Table 5.1.1.1 Clinical Studies of Zaleplon			
Protocol No. Start/ Stop Date	**Study Design**	**Study Drug Dose, Route, Duration**	**Enrolled ITT / Safety**
L846240192 4/ 92- 11/ 92	Phase I, double- blind, randomized, single- dose study of memory, psychomotor performance, (part of safety; and tolerability in two groups of healthy men Group 1 received zaleplon 1, 5, 20 mg and Group 2 received zaleplon 3, 10, 20 mg In a separate multiple dose phase, subjects received doses of 10 or 20 mg of zaleplon for seven days	Zal 1 mg, oral, SD Zal 3 mg (3 X 1 mg), oral, SD Zal 5 mg (1 X 5 mg), oral, SD Zal 10 mg (2 X 5 mg), oral, SD Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, SD Zal 40 mg (2 X 5 + 2 X 15 mg mg), oral, SD Doses of zaleplon for single dose- phase Placebo, oral, SD	16/ 16
L846230992 9/ 92- 11/ 92	Phase I, double- blind, randomized, single- dose and multiple- dose study of safety, tolerability in (a part of healthy men L846240192)	Zal 10 mg (2 X 5 mg), oral, QD X 7 days Zal 20 mg (1 X 5 mg + 1 X 15 mg), oral, QD X 7 days Doses of zaleplon for multiple dose- phase Placebo, oral, QD x 7 days	14/ 14
L846/ PK1/ 941002 11/ 94- 11/ 94	Phase I, 2- period crossover, pharmacokinetic/ pharmaco dynamic and safety study in quasi- healthy elderly subjects	Zal 5 mg, oral, SD Zal 10 mg (2 X 5 mg), oral, SD	12/ 11
L846/ ML2/ 951222 3/ 96- Ongoing	Late phase II, open- label, safety and efficacy study in patients with various types of insomnia in the field of psychosomatic medicine	Zal 10 mg (2 X 5 mg), oral, QD X 14 days Zal 15 mg, oral, QD X 14 days Zal 20 mg, (1 X 5 mg + 15 mg), oral, QD X 14 days	83/ 36 completed
L846/ PE2/ 931007 30618 11/ 93- 5/ 94	Early phase II, multicenter, open- label, safety and efficacy study in patients with various types of insomnia in the field of psychiatry	Zal 5 mg, oral, QD X 7 days Zal 10 mg (2 X 5 mg), oral, QD X 7 days Zal 15 mg, oral, QD X 7 days Zal 20 mg, (1 X 5 mg + 1 X 15 mg), oral, QD X 7 days	81/ 79
L846/ PL20/ 941102 12/ 94- Ongoing	Late phase II, open- label, safety and efficacy study in insomnia patients with schizophrenia and affective disorders in the field of psychiatry	Zal 10 mg (2 X 5 mg), oral, QD X 14 days Zal 15 mg, oral, QD X 14 days Zal 20 mg, (1 X 5 mg + 15 mg), oral, QD X 14 days	97/ 86 completed
L846/ PL2D/ 941207 2/ 95- Ongoing	Late phase II, dose- finding, safety and efficacy study in patients with chronic insomnia in the field of psychiatry	Zal 5 mg, oral, QD X 14 days Zal 10 mg (2 X 5 mg), oral, QD X 14 days Zal 20 mg, (1 X 5 mg + 1X 15 mg), oral, QD X 14 days	129/ 88 completed
L846/ PSS/ 940620 30619 10/ 93- 5/ 94	Phase II, open- label, randomized sleep laboratory study of effect of short- term treatment on patients with insomnia	Zal 5 mg, oral, QD X 3 days Zal 10 mg (2 X 5 mg), oral, QD X 3 days	16/ 12
L846/ ME2/ 940426 30617 5/ 94- 12/ 94	Early phase II, multicenter, open- label study to investigate the efficacy, safety, usefulness and dosage of zaleplon (5, 10, 15, or 20 mg) in patients with various types of insomnia in the field of psychosomatic medice	Zal 5 mg, oral, QD X 7 days Zal 10 mg (2 X 5 mg), oral, QD X 7 days Zal 15 mg, oral, QD X 7 days Zal 20 mg, (1 X 5 mg + 1 X 15 mg), oral, QD X 7 days	98/ 90

