Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14149, NM14161, NM14802

Body System/ Preferred Term	Placebo (N=694) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=629) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
HYPOKALEMIA	0		0	1	(0.5)	1	2	(0.3)	2	0		0
HYPERLIPEMIA	0		0	0		0	2	(0.3)	2	0		0
HYPERURICEMIA	0		0	0		0	1	(0.2)	1	0		0
XANTHOMA	0		0	0		0	1	(0.2)	1	0		0
CALCIUM DEFICIENCY BONE	0		0	1	(0.5)	1	0		0	0		0
DEHYDRATION	1	(0.2)	1	0		0	0		0	0		0
VISION DISORDERS	15	(2.4)	15	2	(1.1)	2	7	(1.1)	8	9	(1.4)	10
CONJUNCTIVITIS	7	(1.1)	7	0		0	2	(0.3)	2	3	(0.5)	3
VISION BLURRED	0		0	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
EYE IRRITATION	1	(0.2)	1	0		0	0		0	1	(0.2)	1
ANGIOMATOSIS RETINA	0		0	0		0	0		0	1	(0.2)	1
EYE TWITCHING	0		0	0		0	0		0	1	(0.2)	1
IRIDOCYCLITIS	0		0	0		0	0		0	1	(0.2)	1
XEROPHTHALMIA	0		0	0		0	0		0	1	(0.2)	2
VISUAL DISTURBANCE	2	(0.3)	2	0		0	2	(0.3)	2	0		0
EYE PAIN	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	0		0
CORNEAL ABRASION	0		0	0		0	1	(0.2)	1	0		0
PRESBYOPIA	0		0	0		0	1	(0.2)	1	0		0
BLEPHARITIS	1	(0.2)	1	0		0	0		0	0		0
CONJUNCTIVAL HEMORRHAGE	1	(0.2)	1	0		0	0		0	0		0
EYE INFLAMED	1	(0.2)	1	0		0	0		0	0		0
STYES	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14149, NM14161, NM14802

Body System/ Preferred Term	Placebo (N=694) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=629) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
HEART RATE AND RHYTHM	7	(1.1)	8	3	(1.6)	3	8	(1.3)	10	7	(1.1)	7
PALPITATION	4	(0.6)	5	3	(1.6)	3	5	(0.8)	7	4	(0.6)	4
ARRHYTHMIA	0		0	0		0	2	(0.3)	2	1	(0.2)	1
TACHYCARDIA	3	(0.5)	3	0		0	0		0	1	(0.2)	1
FIBRILLATION ATRIAL	0		0	0		0	0		0	1	(0.2)	1
PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	0		0	0		0	1	(0.2)	1	0		0
PLATELET, BLEEDING & CLOTTING DISORDERS	2	(0.3)	2	0		0	5	(0.8)	5	6	(0.9)	6
BLEEDING DERMAL	2	(0.3)	2	0		0	5	(0.8)	5	6	(0.9)	6
LIVER AND BILIARY SYSTEM DISORDERS	4	(0.6)	7	3	(1.6)	3	3	(0.5)	3	4	(0.6)	4
CHOLECYSTITIS	3	(0.4)	6	0		0	2	(0.3)	2	2	(0.3)	2
CHOLELITHIASIS	0		0	1	(0.5)	1	1	(0.2)	1	2	(0.3)	2
HEPATITIS	0		0	2	(1.1)	2	0		0	0		0
BILIARY COLIC	1	(0.2)	1	0		0	0		0	0		0
VASCULAR (EXTRACARDIAC) DISORDERS	5	(0.8)	7	2	(1.1)	2	2	(0.3)	2	4	(0.6)	4
VARICOSE VEINS	2	(0.3)	2	1	(0.5)	1	0		0	2	(0.3)	2
PHLEBITIS	3	(0.5)	4	0		0	0		0	1	(0.2)	1
VENOUS THROMBOSIS	0		0	0		0	0		0	1	(0.2)	1
CEREBRAL ISCHEMIA	0		0	0		0	1	(0.2)	1	0		0
EMBOLISM - BLOOD CLOT	0		0	0		0	1	(0.2)	1	0		0
ARTERIAL DISORDERS	0		0	1	(0.5)	1	0		0	0		0
THROMBOPHLEBITIS	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14349, EM14361, EM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 80 mg tid (N=685) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
RED BLOOD CELL DISORDERS	2	(0.3)	2	0		0	3	(0.5)	4	2	(0.3)	2
ANEMIA	2	(0.3)	2	0		0	2	(0.3)	3	1	(0.2)	1
ANEMIA IRON DEFICIENCY	0		0	0		0	0		0	1	(0.2)	1
ANEMIA MACROCYTIC	0		0	0		0	1	(0.2)	1	0		0
REPRODUCTIVE DISORDERS, MALE	0		0	0		0	3	(0.5)	4	2	(0.3)	3
PROSTATITIS	0		0	0		0	2	(0.3)	3	1	(0.2)	2
TESTIS PAINFUL	0		0	0		0	0		0	1	(0.2)	1
PROSTATE ENLARGED	0		0	0		0	1	(0.2)	1	0		0
ENDOCRINE DISORDERS	4	(0.6)	4	5	(0.7)	5	2	(0.3)	2	3	(0.4)	3
THYROIDITIS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
HYPOTHYROIDISM	2	(0.3)	2	2	(0.3)	2	0		0	1	(0.2)	1
TUMOR THYROID	0		0	0		0	0		0	1	(0.2)	1
THYROTOXICOSIS	0		0	0		0	1	(0.2)	1	0		0
GOITER	0		0	1	(0.1)	1	0		0	0		0
HYPERTHYROIDISM	1	(0.2)	1	0		0	0		0	0		0
TSH INCREASE	1	(0.2)	1	0		0	0		0	0		0
MYO-, ENDO-, PERICARDIAL & VALVE DISORD.	3	(0.4)	3	3	(0.4)	3	0		0	2	(0.3)	2
ANGINA PECTORIS	2	(0.3)	2	0		0	0		0	1	(0.2)	1
MALF. OF PROSTHESES AND HOMOGRAPHS	0		0	0		0	0		0	1	(0.2)	1
CARDIOMYOPATHY HYPERTROPHIC OBNS	0		0	1	(0.1)	1	0		0	0		0
MITRAL VALVE ABNORMALITY	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_tfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14349, EM14361, EM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 80 mg tid (N=685) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
SPECIAL SENSES OTHER, DISORDERS	4	(0.6)	4	0		0	1	(0.2)	1	1	(0.2)	1
TASTE UNPLEASANT	0		0	0		0	1	(0.2)	1	1	(0.2)	1
TASTE METALLIC	3	(0.5)	3	0		0	0		0	0		0
TASTE SALTY	1	(0.2)	1	0		0	0		0	0		0
NEOPLASM	0		0	0		0	0		0	1	(0.2)	1
MYOMA	0		0	0		0	0		0	1	(0.2)	1
WHITE CELL AND RES DISORDERS	2	(0.3)	2	4	(0.6)	4	1	(0.2)	1	0		0
SWELLING LYMPHNODES	0		0	0		0	1	(0.2)	1	0		0
GLANDS SWOLLEN	0		0	2	(0.3)	2	0		0	0		0
LYMPHADENOPATHY	0		0	1	(0.1)	1	0		0	0		0
LYMPHADENOPATHY CERVICAL	0		0	1	(0.1)	1	0		0	0		0
LYMPH NODES ENLARGED	2	(0.3)	2	0		0	0		0	0		0
APPLICATION SITE DISORDERS	0		0	0		0	1	(0.2)	1	0		0
WOUND HEALING IMPAIRED WITHOUT INFECTION	0		0	0		0	1	(0.2)	1	0		0
COLLAGEN DISORDERS	0		0	0		0	1	(0.2)	1	0		0
ARTHRITIS RHEUMATOID	0		0	0		0	1	(0.2)	1	0		0
NEOPLASM, URINARY SYSTEM	0		0	1	(0.1)	1	0		0	0		0
CARCINOMA RENAL	0		0	1	(0.1)	1	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_tfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, BM14861, BM14802

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
HEMIC AND LYMPHATIC DISORDERS	1	(0.2)	1	0		0	0		0	0		0
LYMPHEDEMA	1	(0.2)	1	0		0	0		0	0		0

(Last Page)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_tfinal\t_ae.sas
Source: ae.xpt, profile.xpt

10.3.4 All Adverse Events; Pooled Safety Studies: First Year

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14349, BM14861, BM14802

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
SUBJECTS WITH AT LEAST 1 ADVERSE EVENT	558	(88.0)	3439	180	(96.8)	1421	572	(91.6)	4319	599	(94.8)	4881
SUBJECTS WITH NO ADVERSE EVENTS	75	(12.0)		6	(3.2)		51	(8.2)		33	(5.2)	
GASTRO-INTESTINAL SYSTEM DISORDERS	352	(55.6)	1032	158	(82.3)	662	452	(72.6)	1966	502	(79.4)	2019
FECAL URGENCY	57	(9.0)	75	56	(31.2)	76	126	(20.2)	159	156	(24.7)	215
ABDOMINAL PAIN	97	(15.3)	151	56	(26.5)	72	142	(22.8)	200	150	(23.7)	208
OILY SPOTTING	9	(1.4)	10	38	(17.7)	53	117	(18.8)	162	149	(25.5)	234
FATTY/OILY STOOL	19	(3.0)	21	16	(7.0)	19	119	(19.3)	152	146	(22.9)	205
FLATUS WITH DISCHARGE	14	(2.2)	18	40	(21.5)	54	115	(18.5)	178	128	(20.3)	182
FLATULENCE	119	(18.6)	145	64	(45.2)	107	124	(19.9)	171	121	(19.1)	148
LIQUID STOOLS	55	(10.3)	84	22	(17.2)	45	94	(15.1)	125	106	(15.6)	134
OILY EVACUATION	4	(0.6)	4	26	(14.0)	46	78	(12.5)	118	90	(14.2)	114
INCREASED DEFECATION	17	(2.7)	19	11	(5.9)	14	47	(7.5)	59	58	(9.2)	66
STOOLS SOFT	41	(6.6)	59	15	(8.1)	15	69	(11.1)	104	56	(8.9)	74
NAUSEA	49	(7.7)	61	20	(10.8)	24	39	(6.3)	49	56	(8.9)	60
FECAL INCONTINENCE	7	(1.8)	12	9	(4.8)	11	33	(5.3)	46	53	(8.1)	66
DECREASED DEFECATION	67	(10.6)	80	17	(9.1)	18	35	(5.6)	41	30	(4.7)	32
ENTERITIS	29	(4.6)	36	2	(1.1)	2	25	(4.0)	26	26	(4.4)	34
HEMORRHOIDS	19	(3.0)	19	6	(3.2)	6	20	(3.2)	23	23	(3.5)	24
INFECTIOUS DIARRHEA	25	(4.3)	31	6	(3.2)	7	25	(4.2)	29	22	(3.5)	22
TOOTHACHE	17	(2.7)	19	8	(4.3)	9	17	(2.7)	19	18	(2.8)	22
VOMITING	22	(3.5)	24	6	(4.3)	9	16	(2.6)	17	18	(2.8)	18
PERIODONTAL BREAKDOWN	5	(0.9)	5	4	(2.2)	4	9	(1.8)	13	17	(2.7)	18
DYSPEPSIA	23	(3.6)	25	6	(3.2)	6	21	(3.4)	29	14	(2.2)	16
ABDOMINAL DISCOMFORT	8	(1.8)	9	1	(0.5)	1	8	(1.8)	9	11	(1.7)	11

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
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Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14349, EM14361, EM14302

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=165) n	(%)	NAE	Orlistat 60 mg tid (N=523) n	(%)	NAE	Orlistat 120 mg tid (N=552) n	(%)	NAE
(...Body System Continues)												
PYROSIS	19	(3.6)	24	6	(3.6)	7	9	(1.4)	9	8	(1.3)	10
GASTRITIS	5	(0.8)	5	4	(2.2)	5	1	(0.2)	1	7	(1.1)	7
ABDOMINAL PAIN LOWER	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	6	(0.9)	6
HEMORRHAGE RECTUM	2	(0.3)	2	1	(0.5)	1	1	(0.2)	1	5	(0.8)	5
FECES BLOODSTAINED	2	(0.3)	3	6	(3.6)	7	0		0	5	(0.8)	5
PAIN PELVIC	1	(0.2)	1	0		0	0		0	5	(0.8)	5
BORBORYGMUS	2	(0.3)	2	0		0	4	(0.6)	5	4	(0.6)	5
FECES DISCOLORED	4	(0.6)	5	1	(0.5)	1	3	(0.6)	6	4	(0.6)	5
RECTAL PAIN	2	(0.3)	2	0		0	2	(0.3)	4	4	(0.6)	5
FLANK PAIN	1	(0.2)	1	1	(0.5)	1	0		0	4	(0.6)	4
FULLNESS ABDOMINAL	5	(0.8)	6	1	(0.5)	1	5	(1.0)	7	3	(0.5)	4
ERUCTATION	1	(0.2)	1	2	(1.1)	2	4	(0.6)	5	3	(0.5)	3
GINGIVITIS	2	(0.3)	2	0		0	1	(0.2)	1	3	(0.5)	3
BUCCAL MUCOSA ULCERATION	0		0	1	(0.5)	1	0		0	3	(0.5)	3
ESOPHAGITIS	1	(0.2)	1	0		0	0		0	3	(0.5)	3
IRRITATION ANAL	0		0	0		0	0		0	3	(0.5)	3
STOMACH UPSET	2	(0.3)	2	2	(1.1)	2	5	(0.8)	5	2	(0.3)	2
FOOD POISONING	1	(0.2)	1	3	(1.8)	3	2	(0.3)	2	2	(0.3)	2
COLIC	0		0	0		0	2	(0.3)	2	2	(0.3)	4
DIVERTICULUM CECUM	0		0	2	(1.1)	2	1	(0.2)	1	2	(0.3)	2
COLONIC POLYPOSIS	1	(0.2)	1	0		0	1	(0.2)	1	2	(0.3)	2
APPENDICITIS	0		0	0		0	0		0	2	(0.3)	2
ABDOMINAL DISTENTION	1	(0.2)	1	1	(0.5)	1	4	(0.6)	4	1	(0.2)	2

(Continued)

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Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14349, EM14361, EM14302

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(...Body System Continues)												
CANKER SORES ORAL	1	(0.2)	1	1	(0.5)	1	3	(0.6)	3	1	(0.2)	1
STOOLS HARD	3	(0.6)	7	0		0	3	(0.6)	3	1	(0.2)	1
MOUTH DRY	2	(0.3)	2	2	(1.1)	2	2	(0.3)	2	1	(0.2)	1
TOOTH DISORDER	1	(0.2)	1	1	(0.5)	1	2	(0.3)	2	1	(0.2)	1
HERNIA UMBILICAL	0		0	0		0	2	(0.3)	2	1	(0.2)	1
MELENA	0		0	0		0	2	(0.3)	2	1	(0.2)	1
TOOTH CARIES	0		0	0		0	2	(0.3)	2	1	(0.2)	3
BURNING ANAL	2	(0.3)	2	2	(1.1)	2	1	(0.2)	1	1	(0.2)	1
DIVERTICULITIS	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
PAROTITIS	0		0	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
GASTROINTESTINAL DISORDER NOS	1	(0.2)	1	0		0	1	(0.2)	1	1	(0.2)	1
FECES UNPLEASANT SMELL	0		0	0		0	1	(0.2)	1	1	(0.2)	2
PAIN ILIACFOSSA	0		0	0		0	1	(0.2)	2	1	(0.2)	1
ULCER	0		0	0		0	1	(0.2)	1	1	(0.2)	1
REFLUX ESOPHAGITIS	2	(0.3)	2	1	(0.5)	1	0		0	1	(0.2)	1
PAIN INGUINAL	1	(0.2)	1	1	(0.5)	1	0		0	1	(0.2)	1
EPIGASTRIC PAIN NOT FOOD-RELATED	2	(0.3)	2	0		0	0		0	1	(0.2)	1
ANAL SPHINCTER DISORDER	1	(0.2)	1	0		0	0		0	1	(0.2)	1
GI HEMORRHAGE	0		0	0		0	0		0	1	(0.2)	1
PAIN MOUTH	0		0	0		0	0		0	1	(0.2)	2
PROCTALGIA	0		0	0		0	0		0	1	(0.2)	1
STOMACH ULCER	0		0	0		0	0		0	1	(0.2)	1
STOOLS SOLID	0		0	0		0	0		0	1	(0.2)	1

(Continued)

