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APPLICATION NUMBER:

022370Orig1s000

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

NDA:	22-370
Name of drug:	Tramadol ER 100, 200 and 300 mg
Indication:	Management of moderate to moderately severe chronic pain in adults
Applicant:	Cipher Pharmaceuticals Limited
Dates:	Received April 14, 2008
Review priority:	Standard
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Joan Buenconsejo, Ph.D.
Concurring reviewers:	Dionne Price, Ph.D.
	Thomas Permutt, Ph.D.
Medical division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical team:	Keith Burkhart, M.D.
	Mwango Kashoki, M.D.
Project manager:	Kathleen Davies

Keywords: NDA review

Cipher Pharmaceuticals Inc has submitted a new NDA (N 22-370) for their extended-release tramadol capsule that references their previous NDA (b) (4). As a background, the Division sent the Applicant an approvable letter for Cip-Tramadol ER Capsules, NDA (b) (4) on May 2, 2007. The original submission comprised a 505(b) (2) NDA, and the reference labeled drug (RLD) was Ultram (immediate-release tramadol tablets). (b) (4)

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(b) (4), the Applicant has opted to conduct two bioequivalence studies against an alternate approved RLD, Ultram ER (extended-release tramadol) tablets. The Applicant considers their product a "pharmaceutical alternative" dosage form to Ultram ER, and is citing the Agency's previous determination of safety and efficacy of Ultram ER as support of the safety and efficacy of the Cip-Tramadol ER capsule. Refer to the review by Dr. Lei Zhang (Clinical Pharmacologist), for details regarding the interactions between the Division and the Applicant over the NDA amendment, as well as FDA's assessment of these new clinical pharmacology studies. Of note, Dr. Zhang did not find any issues requiring statistical evaluation. Therefore, there is no statistical review for this new application.

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Joan Buenconsejo
12/18/2008 01:59:26 PM
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Thomas Permutt
12/18/2008 02:14:33 PM
BIOMETRICS
I concur. Dionne Price, team leader, who would otherwise be asked to concur, is on leave.

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Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	(b) (4)
Name of drug:	Tramadol ER 100, 200 and 300 mg
Indication:	Management of moderate to moderately severe chronic pain in adults
Applicant:	Cipher Pharmaceuticals Limited
Dates:	Received 07/05/06; PDUFA 05/03/07
Review priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical reviewer:	Joan Buenconsejo, Ph.D.
Concurring reviewers:	Dionne Price, Ph.D.
	Thomas Permutt, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical team:	Keith Burkhart, M.D.
	Mwango Kashoki, M.D.
Project manager:	Kathleen Davies

Keywords: NDA review, clinical studies, missing data, multiple comparisons

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

After careful evaluation of the submission, I have not found sufficient evidence to support the use of CIP-Tramadol ER 100 mg, CIP-Tramadol ER 200 mg, or CIP-Tramadol ER 300 mg for the desired indication. (b) (4)

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The Applicant, Cipher Pharmaceuticals Limited, seeks to market CIP-Tramadol extended-release (ER) capsules for the management of moderate to moderately severe chronic pain in adults. The development plan for CIP-Tramadol ER was previously discussed during several meetings (February 22, 2001 through June 14, 2006) between the Applicant and the Division. (b) (4)

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1.3 STATISTICAL ISSUES AND FINDINGS

During my review of the submission, I identified several issues that warranted further consideration. (b) (4)

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2 INTRODUCTION

2.1 OVERVIEW

Ultram (immediate release tramadol) was introduced in 1995 in the United States and is currently marketed in a 50 mg oral tablet. The Applicant, Cipher Pharmaceuticals Limited, seeks to market CIP-Tramadol extended release (ER) capsules for the management of moderate to moderately severe chronic pain in adults. CIP-Tramadol ER incorporates a combination of immediate and extended-release drug delivery properties, which according to the Applicant, may provide rapid and prolonged analgesia. The capsules are multi-particulate dosage forms comprised of extended release beads together with an immediate release component.

The development plan for CIP-Tramadol was introduced to the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products under IND (b) (4). Following the reorganization of the therapeutic areas in the Center for Drug Evaluation and Research, CIP-Tramadol fell under the purview of the Division of Anesthesia, Analgesia, and Rheumatology Products. The key milestones in the clinical development program are highlighted in Dr. Burkhart's review. Statistical issues were discussed during several of the meetings and key issues are summarized below:

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The submission includes (b) (4) one long-term safety study, Study 03.

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Information on safety was also obtained in study Study 05 and in the open-label, uncontrolled long-term study (Study 03) conducted in the United States, Canada and Mexico.

2.2 DATA SOURCES

This statistical review is based on data submitted in Studies 01, 02 and 04.