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Table 5.1.1.2 Patient Drug Exposure in the Zaleplon Development program

Population	Studies Included b	Zaleplon	Comparitors c	Placebo
Phase I/ Clinical Pharmacol. Studies				
Group H - Healthy Volunteers	101,102,103,105,106,107,108,109,111, 112, 113,114,115,116d,117d, 118,119,121,122,123,124,125,126, 127,128, 129,130,131,134,138, 139,140,141,142,143	748e, f	346e	318e
Group I - Special Populations		97 e, f	49e	49e
Hepatically impaired	116			
Renally impaired	117			
Chronic obstructive pulmonary disease (COPD)	120			
Sleep apnea	133			
Group J - Abuse Liability	104, ~~110~~	22 e, f	21e	16e
Group L - All (US, CA, Europe) Phase I		867e, f	416e	383e
Japanese Phase I studies a		37	-	16
Total World Wide Phase I exposure		904	416	399
Phase II/ III Studies				
Group A - Very short- term (1 or 2 day), placebo- controlled, sleep- lab studies	201,202,207,208,209, 210	378e, f	147e	284e
Group B - Short- term (5 or 14 day), parallel- group, placebo- controlled studies	203,205,306 (DB),307, 308 (DB)	1283	142	467
Group C - Long- term (28 day), parallel- group, placebo- controlled studies	204,301,303	786	271	277
Group D - Parallel- group, placebo- controlled studies	203,204,205,301,303, 306(DB), 307,308(DB)	2069	413	744
Group E - Comparator- controlled studies	201,202,203,204,208, 209,301,303,306(DB)	1330e, f	560e	561e
Group F - Extended- treatment, open- label studies	302,304,306(OL), 308(OL), 312	1088f	–	–
Group G - All Phase II and III studies	201,202,203,204,205, 207,208,209,210,301, 302,303,304,306,307, 308,312	2831e, f	560e	1028e
Total Number of Patients/ Subjects in All US, CA, and European Studies		3726e, f	976e	1411e
Japanese Phase II studies a		379	0	0
Total World Exposure		4105	976	1141

a: Table does not list Japanese studies seperately as they were not poolable in any combination for safety analysis

b: Studies are listed by the individual study number in this table and not by the full protocol number, eg, study 0897A1- 312- US/ CA is listed as study 312.

c: In Phase II/ III studies the active comparators included triazolam 0.25 mg, flurazepam 30 mg, zopiclone 7.5 mg, and zolpidem 5 and 10 mg

d: Only the healthy volunteers from studies 116 and 117 are included in Group H.

e: Some patients are counted in more than one treatment group because some studies had cross- over designs.

f: Patients exposed to more than 1 dosage of zaleplon or patients who participated in a double- blind study and its open- label extension are counted only once in this total

Table 5.1.2.1 Demographic Characterisitics of Group D [parallel group, placebo controlled phase II/III studies (see table 5.1.1.2)]							
	Zal <5 mg	Zal 5 mg	Zal 10 mg	Zal 20 mg	All Comp	Placebo	Total
Characteristics	(n = 28)	(n = 609)	(n = 1132)	(n = 300)	(n = 413)	(n = 744)	(n = 3226)
Age (Years)							
Mean	42.4	57.1	50.3	41.1	49.8	52.1	51.0
Standard Deviation	9.6	17.9	17.0	12.5	17.2	17.7	17.5
Range	22 - 59	20 - 90	18 - 92	18 - 67	18 - 85	19 - 95	18 - 95
Age Group, n (%)							
18-64	28 (100)	298 (49)	815 (72)	298 (99)	302 (73)	487 (65)	2228 (69)
>65	–	311 (51)	317 (28)	2 (1)	111 (27)	257 (35)	998 (31)
Sex, n (%)							
Female	16 (57)	375 (62)	689 (61)	184 (61)	234 (57)	451 (61)	1949 (60)
Male	12 (43)	234 (38)	443 (39)	116 (39)	179 (43)	293 (39)	1277 (40)
Ethnic Origin							
Black	–	30 (5)	59 (5)	16 (5)	20 (5)	36 (5)	161 (5)
White	28 (100)	567 (93)	1022 (90)	275 (92)	380 (92)	686 (92)	2958 (92)
Other	–	12 (12)	51 (5)	9 (3)	13 (3)	22 (3)	107 (3)
Type of Insomnia							
Primary Insomnia	28 (100)	174 (29)	670 (59)	171 (57)	179 (43)	357 (48)	1579 (49)
Insomnia-Psychiatric	–	5 (1)	28 (3)	5 (2)	1 (<1)	9 (1)	48 (2)
Nonspecified Insomnia	–	430 (71)	434 (38)	124 (41)	233 (56)	378 (51)	1599 (49)
Duration of Insomnia, Mean (months)	–	135.5	131.8	122.5	140.3	137.5	134.8
Zung Anxiety, Mean	32	33	33	34	33	33	33
Zung Depression, Mean	34	36	35	36	35	35	36