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Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14149, BM14161, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=165) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
TENDERNESS HYPOCHONDRIUM	0		0	0		0	0		0	1	(0.2)	1
FELLETS	11	(1.7)	12	1	(0.5)	2	4	(0.6)	5	0		0
HERNIA INGUINAL	1	(0.2)	1	0		0	3	(0.5)	3	0		0
FECAL FISTULA	0		0	0		0	2	(0.3)	2	0		0
GASTROESOPHAGEAL REFLUX	4	(0.6)	4	1	(0.5)	1	1	(0.2)	1	0		0
REFLUX DUODENO-GASTRIC	2	(0.3)	2	1	(0.5)	1	1	(0.2)	1	0		0
ABDOMINAL MASS	1	(0.2)	1	0		0	1	(0.2)	1	0		0
BLISTERS MOUTH	0		0	0		0	1	(0.2)	2	0		0
CHEWING DIFFICULTY	0		0	0		0	1	(0.2)	1	0		0
COLITIS	0		0	0		0	1	(0.2)	2	0		0
COLON CARCINOMA	0		0	0		0	1	(0.2)	1	0		0
EDEMA MOUTH	0		0	0		0	1	(0.2)	1	0		0
ESOPHAGUS OBSTRUCTION	0		0	0		0	1	(0.2)	1	0		0
HICCUP	0		0	0		0	1	(0.2)	1	0		0
IRRITABLE BOWEL SYNDROME	0		0	0		0	1	(0.2)	1	0		0
PROCTITIS	0		0	0		0	1	(0.2)	1	0		0
HERNIA HIATAL	2	(0.3)	2	2	(1.1)	2	0		0	0		0
PAINFUL DEFECATION	1	(0.2)	1	2	(1.1)	2	0		0	0		0
ANGULUS INFECTIOSUS ORIS	1	(0.2)	1	1	(0.5)	1	0		0	0		0
BAD BREATH	1	(0.2)	1	0		0	0		0	0		0
BURNING TONGUE	1	(0.2)	1	0		0	0		0	0		0
COLON SPASTIC	1	(0.2)	2	0		0	0		0	0		0
ESOPHAGEAL COMPLAINTS	1	(0.2)	1	0		0	0		0	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_rfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14149, BM14161, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=165) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
ILEITIS	1	(0.2)	1	0		0	0		0	0		0
PAIN GINGIVAL	1	(0.2)	1	0		0	0		0	0		0
SALIVARY GLAND ENLARGEMENT	1	(0.2)	1	0		0	0		0	0		0
RESPIRATORY SYSTEM DISORDER	257	(40.5)	461	90	(48.4)	149	251	(40.0)	470	278	(40.2)	491
SINUSITIS	75	(11.8)	101	38	(20.4)	44	83	(13.2)	127	79	(12.5)	105
UPPER RESP TRACT INFECTION	72	(11.4)	98	21	(11.3)	24	77	(12.4)	90	72	(11.4)	91
PHARYNGITIS	51	(8.0)	64	18	(9.7)	18	36	(5.8)	48	68	(10.0)	78
BRONCHITIS	37	(5.8)	45	12	(6.5)	15	42	(6.7)	51	53	(8.1)	63
RHINITIS ALLERGIC ATOPIC	39	(6.2)	52	21	(11.3)	29	42	(6.7)	47	40	(6.3)	52
RHINITIS	19	(3.0)	21	8	(4.3)	8	16	(2.6)	20	18	(2.8)	22
COUGHING	28	(4.4)	29	7	(3.8)	7	19	(3.0)	21	17	(2.7)	19
ANGINA TONSILLARIS	10	(1.6)	12	2	(1.1)	2	8	(1.3)	8	11	(1.7)	11
NASAL CONGESTION	9	(1.4)	9	2	(1.1)	2	15	(2.4)	19	9	(1.4)	9
NOSEBLEED	4	(0.6)	6	1	(0.5)	1	2	(0.3)	3	7	(1.1)	8
PNEUMONIA	5	(0.8)	5	1	(0.5)	1	12	(1.9)	12	6	(0.9)	6
LARYNGITIS	4	(0.6)	5	1	(0.5)	1	3	(0.5)	3	6	(0.9)	6
ASTHMA BRONCHIAL	2	(0.3)	2	2	(1.1)	2	3	(0.5)	3	5	(0.8)	7
ASTHMATIC ATTACK	1	(0.2)	2	1	(0.5)	3	3	(0.5)	5	3	(0.5)	3
DYSPNEA	5	(0.9)	6	0		0	2	(0.3)	3	3	(0.5)	3
SINUSITIS MAXILLARY	1	(0.2)	1	0		0	0		0	3	(0.5)	3
TRACHEOBRONCHITIS	2	(0.3)	2	0		0	2	(0.3)	2	1	(0.2)	1
BRONCHOPNEUMONIA	0		0	0		0	1	(0.2)	1	1	(0.2)	1

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_rfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14349, BM14361, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 60 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=629) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
BRONCHIAL SECRETION EXCESSIVE	0		0	0		0	0		0	1	(0.2)	1
CHRONIC OBSTRUCTIVE LUNG DISEASE	0		0	0		0	0		0	1	(0.2)	1
HOARSENESS	0		0	0		0	0		0	1	(0.2)	1
NASAL MUCOSA SWOLLEN	0		0	0		0	0		0	1	(0.2)	3
PLEURISY	0		0	0		0	0		0	1	(0.2)	1
VOCAL CORD THICKENING	0		0	0		0	0		0	1	(0.2)	1
APNEA	0		0	0		0	1	(0.2)	1	0		0
ASTHMA-LIKE REACTION	0		0	0		0	1	(0.2)	1	0		0
LARYNGOPHARYNGITIS	0		0	0		0	1	(0.2)	2	0		0
PHARYNX DISORDER	0		0	0		0	1	(0.2)	1	0		0
PHLEGM	0		0	0		0	1	(0.2)	2	0		0
RESPIRATORY INSUFFICIENCY	0		0	0		0	1	(0.2)	1	0		0
SARCOIDOSIS	0		0	0		0	1	(0.2)	1	0		0
SINUS CONGESTION	0		0	0		0	1	(0.2)	1	0		0
SNEEZING EXCESSIVE	0		0	0		0	1	(0.2)	1	0		0
STRIDOR	0		0	0		0	1	(0.2)	1	0		0
INFECTION LUNG	0		0	1	(0.5)	1	0		0	0		0
SUBGLOTTIC EDEMA	0		0	1	(0.5)	2	0		0	0		0
IRRITATION PHARYNX	2	(0.3)	2	0		0	0		0	0		0
HYPERVENTILATION	1	(0.2)	1	0		0	0		0	0		0
NASAL POLYP	1	(0.2)	1	0		0	0		0	0		0
NASAL SEPTUM DEVIATION	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IBB\Programming_rfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14349, BM14361, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 60 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=629) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
RESISTANCE MECHANISM DISORDERS	239	(37.7)	981	70	(37.8)	97	225	(35.8)	359	253	(39.7)	389
INFLUENZA SYNDROME	217	(34.2)	329	65	(34.9)	87	199	(31.6)	302	225	(33.6)	340
INFLUENZA	12	(1.9)	12	2	(1.1)	2	11	(1.8)	13	13	(1.7)	13
INFECTION MYCOTIC	9	(1.4)	9	6	(3.2)	6	6	(1.0)	8	7	(1.1)	9
HERPES SIMPLEX	7	(1.1)	9	2	(1.1)	2	10	(1.6)	10	6	(0.9)	8
INFECTION VIRAL	1	(0.2)	1	0		0	3	(0.5)	5	5	(0.8)	5
HERPES ZOSTER	2	(0.3)	2	0		0	2	(0.3)	2	3	(0.5)	3
MONILIASIS	0		0	0		0	3	(0.5)	4	2	(0.3)	2
WHITLOW	1	(0.2)	1	0		0	1	(0.2)	1	2	(0.3)	2
INFECTION	4	(0.6)	4	0		0	3	(0.5)	3	1	(0.2)	1
ABSCESS LOCAL	3	(0.5)	3	0		0	1	(0.2)	1	1	(0.2)	1
HERPES	1	(0.2)	1	0		0	0		0	1	(0.2)	1
ABSCESS LEG	0		0	0		0	0		0	1	(0.2)	1
HERPES GENITALIS	0		0	0		0	0		0	1	(0.2)	2
INFECTION STAPHYLOCOCCAL	0		0	0		0	0		0	1	(0.2)	1
INFECTIOUS MONONUCLEOSIS	0		0	0		0	0		0	1	(0.2)	1
HERPES LABIALIS	2	(0.3)	4	0		0	1	(0.2)	1	0		0
INFECTION GLAND	0		0	0		0	1	(0.2)	1	0		0
SCABIES	0		0	0		0	1	(0.2)	1	0		0
ABSCESS	1	(0.2)	1	0		0	0		0	0		0
ERYSIPELAS	1	(0.2)	1	0		0	0		0	0		0
INFECTION SALMONELLA	1	(0.2)	1	0		0	0		0	0		0
INFESTATION PARASITIC	1	(0.2)	1	0		0	0		0	0		0
SEPTICEMIA CANDIDA ALBICANS	1	(0.2)	1	0		0	0		0	0		0
WOUND INFECTION	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Program: K:\Gemini\IBB\Programming_rfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EMI4349, NMI4361, NMI4802

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
MUSCULO-SKELETAL SYSTEM DISORDERS	242	(38.2)	406	71	(38.2)	110	217	(34.8)	356	288	(35.3)	491
BACK PAIN	61	(9.6)	71	17	(9.1)	20	62	(10.0)	96	66	(10.8)	95
PAIN KNEE	23	(3.6)	26	9	(4.8)	10	19	(3.0)	29	25	(4.0)	30
PAIN LIMBS	14	(2.2)	14	3	(1.6)	3	13	(2.1)	17	20	(3.2)	20
MYALGIA	17	(2.7)	22	10	(5.4)	10	12	(1.9)	16	20	(3.2)	29
SPRAINS AND STRAINS	11	(1.7)	12	4	(2.2)	4	14	(2.2)	16	19	(3.0)	20
ARTHRALGIA	18	(2.8)	30	8	(4.3)	8	13	(2.1)	15	17	(2.7)	19
PAIN FEET	13	(2.1)	17	7	(3.8)	7	18	(2.8)	19	13	(2.1)	17
PAIN SHOULDER	12	(1.9)	12	4	(2.2)	4	18	(2.8)	19	13	(2.1)	16
PAIN NAPE	21	(3.3)	24	3	(1.6)	3	10	(1.6)	22	13	(2.1)	14
TENDINITIS	13	(2.1)	13	3	(1.6)	3	10	(1.6)	12	11	(1.7)	15
LUMBAGO	5	(0.9)	5	0		0	15	(2.4)	16	10	(1.6)	11
PAIN LEG	14	(2.2)	18	3	(1.6)	4	8	(1.3)	11	10	(1.6)	12
ARTHRITIS	11	(1.7)	14	4	(2.2)	4	10	(1.6)	10	6	(1.3)	8
PAIN ARM	14	(2.2)	15	1	(0.5)	1	7	(1.1)	7	6	(1.3)	8
CRAMPS LEG	11	(1.7)	11	1	(0.5)	1	7	(1.1)	8	8	(1.3)	8
PAIN ANKLE	9	(1.4)	10	3	(1.6)	3	4	(0.6)	4	8	(1.3)	8
BONE FRACTURE	11	(1.7)	12	3	(1.6)	3	13	(2.1)	15	6	(0.9)	6
ARTHROSIS	3	(0.6)	3	1	(0.5)	1	6	(1.0)	6	6	(0.9)	6
PAIN HIP	10	(1.6)	12	2	(1.1)	2	9	(1.4)	11	5	(0.8)	5
STIFF NECK	3	(0.6)	3	2	(1.1)	2	3	(0.6)	6	5	(0.8)	6
PAIN WRIST	2	(0.3)	2	2	(1.1)	3	5	(0.8)	5	4	(0.6)	4
BURSITIS	4	(0.6)	4	3	(1.6)	3	4	(0.6)	5	3	(0.5)	3
CRAMPS MUSCLE	3	(0.6)	3	0		0	2	(0.3)	3	3	(0.5)	3
PAIN HAND	2	(0.3)	2	0		0	2	(0.3)	2	3	(0.5)	4

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IBB\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EMI4349, NMI4361, NMI4802

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
SYMPTOMS REFERABLE TO LIMBS	0		0	0		0	0		0	3	(0.5)	3
MUSCULO-SKELETAL BRUISING	2	(0.3)	2	1	(0.5)	1	5	(0.8)	5	2	(0.3)	2
BONE SPUR	5	(0.8)	7	0		0	3	(0.6)	3	2	(0.3)	2
JOINT DISLOCATION	0		0	0		0	3	(0.6)	3	2	(0.3)	2
PAIN RIBS	5	(0.8)	6	1	(0.5)	1	2	(0.3)	2	2	(0.3)	2
PAIN JAW	0		0	1	(0.5)	1	1	(0.2)	1	2	(0.3)	2
INJURY LEG	1	(0.2)	1	1	(0.5)	1	3	(0.6)	3	1	(0.2)	1
TMJ DISORDER	2	(0.3)	2	0		0	3	(0.6)	3	1	(0.2)	1
INJURY UPPER LIMB	3	(0.6)	3	0		0	2	(0.3)	2	1	(0.2)	1
INTERVERTEBRAL DISC DISORDER	4	(0.6)	5	2	(1.1)	2	1	(0.2)	1	1	(0.2)	1
ARTHROPATHY	2	(0.3)	3	0		0	1	(0.2)	1	1	(0.2)	1
ROTATOR CUFF SYNDROME OF SHOULDER	0		0	0		0	1	(0.2)	1	1	(0.2)	1
PAIN POLYARTICULAR	2	(0.3)	2	0		0	0		0	1	(0.2)	1
CRAMPS EXTREMITIES	1	(0.2)	1	0		0	0		0	1	(0.2)	1
EDEMA HAND	0		0	0		0	0		0	1	(0.2)	1
HYDROCELE VAGINALIS	0		0	0		0	0		0	1	(0.2)	1
PAIN FINGER	0		0	0		0	0		0	1	(0.2)	1
PERIARTICULITIS	0		0	0		0	0		0	1	(0.2)	2
STIFFNESS SHOULDER	0		0	0		0	0		0	1	(0.2)	1
TENDOVAGINITIS	0		0	0		0	0		0	1	(0.2)	1
WEAKNESS KNEE	0		0	0		0	0		0	1	(0.2)	1
FASCIITIS	0		0	1	(0.5)	1	3	(0.5)	5	0		0
STIFFNESS EXTREMITIES	2	(0.3)	2	0		0	2	(0.3)	2	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IBB\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14349, EM14361, EM14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
TENDON RUPTURE	0		0	1	(0.5)	1	1	(0.2)	1	0		0
CHONDROMALACIA	1	(0.2)	1	0		0	1	(0.2)	1	0		0
STIFFNESS	1	(0.2)	1	0		0	1	(0.2)	1	0		0
DEFORMITY TOES	0		0	0		0	1	(0.2)	1	0		0
LEG DISCOMFORT	0		0	0		0	1	(0.2)	1	0		0
OSTEOCHONDROPATHY	0		0	0		0	1	(0.2)	1	0		0
OSTEOCHONDROSIS	0		0	0		0	1	(0.2)	1	0		0
OSTEODYSTROPHIA	0		0	0		0	1	(0.2)	1	0		0
POLYMYALGIA RHEUMATICA	0		0	0		0	1	(0.2)	1	0		0
FRACTURE PATHOLOGICAL	0		0	1	(0.5)	1	0		0	0		0
JOINT STIFFNESS	0		0	1	(0.5)	1	0		0	0		0
TEAR OF MENISCUS	0		0	1	(0.5)	1	0		0	0		0
MYOSITIS	2	(0.3)	3	0		0	0		0	0		0
TENDON DISORDER	2	(0.3)	2	0		0	0		0	0		0
BURSITIS OLECRANON	1	(0.2)	1	0		0	0		0	0		0
HALLUX VALGUS	1	(0.2)	1	0		0	0		0	0		0
LIGAMENT DISORDER	1	(0.2)	2	0		0	0		0	0		0
MUSCLE DISORDER	1	(0.2)	1	0		0	0		0	0		0
PAIN STERNUM	1	(0.2)	1	0		0	0		0	0		0
CENTRAL & PERIPH. NERVOUS SYST. DISORD.	190	(30.0)	367	66	(39.8)	131	204	(32.7)	446	217	(34.3)	465
HEADACHE	137	(21.6)	265	50	(26.9)	97	142	(22.8)	327	157	(25.4)	358
DIZZINESS	19	(3.0)	21	9	(4.9)	9	20	(3.2)	24	32	(5.1)	36

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14349, EM14361, EM14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
MIGRAINE	21	(3.3)	40	10	(6.4)	19	21	(3.4)	38	15	(2.4)	22
PARESTHESIA	1	(0.2)	1	0		0	9	(1.4)	12	8	(1.3)	8
VERTIGO	12	(1.9)	14	0		0	14	(2.2)	16	7	(1.1)	8
NEURALGIA SCIATIC	7	(1.1)	7	1	(0.5)	1	6	(1.0)	6	4	(0.6)	4
CARPAL TUNNEL SYNDROME	4	(0.6)	4	0		0	4	(0.6)	4	4	(0.6)	4
GANGLION	0		0	2	(1.1)	2	2	(0.3)	2	6	(0.9)	8
APPETITE LOST	1	(0.2)	1	0		0	3	(0.5)	3	2	(0.3)	2
PTOSIS	0		0	0		0	0		0	2	(0.3)	2
PAIN PARAVERTEBRAL	1	(0.2)	1	0		0	1	(0.2)	1	1	(0.2)	1
PARESTHESIA FOOT	0		0	0		0	1	(0.2)	1	1	(0.2)	1
RADICULITIS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
SPASMS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
TWITCHING	0		0	0		0	1	(0.2)	1	1	(0.2)	1
HYPERTONIA	1	(0.2)	1	1	(0.5)	1	0		0	1	(0.2)	1
NEURALGIA	1	(0.2)	1	0		0	0		0	1	(0.2)	1
TRIGEMINAL NEURALGIA	1	(0.2)	1	0		0	0		0	1	(0.2)	1
APPETITE EXAGGERATED	0		0	0		0	0		0	1	(0.2)	1
BURNING EXTREMITIES	0		0	0		0	0		0	1	(0.2)	1
CONFUSION	0		0	0		0	0		0	1	(0.2)	1
EPILEPSY	0		0	0		0	0		0	1	(0.2)	1
HEAD FULLNESS	0		0	0		0	0		0	1	(0.2)	1
HEADACHE FRONTAL	0		0	0		0	0		0	1	(0.2)	1
NEUROMA	0		0	0		0	0		0	1	(0.2)	1