The electronic datasets for this NDA can be found at:
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3.2 EVALUATION OF SAFETY

Dr. Burkhart reviewed the safety of CIP-Tramadol ER in detail. The reader is referred to Dr. Burkhart's review for information regarding the adverse event profile

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6 LABELING

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7 APPENDIX

(b) (4)

Appendix 7.2: Patient Demographics and Baseline Characteristics – Safety Population

Table 7.2.1: Patient Demographics and Baseline Characteristics – Study TRAMCT02.01

	Tramadol ER 100 mg N=106	Tramadol ER 200 mg N=104	Tramadol ER 300 mg N=112	Placebo N=108	Total N=430
Gender					
Male	38 (35.8%)	42 (40.4%)	35 (31.3%)	47 (43.5%)	162 (37.7%)
Female	68 (64.2%)	62 (59.6%)	77 (68.8%)	61 (56.5%)	268 (62.3%)
Ethnic Group					
Caucasian	80 (75.5%)	75 (72.1%)	80 (71.4%)	78 (72.2%)	313 (72.8%)
Oriental	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.2%)
Hispanic	18 (17.0%)	21 (20.2%)	20 (17.9%)	20 (18.5%)	79 (18.4%)
African	6 (5.7%)	7 (6.7%)	9 (8.0%)	10 (9.3%)	32 (7.4%)
Asian	2 (1.9%)	1 (1.0%)	1 (0.9%)	0 (0.0%)	4 (0.9%)
Other	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.2%)
Age (Years)					
Mean ± SD	62.7 ± 10.18	64.3 ± 9.84	61.9 ± 9.58	62.6 ± 9.93	62.9 ± 9.89
Range	45.0 – 85.0	45.0 – 84.0	45.0 – 83.0	45.0 – 84.0	45.0 – 85.0
Weight (kg)					
Mean ±	86.58 ±	87.10 ±	89.84 ±	86.90 ±	87.63 ±
SD	19.618	21.896	20.939	21.704	21.024
Range	49.9 – 181.4	52.0 – 165.6	47.0 – 158.8	49.4 – 181.9	47.0 – 181.9
Height (cm)					
Mean ±	165.44 ±	166.62 ±	164.73 ±	166.44 ±	165.79 ±
SD	10.521	10.320	10.624	11.583	10.767
Range	142.0 – 189.0	145.0 – 193.0	138.0 – 193.0	137.0 – 190.5	137.0 – 193.0
BMI (kg/m^2)					
Mean ±	31.66 ±	31.34 ±	33.05 ±	31.20 ±	31.83 ±
SD	6.586	7.293	6.934	6.466	6.841
Range	18.2 – 57.4	20.6 – 58.9	22.4 – 58.2	20.0 – 56.7	18.2 – 58.9
Study Joint					
Hip	32 (30.2%)	28 (26.9%)	32 (28.6%)	33 (30.5%)	125 (29.1%)
Knee	74 (69.9%)	76 (73.1%)	80 (71.5%)	75 (69.4%)	305 (70.9%)

Patient population base: Safety: All randomized patients who received at least one dose of study drug.
SD: Standard deviation.
Source: Table 14.1.3

Source: Study Report (02 01) Module 5 Vol 48, page 73

Table 7.2.2: Patient Demographics and Baseline Characteristics – Study TRAMCT02.02

	Tramadol ER 100 mg N=110	Tramadol ER 200 mg N=113	Tramadol ER 300 mg N=110	Placebo N=112	Total N=445
Gender					
Male	32 (29.1%)	24 (21.2%)	36 (32.7%)	30 (26.8%)	122 (27.4%)
Female	78 (70.9%)	89 (78.8%)	74 (67.3%)	82 (73.2%)	323 (72.6%)
Ethnic Group					
Caucasian	101 (91.8%)	101 (89.4%)	101 (91.8%)	102 (91.1%)	405 (91.0%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	9 (8.2%)	10 (8.8%)	6 (5.5%)	9 (8.0%)	34 (7.6%)
African	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	2 (0.4%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	2 (1.8%)	2 (1.8%)	0 (0.0%)	4 (0.9%)
Age (Years)					
Mean ± SD	65.5 ± 9.62	64.2 ± 10.04	67.6 ± 9.41	65.6 ± 9.85	65.7 ± 9.78
Range	45.0 – 88.0	42.0 – 87.0	46.0 – 84.0	45.0 – 89.0	42.0 – 89.0
Weight (kg)					
Mean ±	83.66 ±	82.13 ±	81.42 ±	79.97±	81.79 ±
SD	20.839	17.246	17.984	20.667	19.225
Range	52.2 – 176.9	51.0 – 157.0	51.0 – 137.9	42.6 – 138.0	42.6 – 176.9
Height (cm)					
Mean ±	162.40 ±	161.93 ±	163.10 ±	162.03 ±	162.36 ±
SD	9.854	9.919	10.871	10.591	10.291
Range	146.0 – 191.8	139.7 – 195.6	143.0 – 190.5	140.0 – 188.0	139.7 – 195.6
BMI (kg/m^2)					
Mean ±	31.60 ±	31.42 ±	30.49 ±	30.48 ±	31.00 ±
SD	6.834	6.702	5.421	6.958	6.507
Range	20.1 – 54.0	21.4 – 63.7	20.7 – 46.2	13.0 – 54.4	13.0 – 63.7
Study Joint					
Hip	38 (34.5%)	33 (29.2%)	31 (28.2%)	35 (31.3%)	137 (30.8%)
Knee	72 (65.5%)	80 (70.8%)	79 (71.8%)	77 (68.7%)	308 (69.2%)

