CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA 21-260 Stamp Date: 8/2/01

Trade Name: [redacted] Extended-Release Capsules, 30 mg, 60 mg, 90 mg & 120 mg

Active Ingredient: Morphine Sulfate

Sponsor: Elan Pharmaceutical Research Corp.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Response to Approvable Letter

Background

[redacted] (morphine sulfate) was deemed approvable for marketing in the US on 3/30/01 for use in patients requiring repeated treatment with an opioid analgesic.

Among the issues raised by the Agency in the approvable letter dated 3/30/01, the sponsor was requested to provide data to support the *in vitro* stability of pellets mixed with applesauce and left standing for a period of 30 min.

The sponsor responded to Agency's request by submitting a comparison of the dissolution profiles of morphine sulfate pellets over a 30 min duration. The current review will exclusively address findings of the comparative dissolution testing study.

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Dissolution profiles were obtained for [redacted] pellets mixed with applesauce and allowed to stand for periods of 10, 20 and 30 min (n = 6 per time point). The sample time points used included 1, 3, 6, 12 and 24 hours. Statistical comparsions based on f_2 values were carried out on the profile of morphine sulfate ER pellets and the profiles of morphine sulfate ER pellets mixed with applesauce and transferred to the dissolution vessel. For dissolution curves to be considered similar, f_2 values should be greater than 50.

Table 1. Statistical comparison based on f_2 values

Group of data compared	f2 statistic	No. of time points used (according to 85% criteria)
Stand time 10 minutes vs. 0 minutes	85.79	5
Stand time 20 minutes vs. 0 minutes	72.67	5
Stand time 30 minutes vs. 0 minutes	85.70	5
Stand time 0 minutes vs. without applesauce	52.05	5
Stand time 10 minutes vs. without applesauce	50.59	5
Stand time 20 minutes vs. without applesauce	60.82	5
Stand time 30 minutes vs. without applesauce	55.91	5

Reviewer's Recommendations

The current submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, the sponsor's response is found to be acceptable. The PHARMACOKINETICS subsection of the labeling needs to be revised as follows:

"**Food Effects:** When a 60 mg dose of ——— was administered immediately following a high fat meal, peak morphine concentrations and AUC values were similar to those observed when the dose of ——— was administered in a fasting state, although achievement of initial concentrations were delayed by approximately 1 hour. ——— Therefore, ———can be administered without regard to food. When the contents of a ——— were administered by sprinkling on applesauce, the rate and extent of morphine absorption were found to be bioequivalent to the same dose when administered as an intact capsule.[23] ———

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/s/

Suliman Alfayoumi
10/17/01 02:44:35 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
10/17/01 03:06:15 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-260 **Submission Date:** May 25, 2000

Drug Name, Dose and Formulation:

(morphine sulfate) Extend Release Capsules 30, 60, 90 and 120 mg

Sponsor: Elan Pharmaceutical Research Corporation

Type of Submission: Original NDA **Reviewer:** Shinja R. Kim, Ph.D.

SYNOPSIS:

Morphine is currently available as immediate release or extended release formulations (the majority formulations are administered twice daily). Kadian®, the only once-a-day morphine product in the US, is characterized by a much slower release of morphine than from twice-a-day extended formulation. Elan Pharmaceutical Technologies has developed an extended release formulation of morphine sulphate, ™ designed for once-daily dosing. It appears that onset of delivery of morphine is rapid while providing 24-hour control.

Nine pharmacokinetic/bioavailability studies were submitted under Item 6 of the NDA. The following were investigated in these studies: food effect, administration of intact capsule *vs.* sprinkle (opened capsule), dose proportionality, steady state PK in patients and healthy volunteers, bridging bioequivalence (BE) study, PK-PD and In Vitro-In Vivo Correlation (IVIVC) study.

The overall results from these studies are summarized as follows: (1) The (initial) peak concentration, following single dose of 60 mg capsule across the studies in healthy volunteers, was achieved approximately in 30 minutes in majority of subjects, and their average plasma concentration of morphine ranged 3-6 ng/ml. (2) Food caused no effect on C_{max} and $AUC_{0\text{-}36h}$. However, $AUC_{0\text{-}36h}$ is under estimation of the extent of exposure ($AUC_{0\text{-}36h}$ was approximately 50% of AUC_{∞}). (3) The rate and extent of morphine absorption were found to be BE between capsule intact *vs.* sprinkle (on applesauce) administration. (4) It appeared that C_{max} was increased approximately dose proportionally in the range of 30 to 120 mg following single dose in healthy volunteers. ($AUC_{0\text{-}36h}$ was also dose proportional but $AUC_{0\text{-}\infty}$ was not available). However, it appeared that dose-proportionality was not demonstrated based on $C_{max,\,ss}$ or AUC_{ss} in patients whose dose range was 60-840 mg/day. (5) (QD) was BE with oral morphine solution (q4h/day) or MS Contin® (Bid) at steady state. Steady state was achieved by day 4-5 in majority of patients or healthy volunteers. (6) manufactured in Athlone, Ireland facility to batches manufactured in Gainesville, U.S.A. was BE. (7) Population estimates (and %CV of inter-individual variance) for morphine CL/F and V/F were 278 L/hr (37%CV) and 841 L (85%CV), respectively. Individual CL/F estimates increased with body weight at a rate of 2.33 L/hr/kg, with the typical value centered at a median weight of 84 kg. Visual Analog Scale (VAS) scores and Time-to-rescue were used as the end points to investigate PK-PD relationship. The PK-PD relationship using VAS appeared to be demonstrated, however, the PD parameter value, EC_{50}, was much higher than observed concentrations in patients (e.g., EC_{50} = 1110 ng/ml, maximum observed = 550 ng/ml for M6G). Therefore, it is more appropriate to state that "there was a tendency that as VAS decreases as morphine dose increases", rather than the sponsor's claim of "significant concentration-response relationship was found". The relationship between "Time-to-rescue" and concentrations was not established. (8) IVIVC was not demonstrated, therefore, the model would not be used for setting dissolution specifications and biowaivers.