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14849, BM14861, BM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
PARALYSIS FACIAL PERIPHERAL	0		0	0		0	0		0	1	(0.2)	1
PARESTHESIA FINGERS	0		0	0		0	0		0	1	(0.2)	1
PERIPHERAL COLDNESS	0		0	0		0	0		0	1	(0.2)	1
CRANIAL INJURY NOS	0		0	0		0	3	(0.5)	3	0		0
NUMBNESS FINGERS	0		0	0		0	2	(0.3)	2	0		0
NUMBNESS HAND	0		0	0		0	2	(0.3)	2	0		0
PAIN FACIAL	0		0	1	(0.5)	1	1	(0.2)	1	0		0
PARESTHESIA DISTAL	1	(0.2)	1	0		0	1	(0.2)	1	0		0
PRE-SYNCOPE	1	(0.2)	1	0		0	1	(0.2)	1	0		0
RESTLESS LEGS	1	(0.2)	1	0		0	1	(0.2)	2	0		0
BURNING LEGS	0		0	0		0	1	(0.2)	1	0		0
LIGHT HEADED FEELING	0		0	0		0	1	(0.2)	1	0		0
NUMBNESS EXTREMITIES	0		0	0		0	1	(0.2)	1	0		0
TREMOR HAND	0		0	0		0	1	(0.2)	1	0		0
HYPOESTHESIA	0		0	1	(0.5)	1	0		0	0		0
HYPOREFLEXIA	1	(0.2)	1	0		0	0		0	0		0
NEUROPATHY SENSORY	1	(0.2)	1	0		0	0		0	0		0
NUMBNESS TOES	1	(0.2)	1	0		0	0		0	0		0
PAIN FACIOCRANIAL	1	(0.2)	1	0		0	0		0	0		0
POLYNEUROPATHY	1	(0.2)	1	0		0	0		0	0		0
PRICKLY SENSATION	1	(0.2)	1	0		0	0		0	0		0
TREMOR	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14849, BM14861, BM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
SKIN AND APPENDAGES DISORDERS	119	(18.8)	166	39	(21.0)	49	114	(18.3)	170	122	(19.3)	161
RASH	24	(3.5)	25	12	(6.5)	14	18	(2.9)	25	21	(3.3)	21
XERODERMA	6	(0.9)	6	3	(1.6)	3	5	(1.0)	6	18	(2.1)	15
ECZEMA	5	(0.9)	6	0		0	9	(1.4)	9	12	(1.9)	13
INSECT BITES	7	(1.1)	7	0		0	7	(1.1)	7	11	(1.7)	11
PRURITUS	2	(0.5)	3	1	(0.5)	1	5	(1.0)	5	7	(1.1)	7
URTICARIA	8	(1.8)	10	0		0	6	(1.0)	6	7	(1.1)	7
ACNE NOS	15	(2.4)	15	6	(3.2)	6	9	(1.4)	11	6	(0.9)	6
ALOPECIA	11	(1.7)	11	3	(1.6)	3	5	(0.8)	5	5	(0.8)	5
ERYTHEMA	0		0	1	(0.5)	1	1	(0.2)	1	5	(0.8)	5
DERMATITIS	9	(1.4)	9	1	(0.5)	1	7	(1.1)	7	4	(0.6)	4
CELLULITIS	2	(0.3)	3	0		0	4	(0.6)	4	4	(0.6)	4
DERMATITIS CONTACT	6	(0.9)	7	0		0	5	(0.8)	5	3	(0.5)	3
NAIL DISORDER	1	(0.2)	1	1	(0.5)	1	3	(0.5)	3	3	(0.5)	3
ONYCHOMYCOSIS	1	(0.2)	1	1	(0.5)	1	3	(0.5)	3	3	(0.5)	3
HAIR TEXTURE ABNORMAL	2	(0.3)	2	0		0	3	(0.5)	3	3	(0.5)	3
EDEMA LEGS	1	(0.2)	1	0		0	3	(0.5)	3	3	(0.5)	3
NAILS BRITTLE	2	(0.3)	2	0		0	4	(0.6)	4	2	(0.3)	2
SKIN BURNS	0		0	0		0	4	(0.6)	6	2	(0.3)	2
EDEMA JOINT	0		0	0		0	3	(0.5)	3	2	(0.3)	2
CYST SEBACEOUS	3	(0.5)	4	1	(0.5)	1	2	(0.3)	2	2	(0.3)	2
INFECTION SKIN	2	(0.3)	2	1	(0.5)	1	1	(0.2)	1	2	(0.3)	2
LIPOMA	2	(0.3)	2	0		0	1	(0.2)	1	2	(0.3)	2
TINEA PEDIS	0		0	0		0	1	(0.2)	1	2	(0.3)	2
SKIN DEFECTS SUPERFICIAL	1	(0.2)	1	0		0	0		0	2	(0.3)	2

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14149, BM14361, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
FURUNCULOSIS	0		0	0		0	0		0	2	(0.3)	2
NIPPLES TENDER	0		0	0		0	0		0	2	(0.3)	2
PRURITUS ANI	1	(0.2)	1	1	(0.5)	1	4	(0.6)	7	1	(0.2)	1
ANKLE EDEMA	4	(0.6)	5	0		0	3	(0.5)	5	1	(0.2)	1
TUMOR-LIKE SKIN CONDITION NOS	3	(0.5)	3	1	(0.5)	1	2	(0.3)	3	1	(0.2)	1
DERMATITIS FUNGAL	1	(0.2)	1	0		0	2	(0.3)	2	1	(0.2)	1
PSORIASIS	2	(0.3)	2	0		0	1	(0.2)	1	1	(0.2)	1
PUSTULAR REACTION	2	(0.3)	2	0		0	1	(0.2)	1	1	(0.2)	1
FOLLICULITIS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
HAIR CHANGES	0		0	0		0	1	(0.2)	1	1	(0.2)	1
SKIN DISORDER	1	(0.2)	1	1	(0.5)	1	0		0	1	(0.2)	1
VERRUCA	3	(0.5)	3	0		0	0		0	1	(0.2)	1
EDEMA PERIORBITAL	2	(0.3)	2	0		0	0		0	1	(0.2)	1
BURNING FEET	0		0	0		0	0		0	1	(0.2)	1
ECZEMA PRURITIC	0		0	0		0	0		0	1	(0.2)	1
EXANTHEMA PURPURIC	0		0	0		0	0		0	1	(0.2)	1
MYCOSIS MUCOSAL	0		0	0		0	0		0	1	(0.2)	1
PHOTOSENSITIVITY REACTION	0		0	0		0	0		0	1	(0.2)	1
ROSACEA	0		0	0		0	0		0	1	(0.2)	1
HYPERKERATOSIS	0		0	1	(0.5)	2	2	(0.3)	2	0		0
TUMOR SKIN	0		0	1	(0.5)	1	2	(0.3)	2	0		0
DERMATITIS SEBORRHEIC	1	(0.2)	1	0		0	2	(0.3)	2	0		0
RASH PRURITIC	1	(0.2)	1	0		0	2	(0.3)	2	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
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Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14149, BM14361, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
NEVUS	0		0	0		0	2	(0.3)	2	0		0
SKIN EXCORIATION	0		0	0		0	2	(0.3)	2	0		0
TINEA CORPORIS	0		0	0		0	2	(0.3)	2	0		0
BULLOUS REACTION	2	(0.3)	2	2	(1.1)	2	1	(0.2)	1	0		0
LIP DRYNESS	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	0		0
ALLERGY CONTACT	2	(0.3)	2	0		0	1	(0.2)	1	0		0
NAIL LOSS	1	(0.2)	1	0		0	1	(0.2)	1	0		0
PSORIASIFORM LESIONS	1	(0.2)	1	0		0	1	(0.2)	1	0		0
ACNE PUSTULAR	0		0	0		0	1	(0.2)	1	0		0
FACE EDEMA	0		0	0		0	1	(0.2)	1	0		0
IMPETIGO	0		0	0		0	1	(0.2)	1	0		0
OPEN WOUND OF UPPER LIMB	0		0	0		0	1	(0.2)	1	0		0
RASH IMPETIGINOUS	0		0	0		0	1	(0.2)	1	0		0
SEBORRHEA	0		0	0		0	1	(0.2)	1	0		0
SKIN NODULE	0		0	0		0	1	(0.2)	1	0		0
SWELLING KNEE	0		0	3	(1.6)	3	0		0	0		0
NEURODERMATITIS	0		0	2	(1.1)	2	0		0	0		0
NEVI PIGMENTED	0		0	1	(0.5)	1	0		0	0		0
PHOTOSENSITIVITY ALLERGIC REACT	0		0	1	(0.5)	1	0		0	0		0
DANDRUFF	1	(0.2)	1	0		0	0		0	0		0
HYPERTRICHOSIS	1	(0.2)	1	0		0	0		0	0		0
INTERTRIGO	1	(0.2)	2	0		0	0		0	0		0
NAILGROWTH INHIBITION	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EN14149, EN14161, EN14802

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
NAILS THICKENING	1	(0.2)	1	0		0	0		0	0		0
PAPULAR RASH	1	(0.2)	1	0		0	0		0	0		0
PITYRIASIS	1	(0.2)	1	0		0	0		0	0		0
RHAGADES	1	(0.2)	1	0		0	0		0	0		0
SKIN WRINKLED	1	(0.2)	1	0		0	0		0	0		0
ULCER LEG	1	(0.2)	2	0		0	0		0	0		0
BODY AS A WHOLE - GENERAL DISORDERS	105	(19.5)	175	40	(24.5)	59	128	(20.6)	188	131	(19.1)	261
SURGICAL PROCEDURE	30	(5.0)	35	12	(6.5)	15	27	(4.8)	30	27	(4.3)	29
ASTHENIA	21	(3.9)	26	2	(1.1)	2	27	(4.8)	32	20	(3.2)	23
INSOMNIA	21	(3.9)	26	3	(1.6)	3	15	(2.4)	23	20	(3.2)	21
FATIGUE	5	(0.6)	5	15	(8.1)	17	12	(1.9)	14	16	(2.8)	18
FEVER	8	(1.3)	8	2	(1.1)	2	15	(2.4)	16	12	(1.9)	12
EDEMA	17	(2.7)	19	5	(3.6)	9	14	(2.2)	16	5	(1.4)	10
PAIN POST TRAUMATIC	11	(1.7)	13	2	(1.1)	2	12	(1.9)	12	7	(1.1)	7
TRAUMA	12	(1.9)	12	1	(0.5)	1	9	(1.4)	9	6	(0.9)	6
ALLERGIC REACTION	9	(1.6)	6	2	(1.1)	2	7	(1.3)	7	5	(0.8)	5
NERVOUSNESS	1	(0.2)	2	4	(2.2)	5	5	(1.0)	6	5	(0.8)	5
WOUND	2	(0.3)	2	1	(0.5)	1	0		0	5	(0.8)	5
PAIN BODY	5	(0.9)	6	1	(0.5)	1	4	(0.6)	7	3	(0.5)	3
MALAISE	2	(0.3)	2	0		0	3	(0.5)	3	1	(0.2)	1
ANIMAL BITE	0		0	1	(0.5)	1	2	(0.3)	2	1	(0.2)	1
ABRASIONS	2	(0.3)	2	0		0	2	(0.3)	2	1	(0.2)	1

(Continued)

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Adverse Events in Year 1 of Treatment
Safety Population

Studies: EN14149, EN14161, EN14802

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
LETHARGY	1	(0.2)	1	0		0	2	(0.3)	2	1	(0.2)	1
PAIN	0		0	0		0	2	(0.3)	2	1	(0.2)	1
IRRITABILITY	1	(0.2)	1	0		0	1	(0.2)	1	1	(0.2)	1
WEAKNESS GENERALIZED	0		0	1	(0.5)	1	0		0	1	(0.2)	2
SHIVERING	2	(0.3)	2	0		0	0		0	1	(0.2)	1
FEELING TENSE	0		0	0		0	0		0	1	(0.2)	1
POSTMENOPAUSAL SYNDROME	0		0	0		0	0		0	1	(0.2)	1
SLEEP DISORDER	0		0	0		0	3	(0.6)	3	0		0
AGITATION	0		0	1	(0.5)	2	1	(0.2)	1	0		0
CHEST PRESSURE SENSATION	1	(0.2)	1	0		0	1	(0.2)	1	0		0
DYSTHYMIA	0		0	0		0	1	(0.2)	1	0		0
SOMNOLENCE	1	(0.2)	1	1	(0.5)	1	0		0	0		0
EARLY MORNING WAKENING	1	(0.3)	1	0		0	0		0	0		0
INJURY MULTIPLE	1	(0.3)	1	0		0	0		0	0		0
STAB WOUND	1	(0.2)	1	0		0	0		0	0		0
REPRODUCTIVE DISORDERS, FEMALE	69	(13.1)	120	28	(16.1)	40	76	(12.2)	109	102	(16.1)	148
DYSMENORRHEA	29	(4.4)	43	11	(6.9)	15	29	(4.6)	48	29	(4.6)	47
COLPITIS	15	(2.4)	17	6	(3.2)	7	12	(1.9)	16	22	(3.6)	27
MENSTRUAL IRREGULARITY	5	(0.8)	6	0		0	5	(0.8)	5	7	(1.1)	9
MENOPAUSAL SYNDROME	1	(0.2)	1	2	(1.1)	2	3	(0.6)	3	6	(0.9)	6
AMENORRHEA	0		0	3	(1.6)	3	3	(0.6)	4	4	(0.5)	4
VAGINAL ITCHING	4	(0.6)	4	0		0	3	(0.6)	3	4	(0.6)	4

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IBS\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14349, EM14361, EM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=523) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
BREAST PAIN FEMALE	3	(0.5)	5	3	(1.6)	3	2	(0.4)	2	4	(0.6)	4
MENORRHAGIA	8	(1.3)	11	0		0	2	(0.4)	2	4	(0.6)	4
MENSTRUAL DISORDER	0		0	0		0	2	(0.4)	2	4	(0.6)	4
VAGINAL HEMORRHAGE	3	(0.5)	3	0		0	1	(0.2)	1	4	(0.6)	4
VAGINAL DISCHARGE	0		0	0		0	0		0	4	(0.6)	4
INTERMENSTRUAL BLEEDING	1	(0.2)	1	0		0	3	(0.6)	3	3	(0.4)	3
VULVOVAGINITIS	3	(0.5)	3	0		0	1	(0.2)	1	3	(0.4)	3
NEOPLASM BREAST FEMALE	0		0	0		0	1	(0.2)	1	3	(0.4)	3
PERIMENOPAUSAL SYNDROME	5	(0.8)	5	2	(1.1)	2	0		0	3	(0.4)	3
VAGINAL WALL PROLAPSE	0		0	1	(0.5)	1	0		0	3	(0.4)	3
VAGINAL DISORDER	0		0	1	(0.5)	1	1	(0.2)	1	2	(0.3)	2
CYST BREAST	3	(0.5)	3	0		0	2	(0.4)	2	1	(0.2)	1
UTERINE HEMORRHAGE	2	(0.3)	2	0		0	2	(0.4)	3	1	(0.2)	1
TUMOR UTERUS	0		0	0		0	2	(0.4)	2	1	(0.2)	1
CERVICITIS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
SPOTTING VAGINAL	0		0	0		0	1	(0.2)	1	1	(0.2)	1
VAGINAL PROLAPSE	0		0	0		0	1	(0.2)	1	1	(0.2)	1
TUMOR BREAST	2	(0.3)	2	0		0	0		0	1	(0.2)	1
HYPOMENORRHEA	0		0	0		0	0		0	1	(0.2)	1
MASTOPATHY	0		0	0		0	0		0	1	(0.2)	1
OVARIAN DISORDER	0		0	0		0	0		0	1	(0.2)	1
SPOTTING BETWEEN MENSES	0		0	0		0	0		0	1	(0.2)	1
ULCER VAGINAL	0		0	0		0	0		0	1	(0.2)	1

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS2\Programming_final\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14349, EM14361, EM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=523) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
UTEROVAGINAL PROLAPSE	0		0	0		0	0		0	1	(0.2)	1
VAGINITIS ATROPHIC	0		0	0		0	0		0	1	(0.2)	1
CERVIX LESION	1	(0.2)	1	1	(0.5)	1	3	(0.6)	3	0		0
POLYMENORRHEA	0		0	0		0	2	(0.4)	2	0		0
ABORTION	1	(0.2)	1	0		0	1	(0.2)	1	0		0
FIBROADENOSIS BREAST	1	(0.2)	1	0		0	1	(0.2)	1	0		0
CARCINOMA CERVIX	0		0	0		0	1	(0.2)	1	0		0
CERVICAL DYSPLASIA	0		0	0		0	1	(0.2)	1	0		0
ENDOMETRIOSIS	0		0	0		0	1	(0.2)	1	0		0
OLIGOMENORRHEA	0		0	0		0	1	(0.2)	1	0		0
UTERINE INFLAMMATION	0		0	0		0	1	(0.2)	1	0		0
VAGINAL DRYNESS	2	(0.3)	2	1	(0.5)	1	0		0	0		0
ABORTION UNSPECIFIED	0		0	1	(0.5)	1	0		0	0		0
CERVICAL DISCHARGE	0		0	1	(0.5)	1	0		0	0		0
PERINEAL PAIN FEMALE	0		0	1	(0.5)	1	0		0	0		0
CYST OVARIAN BENIGN	2	(0.3)	2	0		0	0		0	0		0
ABORTION SPONTANEOUS	1	(0.2)	1	0		0	0		0	0		0
BREAST TENSION	1	(0.2)	1	0		0	0		0	0		0
GENITALIA SORE	1	(0.2)	2	0		0	0		0	0		0
MASTITIS	1	(0.2)	1	0		0	0		0	0		0
MENSES ONSET DELAYED	1	(0.2)	1	0		0	0		0	0		0
METRORRHAGIA	1	(0.2)	1	0		0	0		0	0		0
UTERINE PROLAPSE	1	(0.2)	1	0		0	0		0	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS2\Programming_final\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14349, BM14361, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
URINARY SYSTEM DISORDERS	67	(10.6)	95	26	(14.4)	30	68	(10.5)	86	72	(11.4)	99
URINARY TRACT INFECTION	48	(7.6)	64	16	(8.1)	17	49	(7.9)	60	47	(7.4)	60
CYSTITIS	5	(0.8)	5	0		0	2	(0.3)	2	10	(1.5)	10
DYSURIA	2	(0.3)	2	1	(0.5)	1	1	(0.2)	1	5	(0.9)	5
URINARY INCONTINENCE	3	(0.5)	3	1	(0.5)	1	5	(1.0)	6	4	(0.5)	5
MICTURITION FREQUENCY	4	(0.6)	4	2	(1.1)	2	7	(1.1)	7	3	(0.5)	3
BLADDER PROLAPSE	0		0	1	(0.5)	1	1	(0.2)	1	3	(0.5)	3
POLYURIA	3	(0.5)	3	2	(1.1)	2	2	(0.3)	2	2	(0.3)	2
RENAL CALCULUS	2	(0.3)	2	1	(0.5)	1	0		0	2	(0.3)	2
URINARY TRACT BLEEDING	0		0	2	(1.1)	2	3	(0.5)	3	1	(0.2)	1
PYELONEPHRITIS	4	(0.6)	5	0		0	1	(0.2)	1	1	(0.2)	1
URINARY RETENTION	0		0	1	(0.5)	1	0		0	1	(0.2)	1
RENAL COLIC	2	(0.3)	2	0		0	0		0	1	(0.2)	1
CYSTITIS HEMORRHAGIC	0		0	0		0	0		0	1	(0.2)	1
MOONFACE (CUSHING)	0		0	0		0	0		0	1	(0.2)	1
PYELITIS	0		0	0		0	0		0	1	(0.2)	1
URETERAL CALCULUS	0		0	0		0	0		0	1	(0.2)	1
URINE DISCOLORATION	0		0	0		0	0		0	1	(0.2)	1
URETHRITIS	0		0	1	(0.5)	1	1	(0.2)	1	0		0
OLIGURIA	0		0	0		0	1	(0.2)	1	0		0
URINE UNPLEASANT SMELL	0		0	1	(0.5)	1	0		0	0		0
BACTERIURIA	1	(0.2)	1	0		0	0		0	0		0
BLADDER DYSFUNCTION	1	(0.2)	2	0		0	0		0	0		0
EDEMA ORBITAL	1	(0.2)	1	0		0	0		0	0		0
UROGENITAL PROLAPSE	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IBB\Programming_rfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14349, BM14361, BM14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
PSYCHIATRIC DISORDERS	49	(6.8)	58	14	(7.5)	15	48	(7.7)	56	56	(8.7)	65
ANXIETY	10	(1.6)	13	3	(1.6)	3	24	(3.9)	27	28	(4.4)	32
DEPRESSION	33	(5.2)	38	10	(5.4)	11	20	(3.2)	24	24	(3.8)	27
SUICIDE ATTEMPT	0		0	1	(0.5)	1	0		0	1	(0.2)	1
LIBIDO DECREASED	1	(0.2)	1	0		0	0		0	1	(0.2)	1
PSYCHIC DISORDER	1	(0.2)	3	0		0	0		0	1	(0.2)	2
ANXIETY STATE	0		0	0		0	0		0	1	(0.2)	1
CRAVING FOR MILK	0		0	0		0	0		0	1	(0.2)	1
HUNGER ABNORMAL	0		0	1	(0.5)	1	1	(0.2)	1	0		0
ANXIETY ATTACK	1	(0.2)	1	0		0	1	(0.2)	1	0		0
EMOTIONAL LABILITY	1	(0.2)	1	0		0	1	(0.2)	1	0		0
FORGETFULNESS	0		0	0		0	1	(0.2)	1	0		0
MEMORY DISTURBANCE	0		0	0		0	1	(0.2)	1	0		0
ANXIETY NEUROSIS	1	(0.2)	1	0		0	0		0	0		0
HEARING AND VESTIBULAR DISORDERS	27	(4.8)	32	12	(6.5)	13	25	(4.0)	29	38	(5.2)	41
EARACHE	9	(1.8)	10	3	(1.6)	3	4	(0.6)	4	10	(1.6)	11
OTITIS	8	(1.3)	8	6	(3.2)	6	10	(1.6)	10	7	(1.1)	8
OTITIS MEDIA	3	(0.5)	3	0		0	2	(0.3)	4	6	(0.9)	6
OTITIS EXTERNA	3	(0.5)	3	0		0	1	(0.2)	1	4	(0.6)	4
EAR BUZZING	4	(0.6)	4	1	(0.5)	1	3	(0.5)	3	2	(0.3)	5
HEARING DECREASED	0		0	0		0	1	(0.2)	1	2	(0.3)	2
LABYRINTHINE DISORDER	0		0	0		0	0		0	2	(0.3)	2
ATAXIA VESTIBULAR	0		0	0		0	0		0	1	(0.2)	1
DEAFNESS	0		0	0		0	0		0	1	(0.2)	1