Table 5.1.2.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS: EXTENDED- TREATMENT, OPEN-LABEL STUDIES (GROUP F)	
	All Zaleplon
Characteristics	**(n = 1088)**
Age (Years)	
Mean	57.0
Standard Deviation	16.4
Range	19-95
Age Group, n (%)	
18- 64	597 (55)
< 65	491 (45)
Sex, n (%)	
Female	672 (61.8)
Male	416 (38.2)
Ethnic Origin, n (%)	
Black	48 (4.4)
White	1002 (92.1)
Other	38 (3.5)
Type Of Insomnia, n (%)	
Primary Insomnia	543 (49.9)
Insomnia- Psychiatric	16 (1.5)
Insomnia	529 (48.6)
Duration Of Insomnia (Months)	(n = 316)
Mean	160.4
Zung Anxiety Score	(n = 487)
Mean	32.5
Zung Depression Score	(n = 486)
Mean	35.3

Table 5.1.2.3 Demographic and Baseline Characteristics of Group G (all phase II/III studies excluding Japanese studies).

	All Zaleplon	All Comparators	Placebo	Total
Characteristics	(n = 2831)	(n = 560)	(n = 1028)	(n = 3698)
Age (Years)				
Mean	50.6	47.0	49.7	49.7
Standard Deviation	17.4	16.4	17.4	17.3
Range	18 - 95	18 - 85	18 - 95	18 - 95
Age Group, n (%)				
18-64	1980 (70)	449 (80)	733 (71)	2660 (72)
<65	851 (30)	111 (20)	295 (29)	1038 (28)
Sex, n (%)				
Female	1732 (61.2)	302 (53.9)	600 (58.4)	2232 (60.4)
Male	1099 (38.8)	258 (46.1)	428 (41.6)	1466 (39.6)
Ethnic Origin, n (%)				
Black	191 (6.7)	48 (8.6)	83 (8.1)	248 (6.7)
White	2545 (89.9)	496 (88.6)	916 (89.1)	3331 (90.1)
Other	95 (3.4)	16 (2.9)	29 (2.8)	119 (3.2)
Type Of Insomnia, n (%)				
Primary Insomnia	1320 (46.6)	269 (48.0)	443 (43.1)	1673 (45.2)
Insomnia- Psychiatric	40 (1.4)	1 (0.2)	9 (0.9)	47 (1.3)
Insomnia	1237 (43.7)	233 (41.6)	430 (41.8)	1653 (44.7)
Sleep Maintenance Insomnia	28 (1.0)	29 (5.2)	29 (2.8)	30 (0.8)
Healthy Volunteer	206 (7.3)	28 (5.0)	117 (11.4)	295 (8.0)
Duration Of Insomnia (Months)	(n = 936)	(n = 348)	(n = 398)	(n = 1285)
Mean	136.75	126.74	133.44	133.88
Zung Anxiety Score	(n = 2040)	(n = 413)	(n = 741)	(n = 2925)
Mean	33.0	32.9	33.0	33.0
Zung Depression Score	(n = 2039)	(n = 412)	(n = 741)	(n = 2923)
Mean	35.6	35.2	35.4	35.5

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Table 7.2.1.1 LIST OF INVESTIGATORS Study 301

The investigators, their institutional affiliations, and addresses are listed below. The five- digit number in parentheses is the investigator's study number; the number of patients enrolled by each investigator is shown after the designation "n = ." Four (4) additional investigational sites were initiated, but no patients were enrolled and those investigators are not listed below.