Patient population base: Safety: All randomized patients who received at least one dose of study drug.
SD: Standard deviation.
Source: Table 14.1.3
Source: Study Report (02 02) Module 5 Vol 67, page 72

Table 7.2.3: Patient Demographics and Baseline Characteristics – Study TRAMCT02.04 (Primary Analysis Set)

	Tramadol ER 300 mg N=431	Placebo N=140	Total N=571
Gender			
Male	175 (40.6%)	69 (49.3%)	244 (42.7%)
Female	256 (59.4%)	71 (50.7%)	327 (57.3%)
Ethnic Group			
Caucasian	331 (76.8%)	111 (79.3%)	442 (77.4%)
Oriental	4 (0.9%)	0 (0.0%)	4 (0.7%)
Hispanic	29 (6.7%)	6 (4.3%)	35 (6.1%)
American Indian/Alaskan Native	1 (0.2%)	0 (0.0%)	1 (0.2%)
African	55 (12.8%)	19 (13.6%)	74 (13.0%)
Asian	4 (0.9%)	1 (0.7%)	5 (0.9%)
Other	7 (1.6%)	3 (2.1%)	10 (1.8%)
Age (Years)			
Mean ± SD	62.3 ± 9.33	62.8 ± 9.93	62.4 ± 9.48
Range	41 – 86	44 – 90	41 – 90
Weight (kg)			
Mean ± SD	91.94 ± 21.156	91.80 ± 21.356	91.90 ± 21.187
Range	51.7 – 170.1	47.6 – 158.8	47.6 – 170.1
Height (cm)			
Mean ± SD	168.13 ± 10.360	169.57 ± 9.979	168.49 ± 10.277
Range	129.5 – 198.1	147.3 – 193.0	129.5 – 198.1
BMI (kg/m^2)			
Mean ± SD	32.58 ± 7.345	31.89 ± 6.956	32.41 ± 7.251
Range	20.0 – 66.4	19.7 – 54.4	19.7 – 66.4
Study Joint			
Hip	104 (24.1%)	39 (27.9%)	143 (25.0%)
Knee	327 (75.9%)	101 (72.1%)	428 (75.0%)

Patient population base: Safety Population from which the PAS was drawn: The subset of the first 581 patients randomized into the study who received at least one dose of study drug
SD: Standard deviation.
Source: Table 14.1.3P

Source: Study Report (02 04) Module 5 Vol 111, page 93

Table 7.2.4: Patient Demographics and Baseline Characteristics – Study TRAMCT02.04 (All patients who received at least one dose of study medication)

	Tramadol ER 300 mg N=627	Placebo N=210	Total N=837
Gender			
Male	253 (40.4%)	102 (48.6%)	355 (42.4%)
Female	374 (59.6%)	108 (51.4%)	482 (57.6%)
Ethnic Group			
Caucasian	458 (73.0%)	155 (73.8%)	613 (73.2%)
Oriental	5 (0.8%)	1 (0.5%)	6 (0.7%)
Hispanic	50 (8.0%)	13 (6.2%)	63 (7.5%)
American Indian/Alaskan Native	2 (0.3%)	0 (0.0%)	2 (0.2%)
African	93 (14.8%)	34 (16.2%)	127 (15.2%)
Asian	8 (1.3%)	1 (0.5%)	9 (1.1%)
Other	11 (1.8%)	6 (2.9%)	17 (2.0%)
Age (Years)			
Mean ± SD	62.0 ± 9.31	61.9 ± 9.84	62.0 ± 9.44
Range	41 – 86	44 – 90	41 – 90
Weight (kg)			
Mean ± SD	92.17 ± 21.524	92.45 ± 22.353	92.24 ± 21.721
Range	51.7 – 170.1	47.6 – 179.6	47.6 – 179.6
Height (cm)			
Mean ± SD	167.90 ± 10.324	168.85 ± 10.200	168.13 ± 10.295
Range	129.5 – 201.9	137.2 – 193.0	129.5 – 201.9
BMI (kg/m^2)			
Mean ± SD	32.72 ± 7.287	32.30 ± 7.440	32.61 ± 7.323
Range	18.8 – 66.4	19.7 – 67.6	18.8 – 67.6
Study Joint			
Hip	158 (25.2%)	56 (26.7%)	214 (25.6%)
Knee	469 (74.8%)	154 (73.3%)	623 (74.4%)

Patient population base: Safety Population: All patients randomized into the study who received at least one dose of study drug
SD: Standard deviation.
Source: Table 14.1.3F

Source: Study Report (02 04) Module 5 Vol 111, page 95

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/s/

Joan Buenconsejo
3/22/2007 03:59:53 PM
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Dionne Price
3/22/2007 04:06:55 PM
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Thomas Permutt
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