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IBB\Programming_rfinal\t_ae.sas
Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14849, BM14861, BM14862

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=623) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
MOTION SICKNESS	0		0	2	(1.1)	3	4	(0.6)	4	0		0
FULLNESS EARS	3	(0.5)	3	0		0	1	(0.2)	1	0		0
OTOSALPINGITIS	0		0	0		0	1	(0.2)	1	0		0
AURICULAR OR VESTIBULAR DISORDERS	1	(0.2)	1	0		0	0		0	0		0
CARDIOVASCULAR DISORDERS	29	(4.6)	34	12	(6.5)	14	32	(5.1)	84	31	(4.9)	39
CHEST PAIN	14	(2.2)	16	5	(2.7)	5	10	(1.6)	10	16	(2.8)	19
HYPERTENSION	7	(1.1)	8	2	(1.1)	2	17	(2.7)	17	6	(0.9)	6
EDEMA FOOT	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	2	(0.3)	2
CHEST CONGESTION	2	(0.3)	2	0		0	0		0	2	(0.3)	3
EDEMA OF EXTREMITIES	4	(0.6)	4	3	(1.6)	3	1	(0.2)	1	1	(0.2)	1
CONGESTION	2	(0.3)	2	1	(0.5)	2	0		0	1	(0.2)	1
CARDIAC FAILURE	0		0	0		0	2	(0.3)	2	0		0
CHEST DISCOMFORT	2	(0.3)	2	0		0	1	(0.2)	1	0		0
ECG ABNORMAL	0		0	0		0	1	(0.2)	1	0		0
HEART MURMUR	0		0	0		0	1	(0.2)	1	0		0
HYPOTENSION	0		0	1	(0.5)	1	0		0	0		0
AUTONOMIC NERVOUS SYSTEM DISORDER	9	(1.4)	13	9	(4.9)	9	14	(2.2)	16	21	(3.3)	24
HOT FLUSHES	5	(0.9)	6	4	(2.2)	4	6	(1.0)	6	7	(1.1)	7
SYNCOPE	1	(0.2)	1	2	(1.1)	2	1	(0.2)	1	5	(0.8)	5
SWEATING INCREASED	1	(0.2)	1	2	(1.1)	2	2	(0.3)	2	4	(0.6)	4
FLUSHING	0		0	0		0	2	(0.3)	5	3	(0.5)	5

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS8\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14849, BM14861, BM14862

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=623) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
NIGHT SWEATS	1	(0.2)	1	0		0	0		0	2	(0.3)	2
MYDRIASIS	1	(0.2)	1	0		0	0		0	1	(0.2)	1
ALGONEURODYSTROPHY	0		0	0		0	1	(0.2)	1	0		0
EJACULATION CHANGES	0		0	0		0	1	(0.2)	1	0		0
VASOVAGAL ATTACK	0		0	0		0	1	(0.2)	1	0		0
VASOSPASM	0		0	1	(0.5)	1	0		0	0		0
TEAR SECRETION INCREASED	1	(0.2)	1	0		0	0		0	0		0
VISION DISORDERS	20	(3.2)	20	7	(3.8)	7	17	(2.7)	19	20	(3.2)	24
CONJUNCTIVITIS	9	(1.4)	9	3	(1.6)	3	6	(1.0)	6	9	(1.4)	10
VISION BLURRED	0		0	1	(0.5)	1	1	(0.2)	1	2	(0.3)	2
XEROPHTHALMIA	0		0	0		0	1	(0.2)	1	2	(0.3)	3
VISUAL DISTURBANCE	2	(0.3)	2	0		0	3	(0.5)	4	1	(0.2)	1
EYE IRRITATION	1	(0.2)	1	1	(0.5)	1	2	(0.3)	2	1	(0.2)	1
EYE PAIN	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
STYES	1	(0.2)	1	0		0	0		0	1	(0.2)	1
ANGIOMATOSIS RETINA	0		0	0		0	0		0	1	(0.2)	1
BLEEDING SUBCONJUNCTIVAL	0		0	0		0	0		0	1	(0.2)	1
EYE TWITCHING	0		0	0		0	0		0	1	(0.2)	1
IRIDOCYCLITIS	0		0	0		0	0		0	1	(0.2)	1
SCOTOMA FLITTERING	0		0	0		0	0		0	1	(0.2)	1
PRESBYOPIA	0		0	0		0	2	(0.3)	2	0		0
COLOBOMA CHOROID	0		0	0		0	1	(0.2)	1	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS8\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: 8M14849, NN14861, NN14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
CORNEAL ABRASION	0		0	0		0	1	(0.2)	1	0		0
DIPLOPIA	0		0	1	(0.5)	1	0		0	0		0
CATARACT	2	(0.3)	2	0		0	0		0	0		0
BLEPHARITIS	1	(0.2)	1	0		0	0		0	0		0
CONJUNCTIVAL HEMORRHAGE	1	(0.2)	1	0		0	0		0	0		0
EYE INFLAMED	1	(0.2)	1	0		0	0		0	0		0
RETINOPATHY	1	(0.2)	1	0		0	0		0	0		0
METABOLIC AND NUTRITIONAL DISORDERS	19	(3.0)	19	12	(6.5)	12	19	(3.0)	19	18	(2.6)	19
APPETITE INCREASED	8	(1.3)	8	4	(2.2)	4	6	(1.0)	6	5	(0.7)	5
THIRST	2	(0.3)	2	3	(1.6)	3	2	(0.3)	2	2	(0.3)	2
APPETITE DECREASED	2	(0.3)	2	2	(1.1)	2	2	(0.3)	2	2	(0.3)	2
HYPOGLYCEMIA	1	(0.2)	1	0		0	1	(0.2)	1	2	(0.3)	2
GOUT	2	(0.3)	2	0		0	0		0	2	(0.3)	2
HYPERURICEMIA	0		0	0		0	1	(0.2)	1	1	(0.2)	1
DEHYDRATION	2	(0.3)	2	1	(0.5)	1	0		0	1	(0.2)	1
DIABETES MELLITUS	1	(0.2)	1	0		0	0		0	1	(0.2)	1
EDEMA PERIPHERAL	0		0	0		0	0		0	1	(0.2)	2
HYPERCHOLESTEROLEMIA	0		0	0		0	0		0	1	(0.2)	1
HYPOKALEMIA	0		0	1	(0.5)	1	2	(0.3)	2	0		0
HYPERLIPEMIA	0		0	0		0	2	(0.3)	2	0		0
CALCIUM DEFICIENCY BONE	0		0	1	(0.5)	1	1	(0.2)	1	0		0
GLUCOSE TOLERANCE REDUCED	0		0	0		0	1	(0.2)	1	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS8\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: 8M14849, NN14861, NN14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
XANTHOMA	0		0	0		0	1	(0.2)	1	0		0
HEART RATE AND RHYTHM	8	(1.3)	9	5	(2.7)	5	10	(1.6)	10	15	(2.1)	15
PALPITATION	5	(0.8)	6	5	(2.7)	5	7	(1.1)	8	11	(1.7)	10
ARRHYTHMIA	0		0	0		0	2	(0.3)	2	1	(0.2)	1
FIBRILLATION ATRIAL	0		0	0		0	1	(0.2)	1	1	(0.2)	1
TACHYCARDIA	3	(0.5)	3	0		0	0		0	1	(0.2)	1
PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	0		0	0		0	1	(0.2)	1	0		0
PLATELET, BLEEDING & CLOTTING DISORDERS	5	(0.8)	5	0		0	10	(1.6)	11	10	(1.5)	10
BLEEDING DERMAL	5	(0.8)	5	0		0	8	(1.3)	9	7	(1.1)	7
BRUISING ABNORMAL	0		0	0		0	2	(0.3)	2	3	(0.5)	3
LIVER AND BILIARY SYSTEM DISORDERS	7	(1.1)	12	4	(2.2)	4	8	(1.3)	8	8	(1.3)	9
CHOLELITHIASIS	1	(0.2)	1	2	(1.1)	2	3	(0.5)	3	5	(0.8)	5
CHOLECYSTITIS	5	(0.8)	10	0		0	4	(0.6)	4	3	(0.5)	3
BILIARY COLIC	1	(0.2)	1	0		0	1	(0.2)	1	0		0
HEPATITIS	0		0	2	(1.1)	2	0		0	0		0
VASCULAR (EXTRACARDIAC) DISORDERS	8	(1.3)	9	2	(1.1)	2	5	(0.8)	5	8	(1.3)	9
VARICOSE VEINS	2	(0.3)	2	1	(0.5)	1	1	(0.2)	1	5	(0.8)	5
PHLEBITIS	4	(0.6)	5	0		0	0		0	2	(0.3)	2
NECROSIS VASCULAR	0		0	0		0	0		0	1	(0.2)	1

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS8\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14149, NN14161, NN14302

Body System/ Preferred Term	Placebo (N=634) n (%)	Placebo (N=634) NAE	Orlistat 30 mg tid (N=185) n (%)	Orlistat 30 mg tid (N=185) NAE	Orlistat 60 mg tid (N=522) n (%)	Orlistat 60 mg tid (N=522) NAE	Orlistat 120 mg tid (N=682) n (%)	Orlistat 120 mg tid (N=682) NAE
(...Body System Continues)								
VENOUS THROMBOSIS	0	0	0	0	0	0	1 (0.2)	1
CEREBRAL ISCHEMIA	0	0	0	0	2 (0.4)	2	0	0
EMBOLISM - BLOOD CLOT	0	0	0	0	1 (0.2)	1	0	0
STROKE	0	0	0	0	1 (0.2)	1	0	0
ARTERIAL DISORDERS	0	0	1 (0.5)	1	0	0	0	0
HEMANGIOMA	1 (0.2)	1	0	0	0	0	0	0
THROMBOPHLEBITIS	1 (0.2)	1	0	0	0	0	0	0
ENDOCRINE DISORDERS	8 (1.6)	8	3 (1.5)	3	5 (0.8)	5	4 (0.5)	5
HYPOTHYROIDISM	2 (0.3)	2	2 (1.1)	2	1 (0.2)	1	2 (0.3)	2
THYROIDITIS	0	0	0	0	1 (0.2)	1	2 (0.3)	2
TUMOR THYROID	0	0	0	0	1 (0.2)	1	1 (0.2)	1
GENITAL DISORDER	1 (0.2)	1	0	0	1 (0.2)	1	0	0
THYROTOXICOSIS	0	0	0	0	1 (0.2)	1	0	0
GOITER	2 (0.3)	2	1 (0.5)	1	0	0	0	0
TSH INCREASE	2 (0.3)	2	0	0	0	0	0	0
HYPERTHYROIDISM	1 (0.2)	1	0	0	0	0	0	0
REPRODUCTIVE DISORDERS, MALE	2 (0.3)	2	0	0	4 (0.8)	5	3 (0.5)	4
PROSTATITIS	1 (0.2)	1	0	0	2 (0.3)	4	2 (0.3)	3
TESTIS PAINFUL	0	0	0	0	0	0	1 (0.2)	1
PROSTATE ENLARGED	1 (0.2)	1	0	0	2 (0.3)	2	0	0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS8\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: BM14149, NN14161, NN14302

Body System/ Preferred Term	Placebo (N=634) n (%)	Placebo (N=634) NAE	Orlistat 30 mg tid (N=185) n (%)	Orlistat 30 mg tid (N=185) NAE	Orlistat 60 mg tid (N=528) n (%)	Orlistat 60 mg tid (N=528) NAE	Orlistat 120 mg tid (N=682) n (%)	Orlistat 120 mg tid (N=682) NAE
MYO-, ENDO-, PERICARDIAL & VALVE DISORD.	3 (0.5)	3	1 (0.5)	1	3 (0.6)	3	3 (0.5)	3
ANGINA PECTORIS	2 (0.3)	2	0	0	2 (0.5)	2	1 (0.2)	1
CORONARY INFARCTION	0	0	0	0	0	0	1 (0.2)	1
MALF. OF PROSTHESES AND HOMOGRAPHS	0	0	0	0	0	0	1 (0.2)	1
PERIMYOCARDITIS	0	0	0	0	1 (0.2)	1	0	0
CARDIOMYOPATHY HYPERTROPHIC CONG	0	0	1 (0.5)	1	0	0	0	0
MITRAL VALVE ABNORMALITY	1 (0.2)	1	0	0	0	0	0	0
RED BLOOD CELL DISORDERS	5 (0.8)	5	2 (1.1)	3	4 (0.6)	5	2 (0.3)	2
ANEMIA	3 (0.5)	3	2 (1.1)	3	3 (0.6)	4	1 (0.2)	1
ANEMIA IRON DEFICIENCY	0	0	0	0	0	0	1 (0.2)	1
ANEMIA MACROCYTIC	0	0	0	0	1 (0.2)	1	0	0
SERUM IRON REDUCED	2 (0.3)	2	0	0	0	0	0	0
NEOPLASM	1 (0.2)	1	0	0	1 (0.2)	1	2 (0.3)	2
TUMOR	1 (0.2)	1	0	0	1 (0.2)	1	1 (0.2)	1
MYOMA	0	0	0	0	0	0	1 (0.2)	1
SPECIAL SENSES OTHER, DISORDERS	5 (0.8)	5	0	0	1 (0.2)	1	1 (0.2)	1
TASTE UNPLEASANT	0	0	0	0	1 (0.2)	1	1 (0.2)	1
TASTE METALLIC	3 (0.5)	3	0	0	0	0	0	0
TASTE BITTER	1 (0.2)	1	0	0	0	0	0	0
TASTE SALTY	1 (0.2)	1	0	0	0	0	0	0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\IS8\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14149, NM14161, NM14202

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
APPLICATION SITE DISORDERS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
WOUND HEALING IMPAIRED WITHOUT INFECTION	0		0	0		0	1	(0.2)	1	1	(0.2)	1
WHITE CELL AND RES DISORDERS	4	(0.8)	4	4	(2.2)	4	4	(0.8)	4	0		0
LYMPH NODES ENLARGED	3	(0.6)	3	0		0	2	(0.4)	2	0		0
GLANDS SWOLLEN	0		0	2	(1.1)	2	1	(0.2)	1	0		0
SWELLING LYMPHNODES	0		0	0		0	1	(0.2)	1	0		0
LYMPHADENOPATHY CERVICAL	1	(0.2)	1	1	(0.5)	1	0		0	0		0
LYMPHADENOPATHY	0		0	1	(0.5)	1	0		0	0		0
COLLAGEN DISORDERS	0		0	0		0	1	(0.2)	1	0		0
ARTHRITIS RHEUMATOID	0		0	0		0	1	(0.2)	1	0		0
NEOPLASM, URINARY SYSTEM	0		0	1	(0.5)	1	0		0	0		0
CARCINOMA RENAL	0		0	1	(0.5)	1	0		0	0		0
HEMIB AND LYMPHATIC DISORDERS	1	(0.2)	1	0		0	0		0	0		0
LYMPHEDEMA	1	(0.2)	1	0		0	0		0	0		0
NEOPLASM, RESPIRATORY SYSTEM	1	(0.2)	1	0		0	0		0	0		0
NEOPLASM PHARYNX MALIGNANT	1	(0.2)	1	0		0	0		0	0		0