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Table 7.2.1.3 Schedule of assessments for study 301

	Screen	Placebo run in			Double blind treatment phase								Placebo		No dose		
Procedure	-28 to -8	-7	-6 to -2	-1	1	2 to 7	8	9 to 14	15	16 to 21	22	23 to 28	+1	+2 to +3	+4	+5 to +7	Follow up
Medical history	X																
Eligibility	X	X			X												
Zung anxiety/ depression	X																
Psychiatric interview	X																
CNS medication washout	X																
Physical examination	X				X				X								X
Vital signs	X	X			X		X		X		X		X				X
Neurologic assessment	X	X			X				X								X
ECG (12 lead)																	X
Clinical labs	X	X											X				X
Urine drug screen	X	X							X								X
Serum -HCG pregnancy test	X																X
Urine -HCG pregnancy test		X															
Patient daily diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Presleep questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Postsleep questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Profile of Mood States		X			X		X		X		X		X		X		
Tyrer Symptom Checklist				X				X				X	X	X			
Drug compliance check					X		X		X		X		X				X
Single- blind placebo		X	X	X									X	X			
Study drug administration					X	X	X	X	X	X	X	X					
Adverse experiences			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 7.2.1.5 OBSERVED CASES ANALYSIS (301-US) X=Median **time to sleep onset** (minutes)

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	118	69.3	118	45.4	113	43.6	108	40.7	101	45.6
Zaleplon 10 mg	119	62.5	119	40.7	113	36.4	107	35.7	102	35.0
Zaleplon 20 mg	116	61.1	116	35.7	111	31.7	104	30.0	101	30.0
Zolpidem 10 mg	115	60.7	115	45.7	109	46.4	105	44.3	98	34.3
PLACEBO	118	66.4	118	57.5	113	49.3	109	45.0	107	47.1
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem										
Zaleplon 5mg vs Placebo			0.04		0.81		0.07		0.90	
Zaleplon 10 mg vs Placebo			0.002		0.11		0.01		0.08	
Zaleplon 20 mg vs Placebo			<0.001		<0.001		<0.001		<0.001	
Zolpidem 10 mg vs Placebo			0.008		0.50		0.24		0.03	

Table 7.2.1.6 LAST OBSERVATION CARRIED FORWARD ANALYSIS (301-US) X=Median **time to sleep onset** (minutes) ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	118	69.3	118	45.4	118	43.6	118	41.8	118	46.4
Zaleplon 10 mg	119	62.5	119	40.7	119	36.4	119	36.4	119	36.7
Zaleplon 20 mg	116	61.1	116	35.7	116	31.6	116	30.0	116	30.0
Zolpidem 10 mg	115	60.7	115	45.7	115	47.1	115	46.4	115	36.4
PLACEBO	118	66.4	118	57.5	118	51.1	118	48.6	118	48.9
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem										
Zaleplon 5mg vs Placebo			0.44		0.73		0.05		0.72	
Zaleplon 10 mg vs Placebo			0.002		0.07		0.004		0.03	
Zaleplon 20 mg vs Placebo			<0.001		<0.001		<0.001		<0.001	
Zolpidem 10 mg vs Placebo			0.008		0.44		0.21		0.03	