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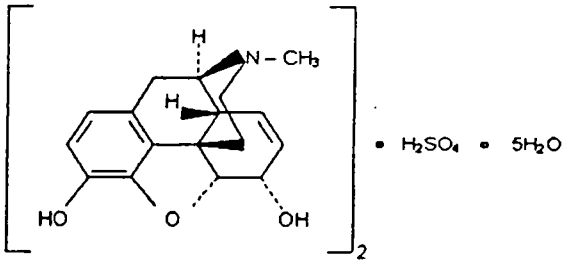
BACKGROUND:

——— (morphine sulfate) ———: Extended Release ——— Capsules 30, 60, 90, and 120 mg contain both immediate release and extended release beads of morphine sulfate for oral administration. Chemically, morphine sulfate is 7,8-didehydro-4,5 alpha-epoxy-17-methyl-morphinan-3,6 alpha-diol sulfate (2:1) (salt) pentahydrate with a molecular weight of 758. Morphine sulfate is soluble in water and slightly soluble in alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pKa is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). The structure is shown below:



The sponsor stated ——— Capsules are indicated for the relief of moderate to severe pain and are intended for use in patients who require repeated dosing with opioid analgesics over periods of more than a few days. ——— capsules are to be administered on a once-a-day schedule.

Morphine is considered to be an intermediate to high clearance drug subject to extensive first pass metabolism, with oral bioavailability of 25-50%, presystemic metabolism of 50-66% and a plasma half-life of approximately 3 hours. Main metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). While M3G has been shown to possess little or no analgesic effect, the minor metabolite M6G is active. There is also some evidence of enterohepatic recycling of morphine and its metabolites.

SUMMARY

1. What are the characteristics of the to-be-marketed Morphine sulfate Controlled Release formulation?

Elan Pharmaceutical Technologies has developed a morphine sulphate formulation designed for once daily dose administration. The sponsor stated that this formulation was designed to give a [redacted] of action followed by extended release of the drug (90/10 ratio of ER/IR), maintaining therapeutic plasma concentrations over the dosing interval. The extended release component of this formulation was designed using [redacted] of the various excipients, and prepared by the application of [redacted] technology. This technology is based upon [redacted] (i.e., [redacted]

The different strengths differs only in the fill weight of the capsule, and drug product composition is shown in Table 1.

The mechanism of drug release from the extended release portion of the formulation is as follows: [redacted] The actual release rate is governed by the quantity of rate controlling polymer coated to the multiparticulates.

Table 1

Component	Composition (mg/capsules)			
	30 mg	60 mg	90 mg	120 mg
Morphine sulfate USP	30	60	90	120
Sugar spheres NF	[redacted]			
Fumaric acid NF				
Talc USP				
Sodium lauryl sulfate NF				
Povidone USP				
[redacted]				
[redacted]				
[redacted]				
Gelatine capsule				

2. Does [redacted] plasma concentrations-time profile support the sponsor's claim of [redacted]?

Shape of [redacted] Curve (Studies 0596008, 0596009, 0698002, and 0299001): The mean plasma profile of morphine following single dose administration of [redacted] (under fasting conditions) across the studies showed a rapid increase in plasma concentrations reaching (initial) peak concentrations in approximately 30 minutes (in majority subjects). There appeared to be a slow decline in concentrations, between 2 and 10 hours, followed by a secondary rise in concentrations at

around 12 - 24 hours after drug administration. The average plasma concentration of morphine following 60-mg single dose of [redacted] ranged approximately from 3 to 6 ng/ml. The t_{max} of morphine from [redacted] was more variable as compared to the oral solution (q4h x 6) or to MS Contin (twice daily tablets). The sponsor explained that the release profile of morphine from [redacted] has lower fluctuation in concentrations compared to the other formulations and therefore any small increase in plasma concentration could be considered as a peak concentration. The mean PK parameter values are shown in Table 2 (for morphine) were based on single dose administration of [redacted]® 60 mg.

Table 2: Summary of PK morphine parameters following 60-mg single-dose

Parameter	[redacted] 60 mg
$AUC_{0-\infty}$ (ng/mL•h)[a]	261.9 ± 81.4
C_{max} (ng/mL)[b]	7.2 ± 3.3
t_{max} (h)[b]	11.1 ± 7.6
$t_{1/2}$ (h)[a]	21.8 ± 9.3

[a] Based on 0698002 and 0299001 studies
[b] Based on 0596008, 0596009, 0698002 and 0299001 studies

Morphine metabolite ratios (Study 0596008, 0596009, 0698002, 0299001 and TRGO04-01): The sponsor reported that the plasma concentrations were approximately 40 times greater for M3G and 5 fold greater for M6G compared to morphine, by comparing the mean AUC ratios of M3G and M6G to morphine, following single dose administration of 60 mg [redacted] to healthy volunteers (inaccurate; ratio should be calculated from the same subject and then averaged across the subjects). The plasma concentrations were 54 times greater for M3G and 9-fold greater for M6G compared to morphine following steady state administration to patients with moderate to severe chronic pain.

3. Is [redacted] as bioavailable as Immediate Release or other Controlled Release products?

Relative bioavailability (Studies 0596008, 0197006 and TRGO04-01): The pivotal single-dose and food effect study in healthy volunteers (Study 0596008) compared the bioavailability (BA) of single dose [redacted] 60 mg to an oral solution (Roxane, 10 mg Q4hx6). However, BA could not be evaluated due to a truncated sampling schedule (i.e., up to 36 hrs post dose) for [redacted] The pilot steady state study in healthy volunteers (Study 0197006) evaluated [redacted] 60 mg, dosed daily for 5 days and the oral solution (Oramorph) dosed Q4h for 5 days. This study showed that [redacted] was bioequivalent to the oral solution, based on morphine AUC_{ss}. In another steady state study (TRGO04-01) compared [redacted] dosed once daily with MS Contin dosed twice daily in patients with chronic, moderate to severe pain. The results of this study showed that [redacted] was bioequivalent to MS Contin for morphine and its metabolites (i.e., M3G and M6G).

4. Is the pharmacokinetics different in patients compared to that of healthy subjects?

Study 197006: PK of [redacted] 60mg dosed once-daily for 5 days in healthy volunteers was investigated using the medium (PD14625) and slow (PD14626) lots. Also, 10 mg of the oral solution (Oramorph®), 6 times daily for 5 days, was included in the study. Based on analysis with trough concentrations all subjects reached steady state by day 3 with treatment PD14625 and eight evaluable

subjects were at steady state by day 5 with treatment PD14626. Both [redacted] formulations were bioequivalent to Oramorph® in terms of steady state AUC. The results are shown for morphine in the table below.