(Last Page)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\182\Programming_tfinal\t_ae.sas Source: ae.xpt, profile.xpt

10.3.5 All Adverse Events; Study NM17247

ae11 Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NM17247
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	106 (54)	137 (70)
Total Number of AEs	221	354
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	64 (33)	112 (57)
FATTY/OILY STOOL	5 (3)	44 (22)
FECAL URGENCY	11 (6)	33 (17)
FLATULENCE	21 (11)	13 (7)
INCREASED DEFECATION	7 (4)	17 (9)
DECREASED DEFECATION	14 (7)	9 (5)
OILY SPOTTING	-	22 (11)
FLATUS WITH DISCHARGE	3 (2)	18 (9)
STOOLS SOFT	7 (4)	11 (6)
ABDOMINAL DISTENSION	11 (6)	3 (2)
ABDOMINAL PAIN NOS	6 (3)	8 (4)
ABDOMINAL PAIN UPPER	6 (3)	6 (3)
NAUSEA	7 (4)	5 (3)
LIQUID STOOLS	6 (3)	5 (3)
OILY EVACUATION	1 (<1)	6 (3)
DYSPEPSIA	-	6 (3)
FECAL INCONTINENCE	-	6 (3)
VOMITING NOS	3 (2)	3 (2)
SORE THROAT NOS	2 (1)	3 (2)
GASTRO-OESOPHAGEAL REFLUX DISEASE	2 (1)	2 (1)
ABDOMINAL PAIN LOWER	1 (<1)	2 (1)
FAECES HARD	-	3 (2)
HAEMORRHOIDS	-	2 (1)
OESOPHAGEAL REFLUX	1 (<1)	1 (<1)
BOWEL SOUNDS ABNORMAL	1 (<1)	-
DEFECATION FREQUENCY INCREASED	-	1 (<1)
FAECES DISCOLOURED	-	1 (<1)
GUM PAIN	1 (<1)	-
HAEMATEMESIS	1 (<1)	-
STOMATITIS	-	1 (<1)
STOOLS WATERY	-	1 (<1)

(body system continuing ...)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.

ae11 Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NM17247
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
(... body system continuing)		
UMBILICAL HERNIA NOS	-	1 (<1)
Total Number of AEs	117	233
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	28 (14)	42 (21)
UPPER RESPIRATORY TRACT INFECTION NOS	5 (3)	11 (6)
NASOPHARYNGITIS	5 (3)	6 (3)
SINUSITIS NOS	3 (2)	8 (4)
BRONCHITIS NOS	1 (<1)	5 (3)
HERPES SIMPLEX	3 (2)	2 (1)
URINARY TRACT INFECTION NOS	4 (2)	1 (<1)
GASTROENTERITIS VIRAL NOS	4 (2)	-
INFLUENZA	3 (2)	-
EAR INFECTION NOS	1 (<1)	1 (<1)
PHARYNGITIS NOS	1 (<1)	1 (<1)
TOOTH ABSCESS	-	2 (1)
VIRAL INFECTION NOS	1 (<1)	1 (<1)
CROUP INFECTIOUS	-	1 (<1)
FUNGAL INFECTION NOS	-	1 (<1)
GASTROENTERITIS NOS	-	1 (<1)
KIDNEY INFECTION NOS	-	1 (<1)
MASTOIDITIS NOS	-	1 (<1)
ORAL INFECTION NEC	-	1 (<1)
OTITIS MEDIA NOS	-	1 (<1)
PHARYNGITIS STREPTOCOCCAL	-	1 (<1)
SKIN PAPILLOMA	-	1 (<1)
UPPER RESPIRATORY TRACT INFECTION VIRAL NOS	-	1 (<1)
VAGINAL CANDIDIASIS	1 (<1)	-
VAGINITIS BACTERIAL NOS	-	1 (<1)
Total Number of AEs	32	49

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01DEC2003:14:58:21 (2 of 7)

ae11 Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NM17247
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	16 (8)	14 (7)
HEADACHE NOS	5 (3)	9 (5)
DIZZINESS (EXC VERTIGO)	2 (1)	4 (2)
MIGRAINE NOS	5 (3)	1 (<1)
SINUS HEADACHE	1 (<1)	2 (1)
TASTE DISTURBANCE	2 (1)	-
CARPAL TUNNEL SYNDROME	1 (<1)	-
DIZZINESS POSTURAL	1 (<1)	-
INSOMNIA NEC	1 (<1)	-
PARAESTHESIA NEC	1 (<1)	-
Total Number of AEs	19	16
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS		
Total Pts With at Least one AE	12 (6)	14 (7)
MYALGIA	3 (2)	5 (3)
BACK PAIN	2 (1)	2 (1)
ARTHRALGIA	1 (<1)	2 (1)
TENDONITIS	2 (1)	1 (<1)
INTERVERTEBRAL DISC PROLAPSE	-	2 (1)
MUSCLE CRAMPS	1 (<1)	1 (<1)
ARTHRITIS NOS AGGRAVATED	1 (<1)	-
MUSCLE SPASMS	-	1 (<1)
PAIN IN LIMB	1 (<1)	-
PLANTAR FASCIITIS	1 (<1)	-
Total Number of AEs	12	14
SKIN & SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	9 (5)	5 (3)
DERMATITIS NOS	4 (2)	2 (1)
ECCHYMOSIS	2 (1)	2 (1)
DERMATITIS CONTACT	1 (<1)	-
INGROWING NAIL	1 (<1)	-
ROSACEA	1 (<1)	-
URTICARIA NOS	-	1 (<1)
Total Number of AEs	9	5

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01DEC2003:14:58:21 (3 of 7)

aell Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NN17247
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	7 (4)	6 (3)
SINUS CONGESTION	2 (1)	2 (1)
COUGH	3 (2)	-
ASTHMA AGGRAVATED	-	2 (1)
ASTHMA NOS	1 (<1)	-
NASAL CONGESTION	1 (<1)	-
POSTNASAL DRIP	-	1 (<1)
PULMONARY CONGESTION	1 (<1)	-
RHINORRHOEA	-	1 (<1)
Total Number of AEs	8	6
INJURY AND POISONING		
Total Pts With at Least one AE	3 (2)	8 (4)
ARTHROPOD BITE	-	2 (1)
JOINT SPRAIN	1 (<1)	1 (<1)
ABRASION NOS	-	1 (<1)
ANIMAL BITE	1 (<1)	-
LACERATION	-	1 (<1)
LIGAMENT SPRAIN	1 (<1)	-
MUSCLE INJURY NOS	-	1 (<1)
MUSCLE SPRAIN	-	1 (<1)
PERIORBITAL HAEMATOMA	-	1 (<1)
Total Number of AEs	3	8
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	5 (3)	3 (2)
ANXIETY NEC	4 (2)	-
BIPOLAR DISORDER NEC	-	1 (<1)
BRUXISM	-	1 (<1)
DEPRESSION AGGRAVATED	-	1 (<1)
DEPRESSION NEC	-	1 (<1)
MOOD SWINGS	1 (<1)	-
Total Number of AEs	5	4

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01DEC2003:14:58:21 (4 of 7)

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ae11 Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NN17247
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	4 (2)	3 (2)
CHEST PAIN NEC	1 (<1)	-
INFLAMMATION LOCALISED	-	1 (<1)
INFLUENZA LIKE ILLNESS	1 (<1)	-
LETHARGY	1 (<1)	-
PAIN NOS	-	1 (<1)
PAIN TRAUMA ACTIVATED	-	1 (<1)
WEAKNESS	1 (<1)	-
Total Number of AEs	4	3
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Total Pts With at Least one AE	2 (1)	5 (3)
DYSMENORRHOEA	1 (<1)	2 (1)
BARTHOLIN'S CYST	-	1 (<1)
BREAST PAIN	-	1 (<1)
CERVICAL DYSPLASIA	1 (<1)	-
MENORRHAGIA	-	1 (<1)
Total Number of AEs	2	5
EYE DISORDERS		
Total Pts With at Least one AE	3 (2)	2 (1)
CATARACT UNILATERAL	1 (<1)	-
CONJUNCTIVITIS NEC	1 (<1)	-
EYE PAIN	1 (<1)	-
PHOTOPHOBIA	1 (<1)	-
RED EYE	-	1 (<1)
VITREOUS FLOATERS	-	1 (<1)
Total Number of AEs	4	2
CARDIAC DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
OEDEMA LOWER LIMB	1 (<1)	1 (<1)
Total Number of AEs	1	1

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01DEC2003:14:58:21 (5 of 7)

Appears This Way
On Original

aell Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NM17247
Analysis: SAFETY Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
DEHYDRATION	-	1 (<1)
HYPERTRIGLYCERIDAEMIA	1 (<1)	-
Total Number of AEs	1	1
NEOPLASMS BENIGN AND MALIGNANT (INCLUDING CYSTS AND POLYPS)		
Total Pts With at Least one AE	-	2 (1)
CYST NOS	-	1 (<1)
SQUAMOUS CELL CARCINOMA	-	1 (<1)
Total Number of AEs	-	2
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	2 (1)	-
FLUID RETENTION	1 (<1)	-
URINATION ABNORMAL NOS	1 (<1)	-
Total Number of AEs	2	-
VASCULAR DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
HAEMATOMA NOS	1 (<1)	-
HYPERTENSION NOS	-	1 (<1)
Total Number of AEs	1	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
LYMPHADENOPATHY	-	1 (<1)
Total Number of AEs	-	1
EAR AND LABYRINTH DISORDERS		
Total Pts With at Least one AE	1 (<1)	-
LABYRINTHITIS NOS	1 (<1)	-
Total Number of AEs	1	-

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01DEC2003:14:58:21 (6 of 7)

ae11 Summary of Adverse Events by Body System and Trial Treatment
Protocol(s): NM17247
Analysis: SAFETY Center: ALL CENTERS

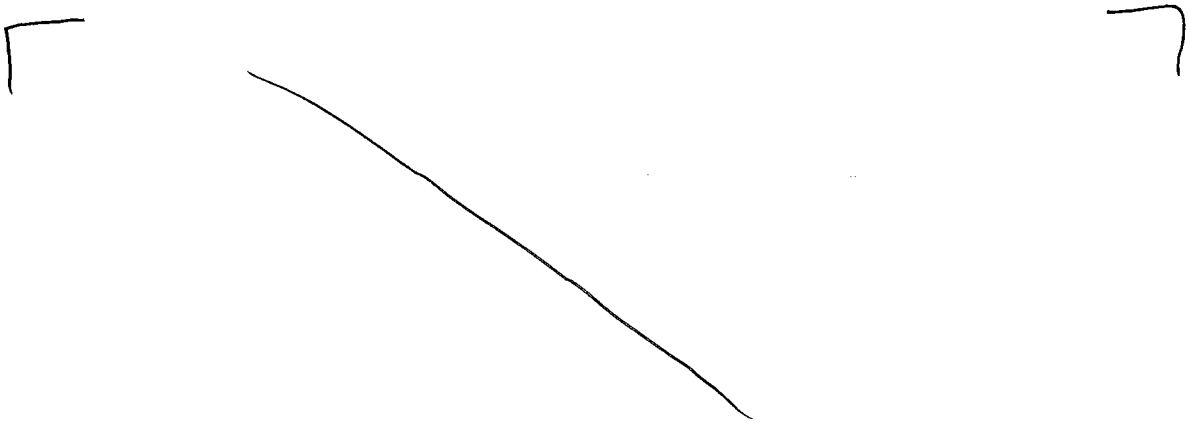
Body System/ Adverse Event	PLACEBO N = 195 No. (%)	ORLISTAT 60 mg N = 196 No. (%)
IMMUNE SYSTEM DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
ALLERGY AGGRAVATED	-	1 (<1)
Total Number of AEs	-	1
INVESTIGATIONS		
Total Pts With at Least one AE	-	1 (<1)
BLOOD IN STOOL	-	1 (<1)
Total Number of AEs	-	1
SURGICAL AND MEDICAL PROCEDURES		
Total Pts With at Least one AE	-	1 (<1)
POST-OPERATIVE PAIN	-	1 (<1)
Total Number of AEs	-	1

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01DEC2003:14:58:21 (7 of 7)

10.4 Cut-offs for Marked Laboratory Abnormalities

Table 10.4.A. Cut-offs for Marked Laboratory Abnormalities					
Laboratory Test	**Units**	**Pooled Studies**		**NM17247**	
		Low	**High**	**Low**	**High**
Hemoglobin	g/L	100	199	110	200
Hematocrit	fraction	0.30	0.60	0.36	0.60
RBC	10^{12}/L	3.0	8.0	3.50	5.60
WBC	10^{9}/L	3.0	20.0	3.0	18.0
Neutrophils	10^{6}/L	1000	15000	1500	---
Eosinophils	10^{9}/L	0	1.4	0	1.5
Basophils	10^{9}/L	0	0.40	0	0.30
Monocytes	10^{9}/L	0	2.00	0.08	2.0
Lymphocytes	10^{9}/L	0.5	10.0	1.0	6.3
Platelets	10^{9}/L	100	700	100	700
AST (SGOT)	U/L	0	150	0	50
ALT (SGPT)	U/L	0	150	0	60
GGT	U/L	0	152	0	120
Alkaline phosphatase	U/L	0	375	0	190
Total bilirubin	µmol/L	0	61.6	0	34.2
Creatinine	µmol/L	0	221	0	154
BUN	mmol/L	0	17.9	0	14.3
Creatine phosphokinase	U/L	0	500	---	---
Sodium	mmol/L	130	150	130	150
Potassium	mmol/L	3.0	6.2	3.0	6.0
Chloride	mmol/L	80	120	95	115
Calcium	mmol/L	1.75	2.99	2.00	2.90
Phosphorus	mmol/L	0.61	2.26	0.75	1.60
Albumin	g/L	20	80	27	---
Total protein	g/L	45	100	55	87
TSH	µU/mL	0	10	0	10.0

10.5 Line-by-Line Labeling Review



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✓ Draft Labeling

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/s/

Julie Golden
3/8/2006 10:12:22 AM
MEDICAL OFFICER

Eric Colman
3/8/2006 01:13:30 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-887
Submission Code	000
Letter Date	June 6, 2005
Stamp Date	June 7, 2005
PDUFA Goal Date	April 7, 2006
Reviewer Name	Karen B. Feibus, M.D.
Review Completion Date	December 1, 2005 (amended February 13, 2006)
Established Name	orlistat
(Proposed) Trade Name	Alli
Therapeutic Class	pancreatic lipase inhibitor
Applicant	GlaxoSmithKline Consumer Healthcare
Priority Designation	S
Formulation	60 mg capsules
Dosing Regimen	1 – 2 capsules up to TID with fat containing meals
Indication	weight loss
Intended Population	overweight adults ages 18 years and older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

An approvable action is recommended.

This reviewer believes that NDA 21-887 is approvable when the actual use study results are considered together with the entirety of data regarding orlistat safety and efficacy and label comprehension. Nearly all orlistat users dosed orlistat according to label directions and followed a diet plan, and 92% of orlistat users were overweight or obese by strict BMI criteria. Despite poor self-selection results in the actual use study, the label comprehension study performed with a label nearly identical to the NDA 21-887 label suggests that label warnings were understood by more than 85% of consumers.

Consistent with recommendations from the January 23, 2006, Advisory Committee meeting, stronger, more explicit language is needed in the *Do Not Use* warning for cyclosporine users. More effective labeling language is needed to describe correct multivitamin use while using orlistat OTC. In addition the *Do Not Use if you are not overweight* label element should be tested. Following the label modifications, the final proposed label should be tested in a label comprehension study that incorporates a self-selection process.

An addendum to this review will be added when the ODS report on the potential association between orlistat use and pancreatitis is completed and reviewed.

1.2 Recommendation on Postmarketing Actions

No recommendations on postmarketing actions are appropriate at this time.

1.3 Summary of Clinical Findings

GlaxoSmithKline Consumer Healthcare, L.P. (GSKHC), submitted NDA 21-887 for orlistat 60 mg capsules to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet. The proposed trade name is *Alli*. The proposed dosing regimen is 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day (TID) with a labeled six-month duration of use. Orlistat, tetrahydrolipistatin, is a reversible pancreatic lipase inhibitor that acts by inhibiting the absorption of approximately 30% of dietary fat.

1.3.1 Brief Overview of Clinical Program

GSKHC submitted data from seven studies to support the safety and efficacy of orlistat OTC 60 mg as an OTC weight loss product. The safety and efficacy of orlistat 120 mg for the treatment

of obesity and weight management was reviewed and approved in NDA 20-766 in April 1999. Four of the currently submitted trials were submitted to NDA 20-766 but also contained 60 mg orlistat treatment arms. Three additional studies, including the actual use study reviewed in this document, were submitted in their entirety to NDA 21-887. Brief descriptions of these studies are provided in the table below:

Table A: Studies submitted to NDA 21-887 for orlistat OTC, 60 mg

Study No./Completion Date/NDA #	Type of study	Role in OTC NDA	Duration of study	BMI (kg/m^2)	Orlistat treatment	Number of subjects
NM14161 February 1995 N20-766	Weight loss study using primary care providers	Safety and efficacy	2 yrs	30 – 43	Placebo 60 mg 120 mg	212 213 210
BM14150 May 1995 N20-766	Dose-ranging study	Safety and efficacy	6 mths	28 – 43	Placebo 30 mg 60 mg 120 mg 240 mg	124 122 123 120 117
BM14149 February 1996 N20-766	Weight loss study	Safety and efficacy	2 yrs	28 – 43	Placebo 60 mg 120 mg	237 239 242
NM14302 March 1996 N20-766	Weight maintenance effect of orlistat after 6 month period of weight loss with diet alone	Safety	18 mths*	28 – 38	Placebo 30 mg 60 mg 120 mg	185 186 171 180
RCH-ORL-002 December 2001 N21-887	Evaluation of orlistat treatment in a "naturalistic setting"	Safety	4 wks	**	60 mg	162
NM17247 October 2003 N21-887	Weight loss study in a primary care setting	Safety and efficacy	4 mths	25 – 28	Placebo 60 mg	195 196
NM17285 October 2003 N21-887	Pilot actual use study	Actual use and safety	3 mths	**	60 – 120 mg	284

*12 months of drug treatment
** These studies were intended to simulate an OTC environment; no BMI restrictions imposed.