Table 7.2.1.9 OBSERVED CASE ANALYSIS (301-US) X=Median **number of awakenings,** ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	115	2.0	108	1.9	105	1.7	96	1.7	90	1.7
Zaleplon 10 mg	117	1.9	112	1.7	106	1.7	103	1.7	91	1.6
Zaleplon 20 mg	114	2.0	109	1.8	98	1.5	92	1.4	90	1.6
Zolpidem 10 mg	112	2.1	108	1.6	99	1.5	94	1.7	89	1.7
PLACEBO	116	2.1	116	1.7	109	2.0	101	1.9	102	1.7
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem										
Zaleplon 5mg vs Placebo			.89		.11		.78		.77	
Zaleplon 10 mg vs Placebo			.99		.32		.90		.31	
Zaleplon 20 mg vs Placebo			.64		<.001		.02		.23	
Zolpidem 10 mg vs Placebo			.009		<.001		.25		.06	

Table 7.2.1.10 LAST OBSERVATION CARRIED FORWARD ANALYSIS (301-US) X=Median **number of awakenings**, ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	115	2.0	108	1.9	105	1.6	96	1.6	90	1.6
Zaleplon 10 mg	117	1.9	112	1.7	106	1.7	103	1.7	91	1.6
Zaleplon 20 mg	114	2.0	109	1.8	98	1.4	92	1.4	90	1.5
Zolpidem 10 mg	112	2.1	108	1.6	99	1.5	94	1.7	89	1.8
PLACEBO	116	2.1	116	1.7	109	1.9	101	1.9	102	1.7
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem										
Zaleplon 5mg vs Placebo			.89		.17		.70		.31	
Zaleplon 10 mg vs Placebo			.99		.53		.99		.73	
Zaleplon 20 mg vs Placebo			.64		<.001		.01		.10	
Zolpidem 10 mg vs Placebo			.009		<.001		.26		.24	

Table 7.2.2.1 Investigators and Sites for Study 303 EU/CA

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Table 7.2.2.2 Schedule of Events and Assessments for Study 303														
	Initial Screening	Single Blind Placebo		Randomized Treatment Phase								Single Blind Placebo		Follow-up
PROCEDURES	NIGHTS	-7	-6 to -1	1	2 to 7	8	9-14	15	16-21	22	23-28	+1	+2 +3	+7 - +10
RANDOMISATION				X										
MEDICAL HISTORY	X													
ELIGIBILITY	X			Xa										
URINE DRUG SCREEN		Xb						X						X
PHYSICAL EXAMINATION e	X	Xd						Xe						X
VITAL SIGNS c	X	Xd		X a,d		Xd		Xd		Xd		Xd		X
IMPAIRMENT ASSESSMENT e	X	Xd		X a,d		Xd		Xd		Xd		Xd		X
LABORATORY TESTS e	X	Xd,f										Xd		X
PREGNANCY TEST (if applicable)														
Serum beta- HCG	X													X
Urine beta- HCG		Xg												
ROUTINE ECG c	X													X
DRUG ADMINISTRATION		X	X	X	X	X	X	X	X	X	X	X	X	
DRUG COMPLIANCE CHECK				X		X		X		X		X		X
ADVERSE EVENTS g		X	X	X	X	X	X	X	X	X	X	X	X	X
ZUNG A AND D	X													
PATIENT DIARY		X	X	X	X	X	X	X	X	X	X	X	X	X
PRE-SLEEP QUESTIONNAIRE		X	X	X	X	X	X	X	X	X	X	X	X	X
POST-SLEEP QUESTIONNAIRE		X	X	X	X	X	X	X	X	X	X	X	X	X
POMS	X			X		X		X		X		X	X	
TYRER			X				X				X	X		

a: Was assessed before randomisation and initiation of double blind dose administration.

b: During the day in the trial centre, prior to the dose that night (at home). The substances screened for the urine drug screen included amphetamines, cocaine, opiates, benzodiazepines, cannabis, barbiturates, zopiclone. Zolpidem was to be included prior to randomisation only.

c: Procedures should be performed at final visit for early drop- outs.

d: Was assessed/ completed during the day before the period of sleep. Retests could be done as needed..

e: Interim physical examination, aimed at detecting treatment- emergent symptoms - any significant adverse change was noted in the adverse event section of the case report form.

f: Patient with baseline laboratory test results in the placebo run- in phase (Night -7) that violated the inclusion/ exclusion criteria was removed from the study. If blood samples for laboratory tests performed at initial screening were taken within 14 days of Night -7, these could be used as baseline (provided that wash- out of prior CNS medication was complete) and blood samples and the urine beta- HCG test were not needed on the day prior to Night -7).

g: Any patient experiencing a severe, life- threatening or reportable adverse event during the placebo run- in phase (Nights -7 to -1) was excluded from the study.