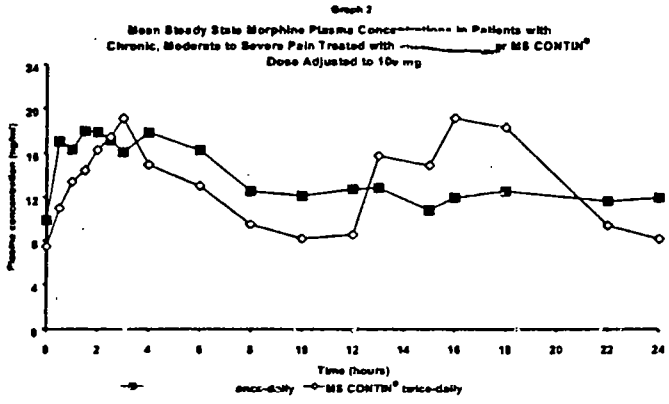
Parameter	Medium lot (A)	Slow lot (B)	Oramorph® (C)	90% CI comparison	
				A:C	B:C
AUC (ng/ml.h)	273.3 ± 81.2	276.1 ± 61.2	279.1 ± 63.0	86 -108	88 -111
C_{max} (ng/ml)	18.77 ± 7.1	17.4 ± 6.7	20 ± 4.8	73 – 109	69 - 103
C_{min} (ng/ml)	7 ± 2.4	7.8 ± 2.8	6.6 ± 2.2	94 – 116	105 – 130
%FL	106.4 ± 78.1	87.6 ± 76.2	116.2 ± 26.7	-	-

Study TRG-01: Doses were individually titrated to [redacted] 'QD) or MS Contin (BID) for approximately 10 days. The results, by analyzing morphine trough concentrations, from [redacted] showed that 5 out of the 8 evaluable patients reached steady state by Day 4 (2 other patients reached at Day 2 and 5, and steady state attainment could not be established for one patient due to highly variable trough data). [redacted]™ was within the 90% of confidence limits compared to MS Contin® with respect to AUC (see table below). The morphine peak to trough fluctuation [(C_{max} - C_{min})/C_{max}] for [redacted]™ dosed once-daily was lower compared to that of MS Contin® dosed twice-daily (Table below). The mean plasma morphine concentrations-time curves following Morphelan™ and MS Contin® are shown in the figure below. In addition, this study provides 505b(2) linkage.

PK parameters (Mean ± SD, dose adjusted to 100mg)

Parameter	[redacted]™	MS CONTIN®	90% CI
	(n = 7)	(n = 8)	
AUC (ng/ml.h)	322.8 ± 153.9	312.0 ± 120.8	86 - 107
C_{max} (ng/ml)	21.2 ± 10.6*	26.1 ± 7.6	63 - 89
C_{min} (ng/ml)	8.9 ± 4.7*	5.4 ± 2.9	146 - 193
% FL	93.4 ± 19.6*	167.4 ± 43.7	

* Statistically significant difference at $P < 0.05$



5. What is the effect of food, and does food will cause any dose dumping?

The apparent elimination $t_{1/2}$ or $AUC_{0-\infty}$ were not estimable for ———60 mg) in food effect study (#0596008), due to the sampling duration lasted 36 hours and plasma levels for ——— were still sustained at this time. Consequently, AUC_{last} (i.e., AUC_{0-36h}) is an underestimate of the extent of exposure, but C_{max} was outside of 80-125% of 90% confidence intervals (CI). However, the differences in C_{max} are small and may not be clinically meaningful. T_{max} for morphine, M6G and M3G occurred (fast and fed) at 18 ± 12 and 9 ± 5hrs, 6 ± 8 and 9 ± 3 hrs, and 10 ± 11 and 12 ± 5 hrs, respectively. Following ——— administration, in general, plasma concentration profiles of morphine and it metabolites displayed such a broad peak, that implication of t_{max} appears to be not significant (*i.e.*, concentration difference between 18 and 9 hrs was not so significant). Also noted that PK-PD analysis indicated that there was large inter-individual variability. Therefore, ——— can be given without regard to food.

Table 3

Parameter	Morphine		M6G	
	Fasted (A)	Fed (B)	Fasted (A)	Fed (B)
AUC_{0-36} (ng/mL•h)	143.2 ± 72	134.5 ± 26.8	757.5 ± 234	817.7 ± 209.6
90% CI (A/B)	91.3-106.2		101.0-117.6	
C_{max} (ng/mL)	5.9 ± 3.3	6.4 ± 1.8	38.4 ± 23.5	46.4 ± 15.0
90% CI (A/B)	103.7-126.9		113.9-142.8	

6. Can ——— capsule be administered as sprinkle form (on applesauce) without compromising any safety/efficacy effect?

The effect of ——— 60mg capsule intact *vs.* sprinkle (on applesauce) was investigated (#0698002). The two modes of administration were bioequivalent as shown the results in the table below. However, the sponsor has not conducted any *in vitro* stability study (i.e., ——— capsule 'sprinkled on applesauce' and let it sit for 30 minutes will cause any morphine release, and will result in dose-dumping?).

Parameter	Morphine		M6G	
	Sprinkle (A)	Capsule (B)	Sprinkle (A)	Capsule (B)
$AUC_{0-\infty}$ (ng/mL•h)	261.7 ± 88.3	261.0 ± 90.5	1289.4 ± 312.5	1293.1 ± 304.4
90% CI (A/B)	96-106		97-102	
C_{max} (ng/mL)	7.60 ± 2.9	7.36 ± 3.47	43.7 ± 14.1	40.9 ± 9.0
90% CI (A/B)	95-117		97-114	
t_{max} (h)	8.4 ± 10.1	13.0 ± 12.4	7.4 ± 7.9	6.4 ± 7.5
$t_{1/2}$ (h)	16.1 ± 5.2	17.6 ± 6.2	14.5 ± 3.8	14.9 ± 3.8

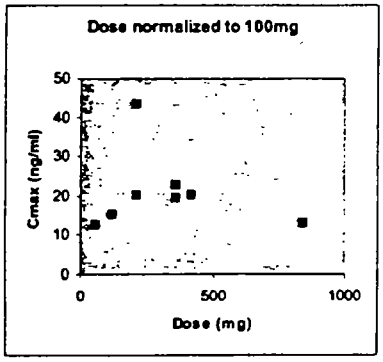
7. Is the pharmacokinetics of the drug linear?