A label development section and pivotal label comprehension study were also submitted to this NDA. These portions of the submission are reviewed by Arlene Solbeck, M.S., interdisciplinary scientist, and Susanna Weiss, Ph.D., behavioral scientist in separate review documents. The orlistat OTC starter pack includes six supplementary support materials: a companion guide (user's guide), QuickFacts cards, a Healthy Eating Guide, a Daily Journal, a Calorie and Fat Counter, and a Welcome Card that introduces the consumer to the behavioral support program. These materials are included as an integral part of the Alli Weight Loss Program. These educational support materials, while based on those used in the actual use study, were designed by the sponsor after completion of the actual use study by Roche, Inc.

The integrated summaries of efficacy and safety submitted by the sponsor are reviewed by Dr. Julie Golden from the Division of Metabolism and Endocrinologic Products. This document

reviews study NM17285, the actual use study. Comments that follow relate to findings from this study unless otherwise specified.

1.3.2 Efficacy

The efficacy of orlistat OTC for weight loss when used in an actual use setting is reviewed in this document based on data from study NM17285. This study was conducted by the drug innovator, Roche, Inc.

The primary objectives of the actual use study were to:

- evaluate the ability of consumers to correctly select or de-select orlistat for personal use based on labeled directions
- provide initial information regarding how consumers use and dose orlistat without physician supervision
- evaluate the adverse event profile in an actual use setting.

Subject weight loss was not a pre-specified study endpoint. The sponsor's secondary objectives were to assess consumer perceptions of orlistat and evaluate the consumer educational materials and website. The consumer educational materials included the following:

1. **How to Lose Weight with Orlistat**
   A 12-page booklet containing information about: how to correctly use and dose orlistat, possible side effects; who should not use orlistat; when to stop using orlistat. The booklet encouraged eating three balanced meals a day, counting calories and fat grams, and provided some instruction in reading a ***Nutritional Facts*** label. The booklet addressed "common dieting pitfalls."

2. **Orlistat Food Diary: Keep track of your progress**
   Subjects were instructed to record foods eaten, physical activity, and to check the orlistat box when they took an orlistat dose.

3. **Fat Counter**
   Pocket-size Harriet Roth's Fat Counter which contained more than 70 pages of information on fat grams and calories for many food items with brand name comparisons.

4. **Fat Wheel**
   A cardboard wheel that provided fat grams and portion sizes for common foods (yogurt, eggs, soups and sauces, cheese, beef, veal and lamb, pork, chicken and turkey, fish and shellfish, beans and peas, vegetables, fruits, breads, pasta and grains, breakfast foods, spreads and dressings, snacks, beverages, frozen sweets, and sweets).

5. **Portion Card**
   A two-sided laminated card with tips about portion and serving sizes.

6. **Diet Success Planner**

A 27-page booklet divided into five sections that included information on setting eating and activity goals, planning meals and food shopping lists, calories and food, healthy cooking and snack suggestions, food exchanges and sample menus, exercise, and dining out.

This three month, actual use trial was a multi-center, pharmacy-based, open-label, three-month trial. Eighteen pharmacies, in six geographical areas of the United States participated in the study. Each pharmacy was equipped with a certified, calibrated scale. In-store advertising was the primary recruitment method, but newspaper advertising was used in areas with slow recruitment.

Eligible subjects were 18 years of age and older and able to participate in telephone follow-up interviews. Individuals who had previously used orlistat were excluded. Recruited individuals were allowed to participate in the self-selection decision but were not allowed to purchase if they were allergic to orlistat, pregnant or breastfeeding, or currently treated with cyclosporine, warfarin, or a medicine for diabetes.

The pharmacy staff followed a script, and all potential subjects were asked to review the label for the proposed product (see section 10.4). The following self-selection question was asked:

Do you think this medication is appropriate for you to use?

Demographic information, medical history, and an objective weight measurement were collected at the time of enrollment. Informed consent was obtained. The REALM test was administered. The purchase decision question was then asked:

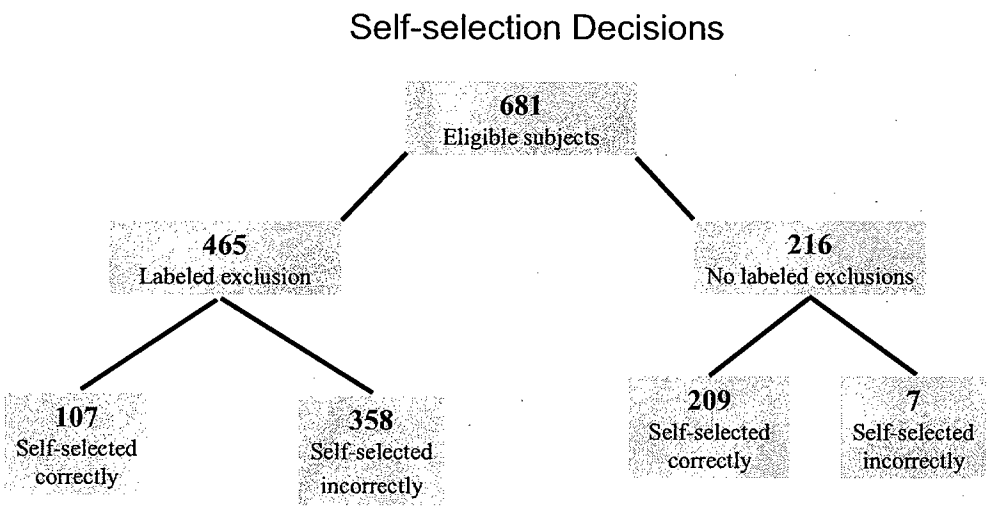
The cost of this mediation is $45 for a bottle of 90 capsules. Would you like to purchase this medication today?

Responses and reasons were recorded. Purchasers were allowed to purchase up to three bottles of study drug at a time but were allowed to return to the pharmacy as often as desired to purchase more medication. Subjects who did not purchase orlistat at the time of enrollment were not allowed to return at a later time to purchase orlistat. Each subject was required to have one follow-up pharmacy visit at some time during the study. Therefore, there was no specified time when a follow-up objective weight measurement was required of all study participants following the weigh-in at enrollment. Four follow-up telephone interviews were scheduled at pre-set intervals of 14, 30, 60, and 90 days plus an end of study telephone interview two weeks after cessation of study drug treatment. Interview timing was allowed to vary within a ten day window. Telephone interviews used a computer-assisted (CATI) program to prompt questions sequentially based on answers entered. Answers were often multiple choice or *best choice* answers chosen by the clinical interviewers. Verbatim answers were recorded only with regard to some defecation pattern adverse event reports.

Study results

A total of 703 individuals was screened. Ultimately, 681 subjects were eligible for study participation (after 22 subjects from one pharmacy site were later excluded due to protocol violations) and participated in the self-selection decision. Of 681 eligible subjects, 79.7%

thought that orlistat was appropriate for them to use, 7.6% thought it was not appropriate for them to use, and 12.6% did not know or were unsure.



- Correct self-selection: 107 + 209 = 316
- 46.4% of all eligible subjects made a correct self-selection decision

Table B: Summary of self-selection and use decisions among actual use study subjects with one or more labeled exclusions (N = 465)

Actual Use Study Label Exclusion criterion (U = unconditional) (C = conditional)	**Subjects with labeled exclusion(s)** (N = 465)	**Appropriate self-selection decision**	**Appropriate use decision**
Allergic to ingredients (U)	0	N/A	N/A
Taking cyclosporine (U)	2 (0.3%)	50.0%	N/A
Taking warfarin (U)	14 (2.1%)	50.0%	N/A
Taking diabetes medicine (U) †	46 (6.8%)	34.8%	N/A
Problems absorbing food (C)	12 (1.8%)	16.7%	0% (0 of 1)
Gallbladder problems (C)	25 (3.7%)	40.0%	28.6% (2 of 7)
High blood pressure (C)	166 (24.4%)	44.0%	38.9% (21 of 54)
High cholesterol/triglycerides (C)	147 (21.6%)	46.3%	42.9% (21 of 49)
More than 30 pounds to lose (C)	346 (50.8%)	21.1%	23.7% (27 of 114)
On diet recommended by doctor (C)	48 (7.0%)	54.2%	50.0% (5 of 10)
Taking another weight loss medicine (C)	33 (4.8%)	12.1%	25.0% (3 of 12)

Table B shows the number and percentage of incorrect self-selection and use decisions for each labeled contraindication. Overall, 465 eligible subjects had a total of 839 labeled contraindications to use. By labeled contraindication, appropriate use decisions were made by subjects 0 – 50% of the time depending on the particular labeled contraindication.

Subjects used orlistat for a mean of 67 days with a range of 3 – 90 days of use. Nearly all users used an appropriate daily dose of orlistat and took the appropriate number of capsules per dose. Ongoing use of orlistat declined throughout the study. Only 46.4% of orlistat users were still using study drug at the Day 90 telephone interview.

Concomitant use of a multivitamin (MVI) containing fat-soluble vitamins is recommended with orlistat use due to documented decreased absorption of vitamins D, E, and beta-carotene and potential decreased absorption of vitamins A and K. To optimize vitamin absorption, the orlistat label instructs consumers to take the MVI at least two hours before or two hours after their orlistat dose. Telephone interview responses revealed that while 75 – 85% of orlistat users took a MVI during the study, only 38% (Day 14 interview) to 53% (Day 90 interview) of orlistat users took the MVI according to the label directions. The reason for this noncompliance is unclear. The communication on the orlistat label may not be clear to consumers or consumers may be confused by conflicting instructions for use on the MVI label. The orlistat labeling does not inform consumers that instructions on the MVI label may be different in relation to timing with food. Results from the label comprehension study suggest that 73% of subjects understood how to use a MVI according to the orlistat label directions.

Seventy-seven to 86% of subjects found the supplemental educational materials helpful. At the beginning of the study, about 80% of subjects were following some kind of diet, but this percentage declined to 61% by the end of the study. Most study subjects following a diet used a reduced calorie and/or low-fat diet as suggested on the label. Seventy-three percent of subjects perceived that orlistat *was helpful in helping them lose weight.*

The mean measured weight loss at the end of study participation was 3.3 kg based on objectively measured weights at the pharmacy in 106 of 237 (44.7%) users who returned to the pharmacy for a last visit as requested. Based on measured weights taken at study day 60 and beyond, 42% of subjects lost more than 5% of their body weight; however, this figure is based on weights from only 25% of the user population. Based on self-report at the final telephone interview, 41% of all study subjects using orlistat lost more than 5% of their body weight, and the mean weight loss was 4.8 kg. However, self-reported weight loss data is based only on reported weight loss for orlistat users who actually lost weight. Data on individuals who did not lose weight or gained weight during the study were not included in these calculations. For comparison, obese subjects who enrolled in randomized, placebo-controlled studies and used orlistat 60 mg and 120 mg lost an average of 4.26 kg and 4.65 kg respectively with six months of treatment; however, weight loss above and beyond that of the placebo group averaged 2.4 – 2.8 kg. Weights during the randomized, controlled trials were objectively measured by study personnel. In general, individuals with higher baseline body mass indexes (BMI) lost more weight than those with lower baseline BMIs both in controlled clinical trials and in the actual use study. The percent body weight lost is fairly consistent across the range of BMIs.

The majority of subjects enrolled in the actual use study complied with dosing instructions and most lost some weight using orlistat and the accompanying behavior support program. Correct multivitamin use among study subjects was inadequate even though it increased from 38% to 54% over the course of the study. The low rates of correct self-selection and use decisions among subjects with labeled exclusions is concerning. Based on LC study results that suggest >85% comprehension on most label warning elements, this poor performance may be based on consumer non-compliance rather than lack of comprehension.

Study results are confounded by incomplete or inadequate objective and prospective data collection. Some reimbursement procedures during the study and certain questions during the telephone interview may have influenced subject behavior during the study.

1.3.3 Safety

This summary of safety data will focus on two areas: safety issues related to self-selection and use decisions and adverse events experienced by subjects during the study.

Ninety-two percent of orlistat users were overweight or obese. No underweight individuals enrolled in the study. Among the 18 women who were not overweight, only three had a BMI < 22 kg/m^2.

Subject self-selection decisions suggest either a problem with label comprehension or extensive disregard for label warnings. As shown in Table B above, the majority of subjects with a labeled contraindication thought that orlistat was appropriate for them to use. Even when self-selection and use decisions are examined for only the labeled exclusions that remain on the proposed NDA label, correct self-selection and use decisions by subjects ranged between 0 – 50% for unconditional exclusions and 12 – 50.0% for conditional exclusions. The sponsor did not provide data to confirm whether subjects with conditional exclusions consulted their healthcare professional as claimed, so incorrect behavioral decisions rates could be higher.

This actual use study did not test consumer behaviors on label elements new to the NDA label. The submitted NDA label contains the following new label communications (see section 10.5):

- *Ask before use* if you have kidney stones
- *Do Not Use* if
  - you are not overweight
  - you have problems absorbing food

As previously mentioned in the efficacy section, orlistat use decreases the absorption of fat soluble vitamins A, D, E, and K and beta-carotene from the intestines. Consistent with current prescription labeling, the proposed OTC label recommends that consumers take a daily multivitamin (MVI) at least two hours before or two hours after orlistat while using the drug. During the study 38 – 53% of orlistat users took the MVI according to label directions. The potential for vitamin deficiency with consumer use for longer than the six month labeled duration of use combined with poor compliance with correct MVI use is concerning.

The actual use study does not offer insight into consumer continuation and discontinuation behaviors because the study did not continue beyond a 90-day drug treatment period. Subject compliance with label communications that address duration of use were not evaluated.

No deaths occurred in the actual use study. There were six serious adverse events that occurred in five subjects: one kidney infection, one methicillin-resistant staphylococcus aureus urinary tract infection (MRSA UTI), one abdominal pain, one chest pain (esophageal spasm), one spontaneous abortion, and one transient ischemic attack (same subject as MRSA UTI). One case of esophageal spasm and one case of abdominal pain in a patient with a history of chronic anemia were considered possibly related to study drug.

Based on orlistat's mechanism of action, defecation pattern adverse events are expected due to the passage of more fat in the stool. Defecation pattern adverse events included:

- oily spotting
- fecal urgency
- liquid stools
- fecal incontinence
- fatty/oily stool
- flatus with discharge
- increased defecation
- decreased defecation
- soft stools
- oily evacuation

Approximately 50% of subjects experienced a defecation pattern adverse event at some time during the study. The incidence was the same regardless of whether subjects used 60 mg or 120 mg of orlistat per dose. Sixty-five to 90% of subjects experiencing various defecation pattern adverse events continued orlistat use without interruption. The remainder of these subjects either interrupted or discontinued orlistat use due to these adverse events. A total of 43 subjects (15.8% user population) discontinued orlistat treatment due to adverse events, and 21 of these events were defecation pattern related. The other adverse events leading to discontinuation in the other 12 subjects were: viral gastroenteritis, upper respiratory tract infections, chest pain, fatigue, hypertension, back injury, abnormal cardiovascular function test, carpal tunnel syndrome, and periorbital edema. The following adverse events were considered treatment-related: upper abdominal pain (3.5%), fatigue (2.5%), headache (2.1%), dyspepsia (1.8%), muscle cramps (1.4%), hemorrhoids (1.4%), chest pain (1.1%), constipation (1.1%), vomiting (0.7%), and frequent bowel movements (0.7%). The overall adverse event profile among actual use study subjects was very similar to the adverse event profile of subjects taking orlistat 60 mg of 120 mg in randomized, controlled clinical trials.

The adverse event profile among actual use study subjects closely parallels the adverse event profile seen among prescription users of orlistat. No new safety signals were detected, and the adverse event profile seen among actual use study subjects does not raise safety concerns for consumer use. However, the frequency of incorrect self-selection and use decisions by subjects with labeled contraindications and incorrect MVI supplementation are unresolved consumer safety concerns. Consumer behavior in an actual use study on orlistat use has not been done using the actual label and supplemental educational materials submitted with this NDA.

A preliminary review (02/08/2006) by Cynthia Kornegay, Ph.D. in the Office of Drug Safety (ODS) suggests a possible association between orlistat use and pancreatitis when using sibutramine as a crude comparator as well as the AERS database as a whole. Prescription labeling and proposed OTC labeling for orlistat include a warning about cholelithiasis. A more detailed ODS review is underway.

1.3.4 Dosing Regimen and Administration

The sponsor proposes a dosing regimen for orlistat 60 mg capsules of one to two capsules with fat-containing meals up to three times per day. Labeling recommends starting with the lower dose. Orlistat must be taken with meals in order to inhibit fat digestion and absorption. The prescription dose for orlistat is 120 mg up to TID. The safety profile of orlistat is very similar at

the 60 mg and 120 mg doses. The dosing regimen proposed is reasonable and supported by dose-ranging studies submitted to NDA 20-766.

1.3.5 Drug-Drug Interactions

Orlistat treatment produces a documented decrease in the absorption of vitamins D, E, and beta-carotene and a potential for decreased absorption of vitamins A and K. Use of orlistat within two hours of cyclosporine dosing reduces serum levels of cyclosporine. Drug-drug interaction studies have shown that orlistat has no effect on the pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended release tablets), oral contraceptives, phenytoin, pravastatin, warfarin, or metformin.[11]

1.3.6 Special Populations

Not applicable.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

On June 6, 2005, GlaxoSmithKline (GSK) Consumer Healthcare, L.P., submitted NDA 21-887 for orlistat 60 mg capsules to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet. The proposed trade name is *Alli*. The proposed dosing regimen is 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day (TID). Orlistat, tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of approximately 30% of dietary fat. Three percent of the drug is systemically absorbed, and most of the absorbed drug is rapidly metabolized to pharmacologically inactive compounds during first pass through the entero-hepatic circulation.

Hoffmann-La Roche, Inc. first submitted an investigational new drug application (IND 31,617) for orlistat capsules on May 13, 1988. On April 23, 1999, NDA 20-766 was approved for the prescription-only marketing of Xenical®, orlistat 120 mg TID. A pediatric indication for children down to the age of 12 years was approved by FDA on June 12, 2004. Xenical use is indicated for obese patients with an initial body mass index (BMI) $\geq$ 30 kg/m^2 or $\geq$27 kg/m^2 in the presence of other risk factors (hypertension, diabetes, dyslipidemia). The product should be used in conjunction with a reduced calorie diet, and indications for use include: obesity management, weight loss, and weight maintenance.