Table 7.2.2.4 LAST OBSERVATION CARRIED FORWARD ANALYSIS (303-EU/CA) X=Median **time to sleep onset,** ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	113	66	113	42	113	36	113	32	113	33
Zaleplon 10 mg	112	57	112	36	112	32	112	30	112	30
Zaleplon 20 mg	116	55	116	33	116	31	116	28	116	29
Zolpidem 10 mg	115	64	114	45	115	37	115	36	115	36
PLACEBO	118	58	118	50	118	48	118	41	118	39
p-values for zaleplon Dunnett's test Control=placebo ANCOVA p value for zolpidem										
Zaleplon 5mg vs Placebo			.02		.01		.04		.37	
Zaleplon 10 mg vs Placebo			.001		.008		.02		.04	
Zaleplon 20 mg vs Placebo			<.001		<.001		<.001		.004	
Zolpidem 10 mg vs Placebo			.07		.05		.04		.55	

Table 7.2.2.5 OBSERVED CASE ANALYSIS (303-EU/CA) X=Median **time to sleep onset**, ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	113	66	113	42	110	35	102	31	102	31
Zaleplon 10 mg	112	57	112	36	110	32	104	30	99	28
Zaleplon 20 mg	116	55	116	33	113	31	108	28	103	27
Zolpidem 10 mg	115	64	114	45	110	37	105	34	100	36
PLACEBO	118	58	118	50	115	47	113	41	107	36
p-values for zaleplon Dunnett's test Control=placebo ANCOVA p value for zolpidem										
Zaleplon 5mg vs Placebo			.01		.006		.01		.22	
Zaleplon 10 mg vs Placebo			.001		.003		.01		.03	
Zaleplon 20 mg vs Placebo			<.001		<.001		<.001		.006	
Zolpidem 10 mg vs Placebo			.05		.006		.04		.54	

Table 7.2.2.6 LAST OBSERVATION CARRIED FORWARD ANALYSIS (303-EU/CA) X=Median **total time slept**, ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	113	313	113	351	113	356	113	370	113	369
Zaleplon 10 mg	112	331	112	370	112	364	112	370	112	371
Zaleplon 20 mg	116	328	116	370	116	369	116	369	116	379
Zolpidem 10 mg	115	330	115	379	115	385	115	381	115	395
PLACEBO	118	334	118	351	118	356	118	360	118	356
p-values for zaleplon Dunnett's test Control=placebo ANCOVA p value for zolpidem										
Zaleplon 5mg vs Placebo			.92		.28		.26		.47	
Zaleplon 10 mg vs Placebo			.11		.24		.43		.10	
Zaleplon 20 mg vs Placebo			.04		.01		.07		.02	
Zolpidem 10 mg vs Placebo			<.001		<.001		<.001		<.001	

Table 7.2.2.7 OBSERVED CASE ANALYSIS (303-EU/CA) X=Median **total time slept**, ITT patients

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	113	313	113	351	110	359	102	384	102	372
Zaleplon 10 mg	112	331	112	370	109	368	103	371	99	384
Zaleplon 20 mg	116	328	116	370	113	369	108	374	103	385
Zolpidem 10 mg	115	330	114	379	110	387	105	385	100	400
PLACEBO	118	334	118	351	115	359	113	365	107	377
p-values for zaleplon Dunnett's test Control=placebo ANCOVA p value for zolpidem										
Zaleplon 5mg vs Placebo			.84		.36		.08		.28	
Zaleplon 10 mg vs Placebo			.13		.52		.77		.26	
Zaleplon 20 mg vs Placebo			.03		.03		.09		.04	
Zolpidem 10 mg vs Placebo			<.001		<.001		<.001		<.001	

Table 7.2.2.8 OBSERVED CASE ANALYSIS (303-EU/CA) X=Median **number of awakenings**, ITT patients