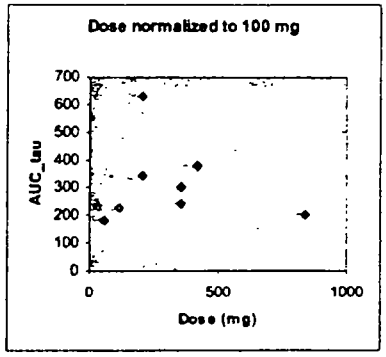
Dose proportionality was assessed following a single dose (30-120 mg) of ———(#0596009). However, blood samples were obtained only up to 36 hours of post dose, consequently, AUC_{last} (i.e., AUC_{0-36h}) is an underestimate of the extent of exposure (therefore it is not adequate/ideal indicator for dose proportionality assessment). Dose proportionality was assumed if the 90% confidence intervals

were within the bioequivalence limits (i.e., 80-125%). 90% confidence intervals were constructed for dose adjusted, dose dependent parameters (table below). The C_{max} comparisons for morphine showed dose linearity across the 60 - 120mg doses but not the 30 mg compared to 60 mg or 120 mg. Doses 30 – 120 mg were proportional in terms of $AUC_{0\text{-}36h}$.

Comparison	Morphine	M6G	Morphine	M6G
	C_{max}		AUC_{last}	
30mg *vs.* 60mg	77 – 94	88 – 137	85 – 94	96 - 115
30mg *vs.* 90mg	80 – 97	85 – 132	89 – 98	99 - 118
30mg *vs.* 120mg	77 – 94	82 – 128	85 – 94	98 - 117
60mg *vs.* 90 mg	94 – 115	77 – 120	100 – 110	94 - 113
60mg *vs.* 120mg	91 – 111	74 – 116	95 – 105	94 - 112
90mg *vs.* 120mg	87 - 107	77 – 120	91 - 100	91 - 109

Nine patients received individually titrated doses of ——— in the range of 60 mg to 840 mg per day (TRG004-001). PK parameters for morphine (i.e., C_{max}, C_{min}, $C_{average}$ and AUC_{tau}) appeared to be non-proportional to dose (C_{max} and AUC_{tau} are shown below).





In summary, dose proportionality with PK parameters appeared to be demonstrated following a single dose of ——— in healthy subjects, but this failed in patients at steady state.

8. Is there an exposure and response relationship?

Population PK analysis was performed using ——— software program. A one-compartment model with first-order absorption and elimination characterized the PK data for all three analytes. Covariates evaluated in the model included weight, age and sex. The results of (pop) PK analysis for morphine and Morphine-6-glucuronide are as follows;

Morphine: Population estimates (and %CV of inter-individual variance) for morphine CL/F and V/F were 278 L/hr (37%CV) and 841 L (85%CV), respectively. Individual CL/F estimates increased with body weight at a rate of 2.33 L/hr/kg, with the typical value centered at a median weight of 84 kg.

M6G: Population estimates (and %CV of inter-individual variance) for morphine-6-glucuronide CL/F and V/F were 62.9 L/hr (31%CV) and 87 L (106%CV), respectively. Individual CL/F estimates increased with body weight at a rate of 0.594 L/hr/kg (at a median = 84 kg).

Exposure and response relationship: Visual Analog Scale (VAS) scores and Time-to-rescue were used as end points to investigate this relationship. In the course of developing the model, M6G appeared to be the best predictor of effect although the improvement over morphine and M3G was marginal. The inhibitory E_{max} model with baseline effect resulted in a better fit to these data when compared to the linear model. However, the population typical value for EC_{50} (1050 ng/ml by base model; 1110 ng/ml final model) was much higher than the maximum observed M6G concentration of approximately 550 ng/ml. This indicated that the observed data were primarily in the linear range of the inhibitory E_{max} PD model, therefore, extrapolation of this model beyond the range of observed data is not appropriate (therefore, the sponsor's claim of "significant concentration-response relationship found" is not proper).

A concentration-response relationship describing a decreased probability of taking rescue medication as a function of morphine or M6G concentration was not demonstrated.

9. Do special populations in terms of demographic factors, organ dysfunction (renal and hepatic) and patients who take other drug(s) concomitantly (drug-drug interaction) require adjustment in dosage regimen?

The sponsor has not conducted any clinical studies to obtain PK information for special populations. This NDA is submitted as 505(b)(2), and the sponsor relied on Kadian® (sustained release of morphine product by Faulding Laboratories) for the special populations section for the labeling, except the 'gender effect: However, the sponsor did not conduct any clinical study with the Kadian®, therefore the sponsor may not use labeling information from Kadian®. The sponsor evaluated 'gender-effect' from the two PK studies (0698002 and 0299001). In these studies, female to male ratios were low (0698002: female = 3, male = 25; 0299001: female = 4, male = 26). Therefore, any findings from these studies can not be considered conclusive.

10. Are the clinical batches manufactured on one site with the clinical and pivotal stability batches manufactured at another different?

Bioeguivalence study was conducted to bridge batches of [redacted] manufactured in Athlone, Ireland facility to batches manufactured in Gainesville, U.S.A., thus linking the clinical batches manufactured in Athlone with the pivotal clinical and stability batches manufactured in Gainesville (#0299001). The formulations used for this are comparable each other (slight difference in excipients). The results indicated no significant differences were found between [redacted] 60mg capsule manufactured at two different sites as shown in the table below.