On June 19, 2001, FDA received a Hoffmann-La Roche, Inc. application for IND 62,758 to investigate the development of orlistat for OTC marketing. In September 2004, GSK acquired ownership of IND 62,758 from Hoffmann-La Roche, Inc. GSK has right of reference to relevant information within IND 31,617 and NDA 20-766, but the ownership of and responsibility for this application remains with Roche. Some of the pivotal Xenical® studies conducted under IND 31,617 included 120 mg and 60 mg orlistat treatment groups.

2.2 Currently Available Treatment for Indications

FDA-approved weight loss and obesity management drug products are regulated though NDAs for prescription products. Drugs marketed prescription-only for obesity management include appetite suppressants and orlistat. There is an over-the-counter (OTC) drug monograph for weight control products, but it is not yet finalized.

Phentermine hydrochloride (HCl)
Phentermine HCl is a sympathomimetic amine with amphetamine-like pharmacologic activities such as appetite suppression (anorexia). The primary action of this drug in treating obesity may be a central nervous system (CNS) or metabolic effect other than appetite suppression. Adult obese patients using dietary management lose more weight when treated with phentermine as

opposed to placebo. The weekly difference in weight loss between treatment groups is a fraction of a pound per week and results are inconsistent from study to study. In a weight reduction program based on exercise, behavioral modification, and caloric restriction, physicians may use phentermine as a short-term (a few weeks) adjunct to obesity management in patients with a body-mass index (BMI) $\geq$ 30 kg/m^2 or with a BMI $\geq$ 27 kg/m^2 and other co-existing risk factors (hypertension, diabetes, hyperlipidemia). Phentermine compounds are taken as an oral tablet or capsule. [5, 9]

Phentermine use is contraindicated in individuals with arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, glaucoma, and known hypersensitivity or idiosyncrasy to the sympathomimetic amines. Primary pulmonary hypertension (PPH) has occurred in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. There have been rare cases of PPH in patients who took phentermine alone. Phentermine is approved as a monotherapy for obesity management and should not be combined use with other drug products for weight loss. [5, 9]

Phentermine has the potential for abuse given its chemical and pharmacological relationship to amphetamine. Abuse of these types of drugs may be associated with psychological dependence and social dysfunction. Sudden cessation of use may lead to withdrawal symptoms including extreme fatigue and mental depression. [5, 9]

Methamphetamine hydrochloride
Methamphetamine HCl is a sympathomimetic amine with CNS stimulant activity. Peripheral pharmacologic actions include elevation of systolic and diastolic blood pressure and weak bronchodilation and respiratory stimulation. The mechanism of action and magnitude of weight loss effect are the same as that defined above for phentermine. While methamphetamine is indicated for the treatment of obesity in conjunction with a weight reduction program in patients refractory to other therapies, the drug carries a black box warning due to its high potential for abuse and drug dependence. Contraindications are the same as those listed for phentermine and also include use of a monoamine oxidase inhibitor within 14 days. [5, 9]

Sibutramine hydrochloride monohydrate
Sibutramine HCl monohydrate is a norepinephrine (NE), serotonin, and dopamine reuptake inhibitor. The parent compound is metabolized to two active amines, M1 and M2. M1 and M2 both inhibit NE, serotonin, and dopamine reuptake in vivo in the human brain. Sibutramine is indicated for the management of obesity, including weight loss and weight loss maintenance, in conjunction with a reduced calorie diet. It is recommended for use in individuals with a BMI $\geq$ 30 kg/m^2 or with a BMI $\geq$ 27 kg/m^2 in the presence of other risk factors (hypertension, diabetes, hyperlipidemia). Use of sibutramine is contraindicated in patients:

- on a MAOI
- with uncontrolled or poorly controlled hypertension
- with cardiovascular disease, congestive heart failure, arrhythmias, or stroke
- with an eating disorder
- taking other centrally acting appetite suppressants

- with hypersensitivity to the drug or the inactive ingredients.

Regular blood pressure monitoring is required during use, as sibutramine use substantially increases blood pressure. No cases of pulmonary hypertension have been reported associated with sibutramine use. [5, 9]

Weight Control Products and OTC Marketing
FDA recognizes weight control as an OTC indication and weight control products have been marketed over-the-counter. The Advanced Notice of Proposed Rulemaking (ANPR) for Weight Control Products for Over-the-Counter Human Use was published on February 26, 1982 (47FR8466). As recommended by the National Academy of Sciences Advisory Review Panel, two appetite suppressants were classified as Class I ingredients (GRAS/GRAE):

1. Phenylpropanolamine (PPA)
2. Benzocaine

FDA's Proposed Rule (Tentative Final Monograph) for Weight Control Drug Products for Over-the-Counter Human Use was published on October 30, 1990 (55FR45788). In 2000, PPA was voluntarily removed from OTC drug products due to an increased risk of hemorrhagic stroke associated with use, and a Final Rule reclassifying PPA as a category II monograph ingredient is pending. A final rulemaking is in progress or benzocaine, which is currently Category III for efficacy for weight control.

The ANPR required inclusion of the following labeling for OTC weight control products:

1. "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because that should be enough time to establish new eating habits."

2. Indication for use:
   "for appetite control to aid weight reduction"
   "an aid for effective appetite control to assist weight reduction"
   "helps curb appetite"
   "appetite depressant in the treatment of obesity"
   "an aid to diet control in conjunction with a physician's recommended diet"
   "an aid in the control of appetite"
   "helps control appetite"
   "for use as an aid to diet control"
   "helps you eat less, weigh less."

At this time, there is no Final Rule.

2.3 Availability of Proposed Active Ingredient in the United States

On April 23, 1999, FDA approved NDA 20-766, orlistat 120 mg (tetrahydrolipistatin) for the long-term treatment of obesity in patients (ages 17 years and above) with a body mass index (BMI) ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 and other risk factors such as hypertension, diabetes, and dyslipidemia. Orlistat should be used in conjunction with exercise and a reduced calorie, low-fat diet for weight loss, maintenance of weight loss, and prevention of weight regain.

On March 19, 2001, Hoffman – La Roche Inc. submitted a NDA supplement for the indication of *combination therapy for improvement in glycemic control in type 2 diabetics who are overweight or obese.* While statistical analyses suggested a possible modest benefit for the combined use of orlistat with a sulfonylurea or with insulin, this benefit was not seen with metformin combination therapy and the decreases in hemoglobin A_1C levels were inconsistent and modest. (1/17/2002, DMEP medical officer review by Joanna K. Zawadzki, M.D.) The additional proposed orlistat indication for type 2 diabetes treatment was not approved.

FDA approved a NDA supplement for the use of orlistat in the management of obesity in adolescent patients ages 12 years and above on December 12, 2003.

2.4 Important Issues With Pharmacologically Related Products

Orlistat is the only member of this pharmacological class of drugs.

2.5 Presubmission Regulatory Activity

On July 17, 2002, prior to GSKHC's acquisition of IND 62,758, Hoffmann-La Roche met with FDA for an end of phase II meeting. As conveyed by the meeting minutes, FDA identified key issues requiring further assessment for OTC orlistat development. GlaxoSmithKline Consumer Healthcare, L.P. addressed these issues in their November 4, 2004, pre-NDA submission. The following issues were discussed by GSK, the Division of Metabolic and Endocrine Products, and the Office of Nonprescription Products at the December 8, 2004 pre-NDA meeting.

2.5.1 Justification for the selection of a 60 mg dose for OTC use and for keeping the 120 mg dose prescription only

In NDA 21-887, the proposed indication for orlistat 60 mg is *promote weight loss in overweight adults when used along with a reduced calorie and low fat diet.* The dose is one to two capsules with each meal containing fat, not to exceed six capsules per day.

2.5.2 Lack of data supporting the safety and effectiveness of orlistat in patients without dietary or exercise counseling

The sponsor submitted results from this pilot actual use study (NM 17285) and study NM 17247 to support the safety and efficacy of orlistat in patients/consumers without dietary or exercise counseling. Study NM 17247 was a six-month, randomized, placebo-controlled, parallel design study in patients with BMI 25 - <28 kg/m^2 in a primary care setting.

2.5.3 Number of allowable OTC treatment courses before a consumer should consult a healthcare provider for alternative approaches to weight loss

Labeling submitted with the current NDA as supplemental educational materials suggests that consumers may repeat the six-month course of OTC orlistat therapy if they have not taken the drug in three months. This information does not appear in the Drug Facts label, and there is no recommendation to speak to a healthcare provider prior to repeating OTC courses of orlistat.

2.5.4 Need for an actual use study to address the following issues:

Does it matter whether both overweight and obese consumers use OTC orlistat?
Do consumers stop using OTC orlistat after six months?
How likely are consumers to use a MVI concomitantly with OTC orlistat treatment?

The pilot actual use study (NM 17285) was a four month study with 90 days of treatment, and the proposed duration of use for OTC orlistat is six months. The sponsor was informed that in order to gather consumer behavioral information on appropriately-timed drug discontinuation, FDA prefers to see an actual use study that lasts longer than the product's labeled duration of use. The sponsor was asked to demonstrate how data from the pilot actual use study could be meaningfully extrapolated to predict consumer behavior at six months.

Based on the pre-NDA meeting package materials and discussion at the pre-NDA meeting, the Agency made the following recommendations regarding the anticipated NDA submission for OTC orlistat:

1. The standards used to evaluate and label effectiveness of OTC weight loss products should be the same as those for prescription weight loss products. As outlined in the 1996 draft guidance, these standards include meeting one of the following two criteria:

   - Demonstration that the drug effect is significantly greater than the placebo effect, and the mean associated weight loss exceeds the mean placebo weight loss by at least 5%.

- Demonstration that the proportion of subjects who reach and maintain a weight loss of at least 5% of their initial body weight is significantly greater in subjects on study drug than on placebo.

- This weight loss should be maintained over 12 months. There is no specific time allowed for weight loss to occur.

2. Based on existing safety and efficacy data, the orlistat dose for OTC marketing can be 60 – 120 mg TID. FDA noted that previously submitted data demonstrate a 3% weight loss overall for subjects treated with orlistat 60 mg TID among previously conducted studies of 4 – 24 months duration. The 3% body weight loss does not meet the weight loss criteria contained in the draft guidance cited above. There are no clear safety concerns to prohibit the 120 mg orlistat dose from going OTC.

3. The sponsor should demonstrate that effective dietary and exercise guidance can be provided in the OTC setting so that consumers optimize and maintain their weight loss. The sponsor should consider conducting a longer (12 month) actual use study that compares active treatment to placebo and enrolls a low literacy population.

4. Any label comprehension studies should be submitted with the NDA for review by the Division of OTC Drug Products.

5. Pediatric studies should be conducted down to at least age 12 years. This population is likely to use this product whether or not individuals meet the criteria for *overweight* or *obese*. The 120 mg dose is approved as a prescription drug in this age group.

6. The sponsor needs to address any safety issues regarding chronic vitamin malabsorption. Co-packaging a multivitamin with 60 mg orlistat should be considered.

7. The potential for misuse among non-overweight individuals, especially those with eating disorders, will need to be addressed.

2.6 Other Relevant Background Information

In 1996, the Division of Metabolic and Endocrine Drug Products developed and issued a draft Guidance for Industry on the Clinical Evaluation of Weight-Control Drugs. This document suggests clinical trial and clinical drug development programs that could demonstrate the safety and efficacy of drugs to reduce body fat and thereby *improve health and self-esteem*. A final Guidance has not been issued, and the draft document is not available to industry.

The Guidance states that efficacy trials for proposed weight loss drug products should be randomized, double-blind, and placebo-controlled for at least the first 12 months of the clinical trial. Data collection under either open-label or blinded conditions should continue for 24 months. All participating study subjects should be instructed in diet, exercise, behavior modification, and other relevant lifestyle changes. Subjects should be moderately to markedly

obese with a BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 for those with co-morbid conditions. Utilization of methods to measure percent body fat and body fat distribution is encouraged. The study population should include minorities and members of both sexes in numbers large enough to allow statistical evaluation under stratified conditions for these sub-groups.

Study subjects should be given a calorie-restricted or controlled diet, behavior modification, and exercise education. In order to identify placebo responders, all subjects should utilize these techniques during an initial six week period. Individuals who do not lose weight or individuals who plateau are randomized to study treatment or placebo.

Results should include actual weight loss and weight loss expressed as percent of body weight or percent of excess over ideal body weight (or BMI).

While the Guidance does not intend for the recommendations to apply to all possible weight-loss drug product evaluations, the following two weight-loss demonstrations are presented as viable primary efficacy outcome variables:

- Demonstration that the mean drug-associated weight loss exceeds the mean placebo-associated weight loss by at least five percent.

- Demonstration that the proportion of subjects who reach and maintain a weight loss ≥ 5% of initial body weight is significantly greater in subjects on the proposed drug than in those on placebo.

Reviewer Comment:

- *At the pre-NDA meeting (12/08/2004), the Division of Metabolic and Endocrine Products stated that the standards used to evaluate and label effectiveness of OTC weight loss products should be the same as those used for prescription weight loss products.*

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The safety and efficacy reviews for orlistat 60 mg, NDA 21-887, were completed by Julie Golden, M.D. from the Division of Metabolic and Endocrine Products and can be found in the Division Files System (DFS).

3.1 CMC (and Product Microbiology, if Applicable)

Martin Haber, PhD, from the Division of Chemistry reviewed the CMC data, and his review can be found in DFS.

3.2 Animal Pharmacology/Toxicology

The sponsor references the nonclinical pharmacology and toxicology data from NDA 20-766 and has not submitted any new data. Fred Alavi, pharmacologist, completed the PharmTox review, and his review can be found in DFS.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is limited to the Actual Use study (NM17285) submitted with this NDA. Submitted labeling for the proposed product is compared to the labeling used in the Actual Use study. Submitted efficacy and safety data from other orlistat clinical trials are reviewed by Julie Golden, M.D., from the Division of Metabolism and Endocrinologic Products. The label comprehension study is reviewed by Susanna Weiss, Ph.D.

This review uses data from pivotal efficacy and safety studies submitted to NDA 20-766 to compare weight loss and adverse event profiles of subjects in the actual use study to the weight loss and adverse events experienced by subjects in randomized, placebo-controlled trials who received dietary counseling from a learned intermediary.

4.2 Tables of Clinical Studies

The following table lists the clinical studies included in NDA 21-887 for orlistat OTC. The sponsor also submitted complete individual study reports for 66 competed clinical pharmacology studies in 1438 patients

Table 1:
Listing of Studies to be included in OTC NDA for orlistat

Study No. / Study Completion Date	Type of Study	Role in OTC NDA	Duration	BMI	Dose
BM14149 February 1996	Weight loss study	Safety & Efficacy	2 yrs	28-43	Placebo 60 mg 120 mg
NM14161 February 1995	Weight loss study using primary care providers	Safety & Efficacy	2 yrs	30-43	Placebo 60 mg 120 mg
NM17247 October 2003	Weight loss study in a primary care setting	Safety & Efficacy	4 mos	25-28	Placebo 60 mg
BM14150 May 1995	Dose-ranging study	Safety & Efficacy	6 mos	28-43	Placebo 30 mg 60 mg 120 mg 240 mg
NM14302 March 1996	Weight maintenance effect of orlistat after 6 month period of weight loss by diet alone	Safety	18 mos*	28-38	Placebo 30 mg 60 mg 120 mg
RCH-ORL-002 December 2001	Evaluation of orlistat in a naturalistic setting	Supportive	4 wks	**	60 mg
NM17285 October 2003	Pilot actual use study	Supportive	3 mos	**	60 mg

*12 months of drug treatment
** These studies were intended to simulate an OTC environment; no BMI restrictions were imposed.

4.3 Review Strategy

Reviewers of NDA 21-887 are as follows:

- Efficacy and safety: Julie Golden, M.D., medical officer, Division of Metabolism and Endocrinologic Products
- Statistics: Joy Mele, statistician, Division of Metabolism and Endocrinologic Products
- Pharmacology/Toxicology: Fred Alavi, pharmacologist, Office of New Drugs
- CMC: Martin Haber, chemist, Division of Pre-marketing Assessment I

- Biopharmacology: Hae Young Ahn, pharmacologist, Division of Clinical Pharmacology and Biopharmaceutics 2
- Actual use study: Karen Feibus, M.D., medical officer, Division of Nonprescription Clinical Evaluation
- Labeling: Arlene Solbeck, M.S., interdisciplinary scientist, Division of Nonprescription Regulatory Development
- Label Comprehension Study: Susanna Weiss, PhD, social scientist, Division of Nonprescription Clinical Evaluation

4.4 Data Quality and Integrity

This reviewer is not aware of any audit processes performed on the applicant's data or analyses.

4.5 Compliance with Good Clinical Practices

For the study being reviewed herein, the sponsor who conducted the study complied with good clinical practices.

4.6 Financial Disclosures

Please refer to the medical officer review by Julie Golden, M.D. No financial disclosures were made specifically with regard to the actual use study.

5 CLINICAL PHARMACOLOGY

The results of the clinical pharmacology review were not available at the time this review was completed. This review includes general information about the pharmacokinetics and pharmacodynamics of orlistat. A more detailed review of this material can be found in the biopharmacology review by Hae Young Ahn from the Office of Clinical Pharmacology and Biopharmaceutics.