Treatment Groups	Treatment Week									
	Baseline*		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	112	2	104	2	100	2	91	2	87	2
Zaleplon 10 mg	111	2	101	2	100	2	95	2	82	2
Zaleplon 20 mg	114	2	103	2	101	2	92	1	86	1
Zolpidem 10 mg	114	2	100	2	99	2	95	2	84	2
PLACEBO	118	2	112	2	113	2	103	2	96	2
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem										
Zaleplon 5mg vs Placebo			.83		.99		.79		.75	
Zaleplon 10 mg vs Placebo			.99		.72		.70		.25	
Zaleplon 20 mg vs Placebo			.16		.35		.38		.26	
Zolpidem 10 mg vs Placebo			.11		.08		.49		.98	

Table 7.2.2.9 LAST OBSERVATION CARRIED FORWARD ANALYSIS (303-EU/CA) X=Median **number of awakenings**, ITT patients

Treatment Groups	Treatment Week									
	Baseline*		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	X	n	X	n	X	n	X
Zaleplon 5 mg	112	2	104	2	112	2	112	2	112	2
Zaleplon 10 mg	111	2	101	2	111	2	111	2	111	2
Zaleplon 20 mg	114	2	103	2	114	2	114	1	114	1
Zolpidem 10 mg	114	2	100	2	114	2	114	2	114	2
PLACEBO	118	2	112	2	118	2	118	2	118	2
p-values for zaleplon Dunnett's test Control=placebo 2 sided pair-wise p value for zolpidem										
Zaleplon 5mg vs Placebo			.83		.91		1.0		.86	
Zaleplon 10 mg vs Placebo			.99		.73		.46		.63	
Zaleplon 20 mg vs Placebo			.16		.59		.78		.19	
Zolpidem 10 mg vs Placebo			.11		.16		.71		.69	

Table 7.2.3.1 Listing of investigators and sites in study 306	
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Table 7.2.3.2 Schedule of events and assessments for study 306

	Initial Screening	Single- Blind Placebo Run- In		Randomized Double- Blind Treatment				Posttreatment Placebo Run- Out		Follow-up Re-evaluation
Dose Night:	-28 to -8	-7	-6 to -1	1	2 to 7	8	9 to 14	+1	+2 to +7	+8 thru +11
Procedure Study Night:	-28 to -8	-7	-6 to -1	1	2 to 7	8	9 to 14	15	16 to 21	22
Medical history	X									
Eligibility	X	X		X						
Zung A and Zung D self- rating scales	X									
Signed informed consent	X									
Prior CNS medication washout	X			X						
Physical examination	X									X
Interim physical exam		X		X		X		X		
Vital signs	X	X		X		X		X		X
Neurologic assessment	X									X
Interim neurologic assessment		X		X		X		X		
Chest X- ray (if needed)	X									
ECG (12- lead)	X									X
Clinical labs	X	X		X				X		X
Urine drug screen	X	X								
Patient daily diary		X	X	X	X	X	X	X	X	
Pre- sleep questionnaire		X	X	X	X	X	X	X	X	
Post- sleep questionnaire		X	X	X	X	X	X	X	X	
Compliance check (drug, diaries, and questionnaires)				X		X		X		X
Single- blind placebo administration		X						X	X	
Double- blind dose administration				X	X	X	X			
Study events		X	X	X	X	X	X	X	X	X

Table 7.2.3.5 OBSERVED CASE ANALYSIS (306-EU) X=Median time to sleep onset (minutes) ITT patients

Treatment Groups	Treatment Week					
	Baseline		Wk 1		Wk 2	
	n	X	n	X	n	X
Zaleplon 5 mg	165	76.7	165	52.5	161	38.8
Zaleplon 10 mg	164	64.8	164	31.3	163	31.0
Zolpidem 5 mg	111	59.2	111	42.0	110	42.2
PLACEBO	107	68.6	105	47.5	101	55.7
p-values for zaleplon Dunnett's test Control=placebo 2-tail pair wise comparison for zolpidem						
Zaleplon 5 mg vs Placebo			.82		<.001	
Zaleplon 10 mg vs Placebo			<.001		<.001	
Zolpidem 5 mg vs placebo			<.001		<.001	