Pharmacokinetic Parameter	[redacted] (60mg) Athlone (Treatment A)	[redacted] (60mg) Gainesville (Treatment B)	90% confidence intervals (A/B)
	Morphine (30 subjects)		
C_{max} (ng/ml)	6.01 (1.35)	6.57 (1.49)	97 – 123
AUC_{0-72} (ng/ml.h)	205.48 (1.28)	211.50 (1.30)	98 – 108
AUC_{inf} (ng/ml.h)	254.48 (1.26)#	252.26 (1.32)†	95 - 107

†Mean of 28 Subjects. #Mean of 27 Subjects

11. Is IVIVC established?

Four —— 60mg development lots differing in in-vitro dissolution were evaluated in the study 1096003. Only morphine was measured. The apparent elimination rate and AUC_{inf} was not estimable for —— in this study, due to short sampling times (i.e., last sampling time was 36 hours post dose and plasma levels for —— were still sustained at this time). Therefore, AUC_{last} underestimated the extent of exposure. A level-A IVIVC linear convolution-based model predicted well except for C_{max} for the —14623 treatment (fast release formulation), which is underestimated by 16.71%, exceeding the FDA limit by 1.71%. Therefore, the model can not and will not be used for setting dissolution specifications and biowaivers. The results of IVIVC model validation are presented in the table below;

treatment	C_{max}				AUC(0-36)			
	Pred. (mg/L)	Obs. (mg/L)	ratio	|%PE| (%)	Pred (mg/L).	Obs. (mg/L)	ratio	|%PE| (%)
—14044	5.84	6.23	0.94	6.25	111.56	128.02	0.87	12.86
—14623	4.81	5.77	0.83	16.71	115.36	125.92	0.92	8.39
—14625	4.03	3.77	1.07	6.65	113.31	109.19	1.04	3.78
—14626	3.33	3.69	0.90	9.98	93.89	104.54	0.90	10.19
mean	4.50	4.87	0.93	9.90	108.53	116.92	0.93	8.80

Lot # —14044 (very fast), Treatment B: Lot # —14623 (fast), Treatment C: Lot # —14625 (medium), Treatment D: Lot # —14626 (slow).

12. Does the dissolution test conditions and specifications appear to be appropriate to the physiological state, and related to in vivo conditions for BA and BE?

Summary of the —— dissolution methods is as follows;

Dosage Form & Strengths:
Apparatus Type:
Media:
Volume & Temperature:
Speed of Rotation:

[ ]

The sponsor provided the table below, which summarizes the clinical and stability data;

Time	Mean Clinical Range	Clinical COA Range	Overall Range	Proposed Specification
1	11 – 14	7 – 18		
3	20 – 23	16 – 27		
6	31 – 36	27 – 40		
12	53 – 61	49 - 66		

The sponsor proposed specification is shown below;

[

Time	1	3	6	8	12	16	24

]

The recommended specification is shown below;

[redacted]

13. Are the bioanalytical methodology validated appropriately?

Determination of morphine and its metabolites (M3G and M6G) in plasma samples from the pharmacokinetic studies were carried out by [redacted] and [redacted], respectively. These analytical methods were specific, sensitive and adequately validated. The assay results were found to be overall acceptable, however, it was less than ideal in some studies, (%CV for QC being >15% reported; ranged from 2 to 20%). In one study (#0197006), it was noted that morphine and its metabolites were analyzed by [redacted] and [redacted], respectively. Percent CV of QC samples for morphine, M3G and M6G ranged [redacted] and [redacted], respectively. Therefore, metabolites data was not reported (i.e., not included for PK analysis).

14. Is the proposed text in the package insert appropriately reflects the drug's properties?

PROPOSED PACKAGE INSERT

Note: Strikeouts and underlined text indicate this reviewer's suggested deletions and additions respectively. Italicized texts are the same as the reference drug, **Kadian®**

Pharmacodynamics

APPENDIX

Analytical Methodology:

Assay Method:

Assay Sensitivity, Precision and Accuracy:

Statistical methods:

Analysis of variance was used to test for treatment differences. Ninety percent (90%) confidence intervals were constructed for the log-transformed and non-transformed C_{max} and AUC_{all} for the fasted versus fed treatments. The mean ratios of fed/fasted treatments were calculated for C_{max} and AUC_{all}.

Results:

Mean PK parameters following log-transformation of data for morphine is presented in Table 1. The 90% confidence intervals for the log-transformed parameters, C_{max} and AUC_{all} for morphine is presented in Table 2, and the mean morphine plasma concentration versus time profile is presented in Figure 1.

The sponsor stated that due to the sustained plasma levels of this formulation post 24 hours, the plasma half-life, elimination rate constant and AUC_{inf} could not be accurately estimated. As a result, AUC_{all} was therefore considered as an estimate of the total exposure of morphine following single dose administration.

Conclusion:

- Food had no significant effect on AUC_{all} and C_{max} of morphine following 60 mg.
- Administration of 60 mg with food resulted in delayed gastric emptying reflected in a delayed t_{max} for morphine (and its metabolites) compared to the fed treatment.
- There was noticeable difference in the shape of curve between the fasted and fed state (see Figure 1).

Comment: Food effect, with respect to $AUC_{0-\infty}$, has not been evaluated due to study design (i.e., last sampling at 36 hr) for 60 mg, and consquently AUC_{all} is not a proper estimator of the total exposure of morphine; AUC_{all} is about 50% of $AUC_{0-\infty}$, (see Table 2 on page 5).

Table 1. Mean log-transformed PK parameters (gsd = geometric standard deviation)

