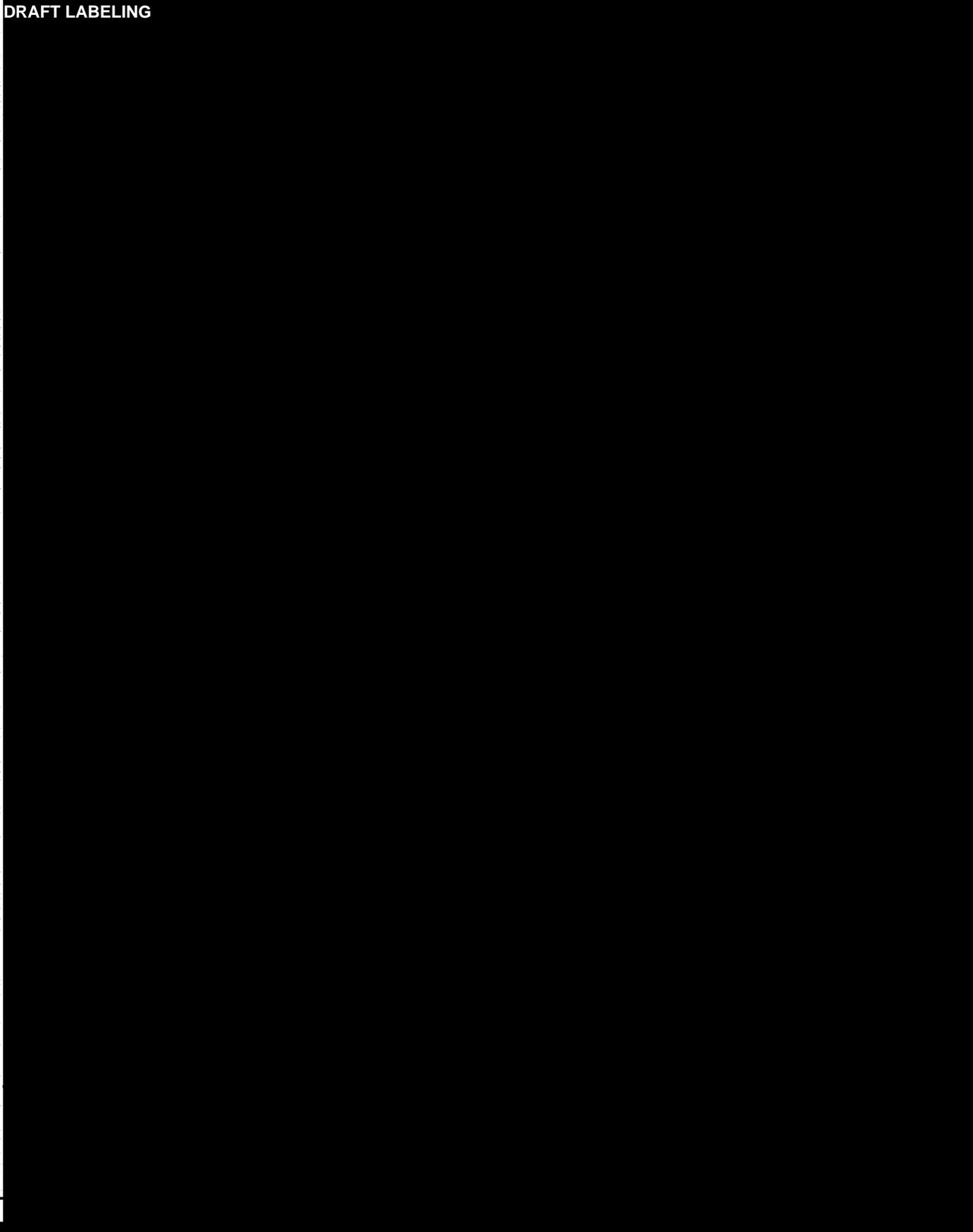
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