5.1 Pharmacokinetics

The chemical name for orlistat is tetrahydrolipistatin. Orlistat is a reversible lipase inhibitor that covalently binds with the active serine residues of gastric and pancreatic lipases thereby

inhibiting the hydrolysis of dietary triglycerides and the absorption of cholesterol. Orlistat inhibits dietary fat absorption by about 30%. Ninety-seven to 99% of ingested orlistat remains unabsorbed in the intestines and is excreted unchanged in the feces. The small amount of orlistat that is absorbed from the gastrointestinal tract is rapidly metabolized to pharmacologically inactive compounds during first pass through the entero-hepatic circulation. Due to orlistat's extremely low bioavailability, no clinically meaningful effects have resulted from orlistat's action on lipoprotein, hepatic, hormone-sensitive, and diacylglycerol lipases. Based on limited data, the half-life of orlistat is approximately one to two hours.[9, 10, 11]

Orlistat treatment produces a documented decrease in the absorption of vitamins A,D, E, and beta-carotene and has the potential to decrease the absorption of vitamin K. A pharmacokinetic study demonstrated an interaction between orlistat and the absorption of beta-carotene and Vitamin E supplements. Concomitant administration of orlistat with a beta-carotene supplement reduces beta-carotene absorption by 30%. Orlistat decreases the absorption of vitamin E acetate by about 60%. Information from the integrated database for phase III orlistat trials, demonstrates that subjects taking 60 mg or 120 mg of orlistat experienced a mean decrease in serum levels of vitamins A, D, and E and beta-carotene compared to subjects taking placebo. For vitamin A (plasma retinol), the difference between placebo and orlistat 120 mg treatment groups was not statistically significant. Subjects taking 60 mg had a significantly lower rate of two consecutive vitamin level measurements below the reference normal range compared to subjects taking 120 mg orlistat. At both doses, mean levels of vitamins A, D, and E, and beta-carotene remained within the reference ranges after six months and one year of treatment.[11] As stated in the medical officer review of orlistat safety for NDA 20-766 (by Eric Coleman, M.D.), long term orlistat treatment does not appear to cause frank vitamin K deficiency as assessed with prothrombin time. However, prothrombin time is not a sensitive indicator of vitamin K deficiency and may remain normal with mild to moderate vitamin K deficiencies. Published literature suggests that fat malabsorption is associated with vitamin K deficiency.[7]

Use of orlistat within two hours of cyclosporine dosing reduces serum levels of cyclosporine.

Drug-drug interaction studies have shown that orlistat has no effect on the pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended release tablets), oral contraceptives, phenytoin, pravastatin, warfarin, or metformin.[10]

5.2 Pharmacodynamics

Alcohol does not affect the pharmacodynamics of orlistat. Please see relevant comments in section 5.1 above.

5.3 Exposure-Response Relationships

Study BM14150 was submitted under NDA 20-766. This study was a multicenter, placebo-controlled, double-blind, double-dummy, parallel group trial that evaluated weight loss achieved with the following doses of orlistat: 30 mg, 60 mg, 120 mg, and 240 mg. Weight loss achieved

with the three higher doses of orlistat was statistically superior to placebo but the weight loss achieved with the 240 mg dose was statistically the same as that achieved with the 120 mg dose.

6 INTEGRATED REVIEW OF EFFICACY

This review evaluates efficacy of orlistat 60 mg, 1 – 2 capsules taken up to TID with fat-containing meals, for weight loss among subjects using the product under actual use conditions in study NM17825. The integrated review of efficacy may be found in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

6.1 Indication

Orlistat OTC, 60 mg is indicated for weight loss in overweight adults when used along with a reduced calorie and low fat diet. The proposed labeled duration of use is six months.

6.1.1 Methods

This review evaluates the efficacy of orlistat OTC 60mg over three months in an actual use setting based on the data from study NM17285.The efficacy data submitted to support the above indication for the proposed product is reviewed in detail by Julie Golden, M.D. from the Division of Metabolism and Endocrinologic Products.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoints for the actual use study were:

- Appropriate self-selection decision
- Appropriate use decision.

Secondary efficacy endpoints included:

- weight loss
- patterns of medicine use
- days on study medicine
- use of a multivitamin
- subjects' use of the supplementary educational materials and their usefulness.

6.1.3 Study Design

Study NM17825 was conducted by former-sponsor, Roche Consumer Health, Inc. and was designed as a pilot study in preparation for a full-scale actual use study of 60 mg orlistat. Upon study review, GlaxoSmithKline Consumer Healthcare (GSK) concluded that the study design, sample size, and resulting data adequately addressed the primary study objectives of evaluating consumer selection and usage behavior in the absence of a learned intermediary. GSK decided that another actual use study was not needed to support NDA 21887 for OTC Orlistat, 60 mg.

Study Objectives

- Primary objectives
  - To evaluate the ability of consumers to correctly select orlistat for their own use based on labeled directions.
  - To provide initial information regarding how consumers use orlistat in the absence of physician supervision, especially in terms of product dosing.

- Secondary objectives
  - Assess consumer perceptions of orlistat under actual use conditions.
  - Assess the consumer educational materials and website.

This three month, pilot actual use trial was a multi-center, pharmacy-based, open-label, three-month trial. Eighteen pharmacies, in six geographical areas of the United States (AZ, CA, MD, MN, MO, UT), participated in the study. Each pharmacy was equipped with a certified, calibrated scale. In-store advertising was the primary recruitment method. One poster and easel, and one counter-sized sign were provided to each pharmacy site. During the study, recruitment numbers were too low at seven pharmacy sites. In these areas, advertisements containing the same information as on the signs were placed in local newspapers to accelerate recruitment at these sites. The ads were run for at least two weeks.

The advertising materials targeted mildly to moderately overweight individuals without defining mildly to moderately overweight. In addition, the materials stated:

> *Enrollment in the study will take approximately 20 minutes and you will be compensated for your time.*

Reviewer comment:

1. *Subject compensation is often used as a recruitment tool in clinical studies. Compensation can create study population and data biases. In this actual use study, compensation during the study may have influenced subjects' use behaviors, such as time of discontinuation.*

Inclusion criteria

- 18 years of age and older
- Self-selected into the study
- Gives written consent to participate
- Able and available to participate in telephone follow-up interviews

Exclusion criteria

- Participated in previously conducted orlistat label comprehension studies
- Allergic to orlistat or one of its ingredients
- Previously on orlistat 120 mg (Xenical®)
- Currently treated with medication for diabetes
- Currently treated with warfarin
- Currently treated with cyclosporine
- Pregnant or breast-feeding.

Enrollment Procedures

1. **First encounter**

   A pharmacist at each participating pharmacy served as the principal investigator for the study site. Study personnel were given a script and instructed to state only the following information to all who inquired about the study:

   - Our pharmacy is part of a national research study for a weight loss drug.
   - You must be at least 18 years of age to be a part of the study.
   - If you wish to participate, you will need to spend about 15 – 20 minutes with the pharmacy staff today.
   - You will have a chance to look at the medicine and decide if you wish to participate.
   - You are free to end your participation at any time.
   - All information you provide to us is confidential.

2. **Self-selection**

   Study personnel gave the orlistat package to the subject and said, *"Imagine you are in a store and this is a new over-the-counter medicine. You can take as much time as you need to look at the packaging. Let me know when you are finished."*

   The front of the orlistat package box displayed the name of the product and a list of the materials in the package, including the study drug. The back of the box displayed the Drug Facts Label.

   When the subject finished examining the orlistat package, study personnel asked, *"Do you think this medication is appropriate for you to use?"* The subject's responses were recorded.

   Regardless of self-selection response, study personnel collected basic demographic information from and administered the Rapid Assessment of Adult Literacy in Medicine (REALM) test to all subjects. In addition, each subject completed an eight page health survey. No informed consent procedure occurred at this time.

Reviewer comment:

1. *A general informed consent should have been obtained prior to requesting basic demographic information and completion of the health survey.*

2. *The sponsor states that training of principal investigators was done during an investigator meeting and during individual site initiation meetings that were conducted before the study began. Study pharmacy staff training occurred at the on-site pharmacy training only. This training included instruction on administration of the REALM test with verbal instruction and role play practice.*

3. **Purchase decision**

Once the above information was collected, study personnel asked each subject the following question, "The cost of this medication is $45 for a bottle of 90 capsules. Would you like to purchase the medication today?" Responses were recorded including reasons why subjects did not want to purchase the study drug or were undecided about whether to purchase.

Reviewer comment:

1. *This reviewer is concerned that the cost of $45 to $90 per month to use this medicine may have significantly affected the demographics of subjects who purchased study drug. While this might reflect true consumer behavior after marketing, it may prevent a thorough assessment of consumer behavior among all potential users.*

4. Informed consent and final enrollment procedures

Subjects who expressed a desire to purchase orlistat underwent informed consent with the pharmacist. Those who did not give informed consent were measured for height and weight and were compensated $20 for their time and concluded their participation.

Inclusion and exclusion criteria were applied to subjects who gave informed consent. Subjects who met exclusion criteria or did not meet inclusion criteria concluded their participation in the study after measurements for height and weight were collected, and they received $20 compensation.

Subjects who met inclusion and exclusion criteria provided personal contact information and contact information for a person who did not live with the subject but would know how to contact the subject. Height and weight measurements were collected, drug was purchased (up to three packages) and the study participant was compensated $20 for his or her time.

Weights were assessed in the pharmacy using standardized, calibrated scales. Weight loss was measured and recorded in whole pounds. Before measuring the subject, subjects were asked to empty their pockets and remove jackets, sweaters, and shoes.

Reviewer Comment:

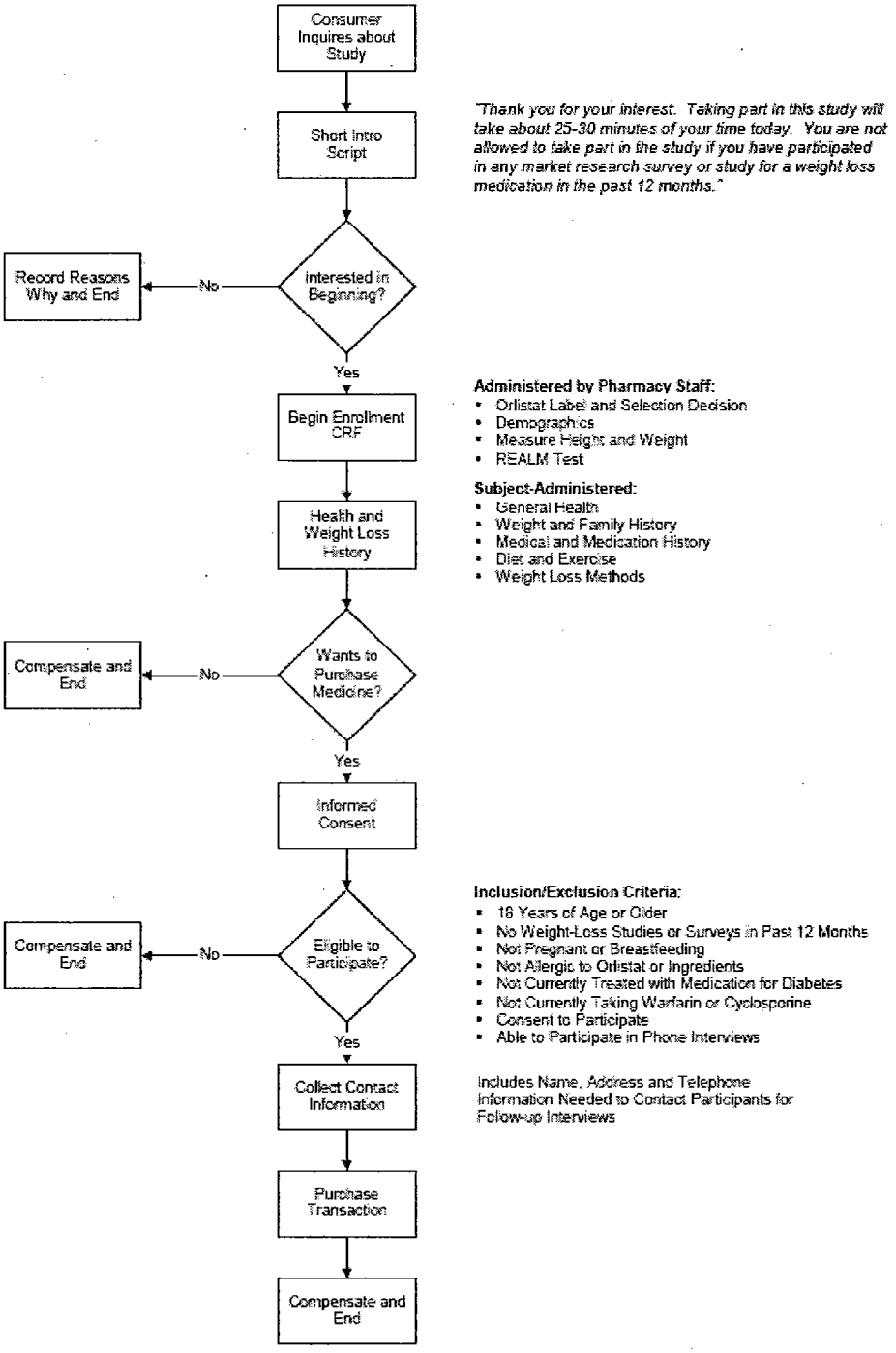
1. *Study personnel were instructed to have subjects empty their pockets and remove any jackets, sweaters, and shoes prior to being weighed at each pharmacy visit.*

2. *Comparing the flow chart summary of the pharmacy enrollment procedure, depicted below, and the sponsor's written description of the procedure, it is not clear whether subjects' heights and weights were measured before or after answering the purchase decision question.*

Figure 1 depicts a flow chart summary of the pharmacy enrollment procedure.

Figure 1:

PHARMACY ENROLLMENT PROCESS



Actual Use Study Procedures

1. Return visits

Subjects were allowed to purchase up to three packages at any one time and could return to the pharmacy as often as desired to purchase additional medication. Each time a subject returned to the pharmacy, a weight was measured on a calibrated scale and recorded on a case report form. Any adverse events spontaneously reported by subjects during pharmacy visits were also recorded on case report forms and faxed immediately to PEGUS research for follow-up by clinical staff.

The study protocol required that subjects participate in at least one pharmacy visit after enrollment. Investigators told subjects to return to the pharmacy at the end of their study participation and to bring the medication packaging, whether empty or not. This instruction was also included in the informed consent.

Reviewer comment:

1. *The return visit form for pharmacy visits instructed pharmacy staff to count the study medication and enter the number of bottles and pills being returned. The subject was allowed to keep any medication they had purchased.*

2. *Adverse event reporting was subject driven. The mentioned event was described on the return visit form. Subjects were asked whether they adjusted their use of the study drug due to the adverse event, whether the event was treated, and when the event resolved. Space was provided for study personnel to record subject comments.*

2. Discontinuation from study

A final telephone interview was conducted any time a subject expressed an intent to end participation or stop using the study medication. Information collected during the final telephone interview included:

- Reasons subjects elected to use the medications they did
- Reasons why subjects may have elected to stop using the medication
- Subjects' insights and perceptions about the medication, their experience in the study, educational materials, the website, etc.

A clinical interviewer made a final follow-up telephone call two weeks later. Subjects were instructed to return all unused study medication to the pharmacy. Study participants who became pregnant during the study were instructed to stop using the test drug and immediately inform the investigator. All pregnancies were reported to PEGUS research within 24 hours. Pregnant patients were monitored until the end of pregnancy.

3. Data collection

Follow-up information was collected through telephone interviews scheduled 14, 30, 60, and 90 days after study. Each interview had a 10-day window for completion. During each interview window, at least eight calls were attempted before a subject was declared as "unable to contact" for that interview window. All subjects remained in the database and were called during the next interview window.

The call schedule was managed with computer assisted telephone interviewing (CATI) software. This software randomly scheduled calls to subjects according to established calling rules, kept track of call attempts and outcomes, and allowed callbacks to be scheduled at specific times. The CATI software accommodated all question types including open-ended, single choice, multiple select, and responses with dates and digits. The software guided the trained clinicians through the interview. Most of the interview questions were standardized and were displayed sequentially on the computer screen. Depending on the answer to one question, the next appropriate question would appear. The interviewer entered the subjects' responses directly into an electronic database. For open-ended or multiple selection questions, responses were recorded verbatim; however for questions requiring a yes/no response, the clinical interviewer may have summarized the subjects' response into a *yes* or ***no*** response.

Appendix 10.1 contains a complete list of CATI interview questions. The following list of questions and topics focuses on key communications during the follow-up telephone interviews:

- Was the subject using or did the subject plan to use the orlistat?
- Did the subject intend to start using the medicine? (A callback was set for this date and the subject was told that a follow-up call would be make to see if they started the medicine)
- Had the subject contacted a healthcare professional since enrollment in the study? If so, what was discussed? What was the name of the healthcare professional? No further contact information was obtained.
- Questions about use of the label, understanding the label and use of support materials provided.
- Questions about patterns of orlistat use: number of capsules per day, number of capsules per dose, doses per day, taken with meals? Were there times and reasons that the subject did not use or used a different amount of the medicine?
- Questions about multivitamin use and timing with orlistat.
- Questions about diet and exercise.
- Questions about discomforts, changes in health status (including pregnancy), hospital visits, and new medications or dietary supplements since starting orlistat.
- Questions about weight loss while using orlistat and satisfaction with the medicine.
- Questions about current and future orlistat use: Are you still using the study medicine? What was the last date you used the medicine? Do you plan to use it

again? When do you plan on using it again? (Nurse uses judgment to classify answer as will use again within 3 months of enrollment, after more than 3 months since enrollment, or don't know).

The End-of-Study Questions were asked at the post-treatment telephone interview, which was conducted approximately two weeks after a subject stopped using orlistat. The main objective of this interview was to acquire adverse event data including resolution of reported events or new events that had occurred since the last interview. The following topics and questions were asked at the End of Study telephone interview:

- Questions about whether subjects thought that orlistat was effective in helping them lose weight and whether they would purchase the drug again.
- Questions about whether subjects consulted their doctor regarding a labeled contraindication. If so, what was discussed. If not, then why.
- Many detailed questions about diet followed, reading nutritional labels, reducing fat in diet, target calories, understanding how to calculate calorie and fat information
- Questions about reasons for exercising and typical exercise done.
- Questions about use of the support materials and the website and their usefulness.
- Open-ended solicitation of other comments about the study, the medicine, or general comments.

In response to a FDA request for further information, the sponsor stated that the subject food diary was included as an educational tool in the weight loss program and was not intended for inclusion in data analysis. Therefore the diaries were not collected or reviewed.

Reviewer comment:

1. *The study materials included a food diary and a place to check off when medication was taken. There was no designated place to record taking a multivitamin. Because the sponsor's product and labeling encourage subjects to keep a diary, the diary becomes a more "naturalistic" tool. Consumers should be encouraged to keep a record of multivitamin use, because this might reinforce compliance with this labeled direction. It would have been useful for study subjects to record adverse events and use of a multivitamin in the diary.. Telephone interviews occurred two to four weeks apart and without a written record, subjects' recall may have been biased.*

2. *The ten day window for completing follow-up telephone interviews is large. Given the wide variety of information collected during these interviews, it is difficult to know how the variability in time of data collection compared with the duration of drug use might confound certain comparisons. For example, the incidence of bowel-related adverse events may be different on Day 14 and Day 24 of drug use. The sponsor does not make it*