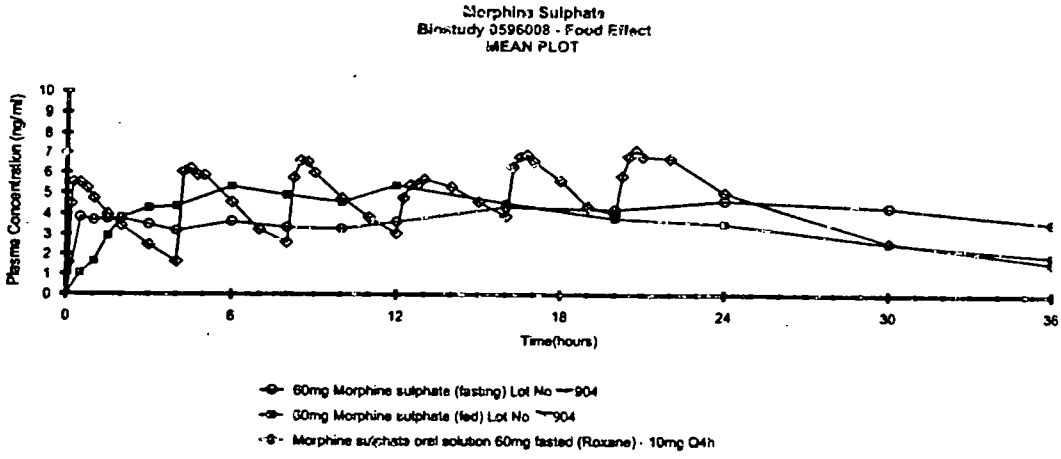
Parameter	Treatment A	Treatment B	Treatment C
	Morphine Mean (gsd), n = 24		
C_{max} (ng/ml)	5.42 (1.15)	6.21 (1.31)	9.24 (1.26)**
Ratio B/A	1.15		
AUC_{all} (ng/ml.h)	133.82 (1.40)	131.77 (1.24)	149.48 (1.22)**
Ratio B/A	0.98		
T_{max} (h)***	18.31 ± 11.87	9.27 ± 4.74	15.07 ± 7.44

*P≤ 0.025 (Bonferroni adjusted P-value to keep the overall level of significance at 5%) statistically significant differences between treatments A and B.
**P≤ 0.025 (Bonferroni adjusted P-value to keep the overall level of significance at 5%) statistically significant differences between treatments A and C.
*** By (non transformed data) arithmetic mean ± SD

Table 2. 90% confidence intervals of log10-transformed data

Comparison	Morphine	
	C_{max}	AUC_{all}
Elan Fed/Fasted	103.68 – 126.86	91.34 – 106.15
Elan fast/Roxane	53.01 – 64.85	83.05 – 96.52

Figure 1. Mean morphine plasma concentration versus time profiles



Protocol #0698002: A study in healthy volunteers to evaluate the relative bioavailability of an elan 60 mg once-daily morphine sulphate formulation when administered in a capsule and in a sprinkle form.

Reference: Volume 22 - 24
Investigators:
Study Center:
Bioanalytical Services, Elan Pharm. Technologies, Monksland, Athlone, Ireland.

Formulation: [redacted] 60mg capsule, Lot No. PS959.

Objective:

- To evaluate the relative bioavailability of [redacted] 60mg capsule when administered as a capsule or the contents sprinkled on food (primary).
- To monitor the subjects adverse events (secondary).

Study Design:
The study was an open label, two treatments, two periods, balanced, randomized study with a seven day washout between treatment periods. Twenty-eight (28) healthy volunteer subjects (18-40 years of age) were enrolled. Subjects were randomized to treatment A or B group:
Treatment A: The contents of one 60 mg capsule were sprinkled over one level tablespoonful of applesauce, over which another level tablespoonful of applesauce was then placed, and the beads were then folded into the applesauce. Following administration, subjects then consumed 240 ml of tap water.
Treatment B: Single oral dose of one 60 mg capsule fasted taken with 240 ml of tap water.

Criteria for Evaluation:
Pharmacokinetic: Individual and mean blood drug concentrations, peak levels (C_{max}), time to peak (t_{max}), area under the drug concentration time curve to the last sampling point (AUC_{all}), to the last quantifiable concentration (AUC_{last}) and extrapolated to infinity (AUC_{inf}), the first order rate constant associated with the terminal portion of the curve (λ_z), and the terminal half-life ($t_{1/2}$). Blood samples were collected at t = Predose (0), 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, and 72 hours

Analytical Methodology:
Assay Method: [redacted]

Assay Sensitivity, Precision and Accuracy:

Protocol #0596009: A Study in Healthy Volunteers to Evaluate the Dose Proportionality of the Elan Once-Daily Morphine Sulphate Capsule Formulation Following Administration of 30 mg, 60 mg, 90 mg and 120 mg Dosage Strengths.

Reference: Volume 19 - 21
Investigators:
Study Center:
Bioanalytical Services, Elan Pharm. Technologies, Monksland, Athlone, Ireland.

Formulation:

Dosage Form	Dose	Lot #
[redacted]	30 mg	[redacted]903
	60 mg	[redacted]904
	90 mg	[redacted]905
	120 mg	[redacted]906
Nalorex® (Naltrexone HCl) DuPont	50 mg	[redacted]122AB

Objective:

- To evaluate dose proportionality of [redacted]™ between 30 mg, 60 mg, 90 mg and 120 mg dosage strengths (primary).
- To monitor the subjects for dose tolerability prior to administration of sequentially higher doses, and adverse events (secondary).

Study Design:

The study was an open label, four treatment, four period, randomised (on entry only) study with a seven day washout between treatment periods. Twenty-eight (28) subjects were to be enrolled to ensure completion of 24. Subjects were given an oral dose of [redacted]™ 30, 60, 90 and 120 mg capsule on each Day 1. Subjects also received a 50 mg [redacted] tablet taken at 24 hours and 1 hour prior to dosing and at 24 hours post dose on each treatment period.

Criteria for Evaluation:

Pharmacokinetic: Individual and mean blood drug concentrations, peak levels (C_{max}), Area under the drug concentration time curve to the last sampling point (AUC_{all}), and time to peak (t_{max}) were estimated. Plasma was sampled at t = Predose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, and 36 hours post dosing.

Analytical Methodology:

Assay Method: [redacted]

Assay Sensitivity, Precision and Accuracy:

[redacted]

Statistical methods:

Analysis of variance was used to test for treatment differences. Linear regression analysis (significant correlation at $p<0.05$) was performed to assess dose proportionality on the dose-dependent parameters (C_{max} and AUC_{all}). Ninety percent (90%) confidence intervals were constructed for dose adjusted, dose dependent parameters. Dose proportionality was assumed if the 90% confidence intervals were within the bioequivalence limits.

Results: Mean PK parameters following log-transformation of data and the results of 90% confidence intervals are shown in Tables 1 and 2, respectively. The mean plasma concentration versus time profiles for morphine, M3G and M6G are presented in Figures 1.

Table 1. Mean dose-normalised log transformed PK parameters: gsd = geometric standard deviation.