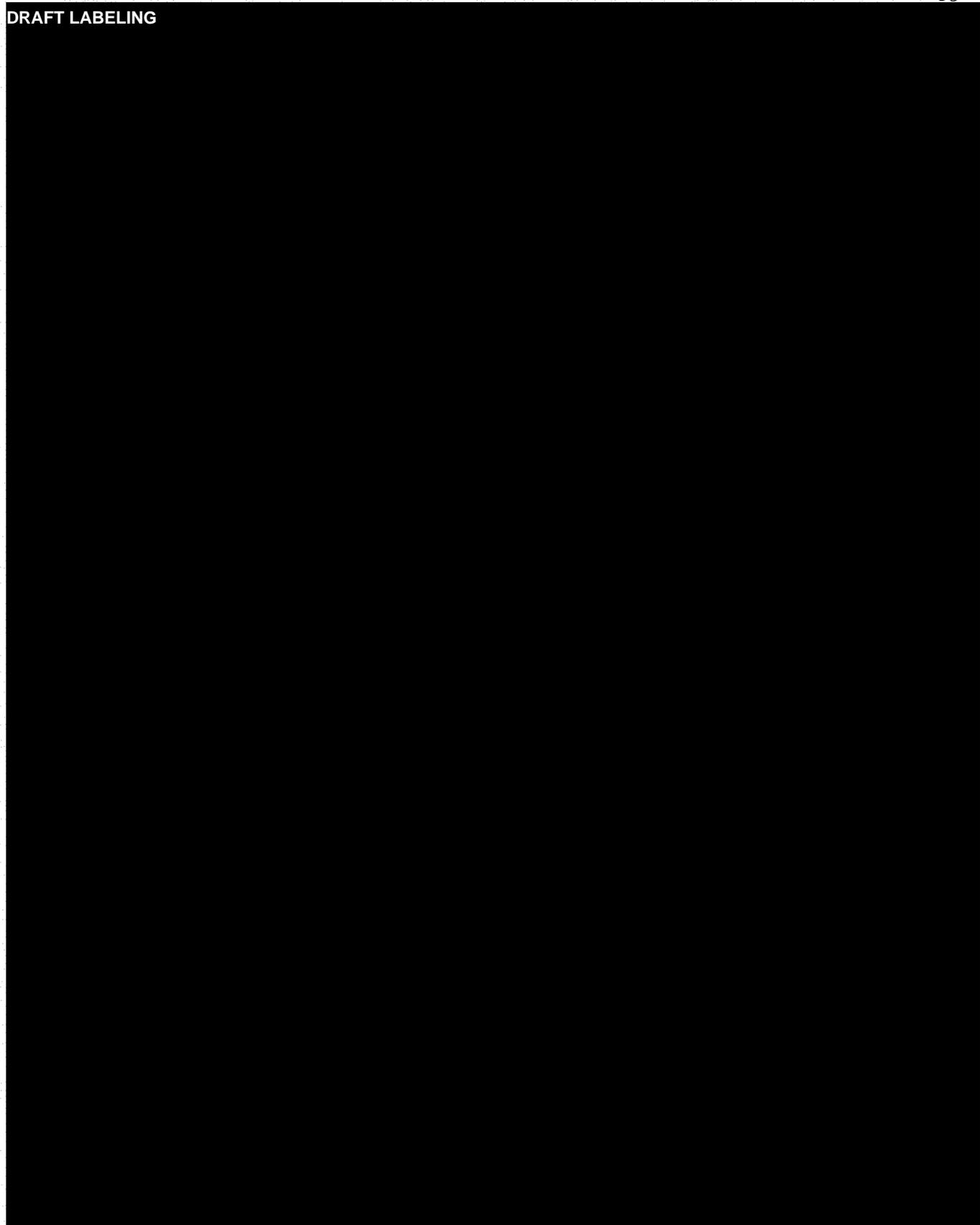
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