Table 7.2.3.6 OBSERVED CASE ANALYSIS (306-EU) X=Median total time slept (minutes) for ITT patients

Treatment Groups	Treatment Week					
	Baseline		Wk 1		Wk 2	
	n	X	n	X	n	X
Zaleplon 5 mg	166	288	166	322	162	326
Zaleplon 10 mg	165	313	165	345	163	326
Zolpidem 5 mg	111	306	111	360	110	350
PLACEBO	107	296	106	318	101	326
p-values for zaleplon Dunnett's test Control=placebo 2-tail pair wise comparison for zolpidem						
Zaleplon 5 mg vs Placebo			.73		.96	
Zaleplon 10 mg vs Placebo			.02		.55	
Zolpidem 5 mg vs placebo			<.001		.01	

Table 7.2.3.7 OBSERVED CASE ANALYSIS (306-EU) X=Median number of awakenings for ITT patients

Treatment Groups	Treatment Week					
	Baseline		Wk 1		Wk 2	
	n	X	n	X	n	X
Zaleplon 5 mg	164	2.3	158	1.8	159	1.9
Zaleplon 10 mg	163	2.2	159	1.8	158	1.9
Zolpidem 5 mg	111	2.2	111	1.7	107	1.7
PLACEBO	107	2.2	107	2.0	100	1.9
p-values for zaleplon Dunnett's test Control=placebo 2-tail pair wise comparison for zolpidem						
Zaleplon 5 mg vs Placebo			.999		.999	
Zaleplon 10 mg vs Placebo			.90		.83	
Zolpidem 5 mg vs placebo			.006		.02	

Table 7.2.4.1 List of Investigators and Sites for Study 307	
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Table 7.2.4.1 List of Investigators and Sites for Study 307	
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Table 7.2.4.3 OBSERVED CASE ANALYSIS (307-US/CA) X=Median time to sleep onset (minutes) ITT patients

Treatment Groups	Treatment Week					
	Baseline		Wk 1		Wk 2	
	n	X	n	X	n	X
Zaleplon 10 mg	242 (484)	63.8 (64.1)	484	40.7	232	35.0
Zaleplon 20 mg	242	64.6	0		229	34.3
PLACEBO	153	68.6	153	49.3	145	50.0
p-values for zaleplon Dunnett's test Control=placebo						
Zaleplon 10 mg vs Placebo			<.001		<.001	
Zaleplon 20 mg vs Placebo					<.001	

Numbers in () indicate that all patients during week one took zaleplon 10 mg and were analysed as such.

Table 7.2.4.4 OBSERVED CASE ANALYSIS (307-US/CA) X=Median total time slept (minutes) ITT patients

Treatment Groups	Treatment Week					
	Baseline		Wk 1		Wk 2	
	n	X	n	X	n	X
Zaleplon 10 mg	242 (484)	321.4 (328.4)	484	358.0	232	362.5
Zaleplon 20 mg	242	334.3	0		229	366.4
PLACEBO	153	337.9	153	351.4	145	355.7
p-values for zaleplon Dunnett's test Control=placebo						
Zaleplon 10 mg vs Placebo			.006		.009	
Zaleplon 20 mg vs Placebo					.001	

Numbers in () indicate that all patients during week one took zaleplon 10 mg and were analysed as such.

Table 7.2.4.5 OBSERVED CASE ANALYSIS (307-US/CA) X=Median number of awakenings, ITT patients						
Treatment Groups	Treatment Week					
	Baseline		Wk 1		Wk 2	
	n	X	n	X	n	X
Zaleplon 10 mg	240 (479)	2.1 (2.2)	461	1.8	217	1.6
Zaleplon 20 mg	239	2.2	0		206	1.8
PLACEBO	152	2.1	147	1.8	137	1.7
p-values for zaleplon Dunnett's test Control=placebo						
Zaleplon 10 mg vs Placebo			.44		.99	
Zaleplon 20 mg vs Placebo					.99	

Numbers in () indicate that all patients during week one took zaleplon 10 mg and were analysed as such.