Parameter	**Treatment A 30mg**	**Treatment B 60mg**	**Treatment C 90mg**	**Treatment D 120mg**
	Morphine, Mean ± SD, 22 subjects			
C_{max} (ng/ml)	14.96 (1.28)*	17.68 (1.42)	16.95 (1.30)	17.56 (1.35)
AUC_{all} (ng/ml.h)	328.71 (1.29)*	367.49 (1.24)	351.94 (1.24)	368.11 (1.25)

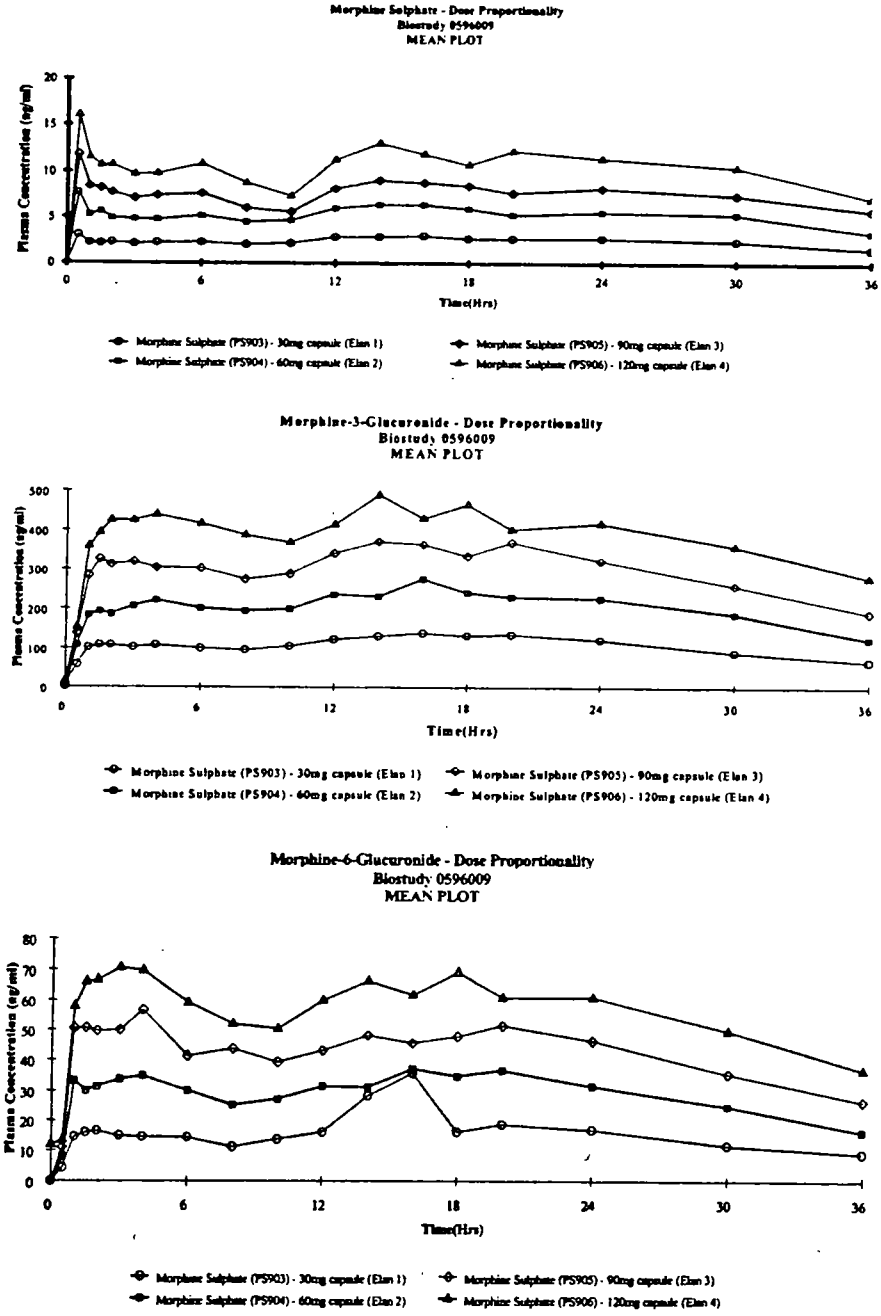
*P ≤ 0.008 (Bonferroni adjusted P-value to keep the overall level of significance at 5%) statistically significant relative to 60mg dose.

Table 2. 90% confidence intervals of dose-normalised log-transformed data

Comparison	Morphine	
	C_{max}	AUC_{all}
30mg *vs.* 60mg	77 – 94	85 – 94
30mg *vs.* 90mg	80 – 97	89 – 98
30mg *vs.* 120mg	77 – 94	85 – 94
60mg *vs.* 90 mg	94 – 115	100 – 110
60mg *vs.* 120mg	91 – 111	95 – 105
90mg *vs.* 120mg	87 - 107	91 - 100

Conclusion: Overall, dose proportionality seemed to be demonstrated following single dose, within the dose ranges studied (based on C_{max} and AUC_{all}; $AUC_{0-\infty}$ not available).

Figure 1. Mean plasma concentration versus time profiles



Protocol #0299001: A study in healthy volunteers evaluating the bioequivalence of Elan's morphine sulphate 60 mg capsule produced at two different manufacturing sites, (Athlone and Gainesville).

Reference: Volume 25 - 27
Investigators:
Study Center:
Bioanalytical Services, Elan Pharmaceutical Technologies, Monksland, Athlone, Ireland.

Formulation:

Dosage Form	Dose	Lot #	Lot Size
[redacted] manufactured by Elan Athlone	60 mg	[redacted]959	[redacted]
[redacted] manufactured by Elan Gainesville	60 mg	[redacted]039920	

Objective:

- To evaluate the bioequivalence of Elan's morphine sulphate 60 mg capsule when produced at two different manufacturing sites, (Athlone, Ireland and Gainesville, USA). (primary).
- To monitor the subjects adverse events (secondary).

Study Design:

The study was an open label, two treatment, two period, balanced, randomized, crossover design study with a seven day washout between treatment periods. Thirty healthy volunteer subjects (18-40 years of age) were enrolled. At each treatment period, the subjects received either an [redacted] 60 mg capsule manufactured at the Athlone, Irend or an [redacted] 60 mg capsule manufactured at the Gainesville, USA.

Criteria for Evaluation:

Pharmacokinetic: Individual and mean blood drug concentrations, peak levels (C_{max}), time to peak (t_{max}), area under the drug concentration time curve to the last sampling point (AUC_{all}), to the last quantifiable concentration (AUC_{last}) and extrapolated to infinity (AUC_{inf}), the first order rate constant associated with the terminal portion of the curve (λ_z), and the terminal half-life ($t½$). Blood samples were collected at t = Predose (0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, and 72 hours

Analytical Methodology:

Assay Method: [redacted]

Assay Sensitivity, Precision and Accuracy:

[redacted]

Statistical methods: Analysis of variance was used to test for treatment differences. Ninety percent (90%) confidence intervals were constructed for the log_{10}-transformed and non-transformed C_{max},

AUC_{last}, AUC_{all} and AUC_{inf}. The bioequivalence criterion (90% confidence intervals 80-125%) for log_{10}-transformed morphine, M3G and M6G data formed the basis for assessing equivalence between the two treatments.

Results: Mean (geometric) PK parameters with the 90% confidence intervals for log-transformed data for morphine is presented in Table. The mean morphine plasma concentration versus time profile is presented in Figure.

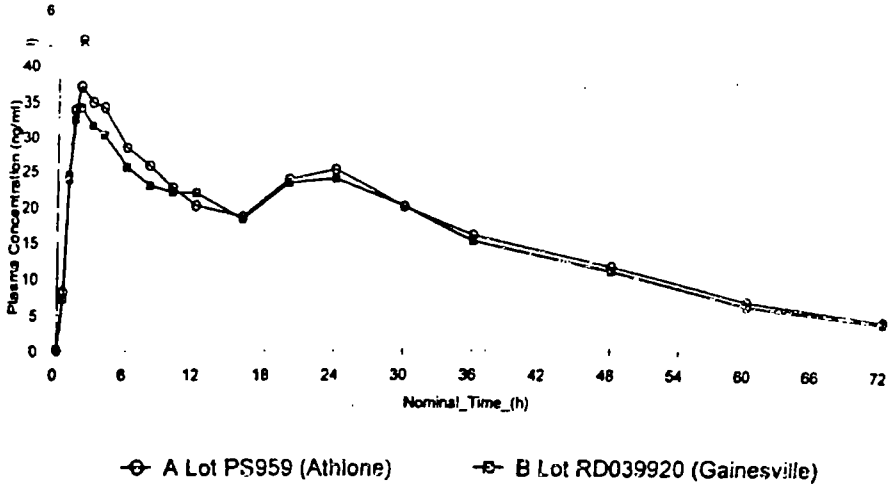
Conclusion: Statistical analysis of the log_{10}-transformed data showed no significant differences between [redacted] 60mg capsule manufactured at two different sites: The results showed that 90% confidence intervals around the log transformed ratios (treatment A/B) for AUC_t, AUC_{all}, AUC_∞, and C_{max} were within the BE criteria of 80-125% for morphine and its metabolites. In addition, no significant differences were observed between the two treatments in t_{max}, $t½$, and λ_z comparisons.

Table. Log_{10}-transformed data: Geometric Mean (gsd)

Pharmacokinetic Parameter	[redacted] (60mg) Athlone (Treatment A)	[redacted] (60mg) Gainesville (Treatment B)	90% confidence intervals (A/B)
	Morphine (30 subjects)		
C_{max} (ng/ml)	6.01 (1.35)	6.57 (1.49)	97 – 123
AUC_{all} (ng/ml.h)	205.8 (1.27)	211.7 (1.30)	98 – 108
AUC_{last} (ng/ml.h)	205.5 (1.28)	211.5 (1.30)	98 – 108
AUC_{inf} (ng/ml.h)	254.5 (1.26)[#]	252.3 (1.32)[†]	95 - 107
t_{max} (h)[a]	8.4 ± 9.8	10.6 ± 13.7	
$T_{½}$ (h)[a]	24.7 ± 9.2[#]	23.0 ± 10.5[†]	

[†]Mean of 28 Subjects [#]Mean of 27 Subjects [a]Arithmatic Mean ± SD

Figure. Mean Morphine plasma concentration versus time graph



Protocol # TRG004-01: An Open Steady-State Pharmacokinetic Study of [redacted] morphine sulfate oral extended release capsules) in Patients with Chronic, Moderate to Severe Pain.

Reference: Volume 28 - 30
Investigators:
Study Center:
Bioanalytical Services, Elan Pharm. Technologies, Monksland, Athlone, Ireland.

Investigational product:

Morphelan™		MS Contin®:	
Dose	Lot #	Dose	Lot #
30 mg	[redacted]903	15 mg	Y941
60 mg	[redacted]904	30 mg	Y951
90 mg	[redacted]905	60 mg	Y971
120 mg	[redacted]906	100 mg	Y981
**Rescue medication: [redacted]			

Objective: To investigate the steady state PK profile of a once daily morphine sulfate formulation, [redacted]™, as compared to that of MS Contin® given every 12 hours in patients with chronic, moderate to severe pain.

Methodology: Each patient was titrated to an individual dose of MS Contin® for a period of at least 7 days (Days -7 to –1) and then converted to a similar dose of [redacted]™ for approximately 10 days (Days 1 to 10). Patients were intensively sampled upon stabilization with MS Contin® (blood samples on the last day) and also on the final day of dosing with [redacted] at the following times: predose (0.0), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 13.0, 15,0, 16.0, 18.0, 22.0 and 24.0 hours for plasma concentrations of morphine and metabolites (M3G and M6G). Also blood samples were collected following [redacted]™ on Days 3, 5, 7, 9 and 10 (for trough conc.). The study used standard measures of efficacy and safety to compare the effects of [redacted] to those of MS Contin®.

Number of Patients (planned and analyzed): Ten patients enrolled in the study, 1 dropped out and 9 patients completed the study. However, plasma data from Patient 6 (after [redacted]) was not included (assay difficulties) for (data) analysis and patient 5 (after MS Contin) had unusually high plasma concentration (data was analyzed with or without patient 5).

Criteria for Evaluation:

Time to achieve steady state: Time to achieve steady-state for [redacted]™ was determined individually on the basis of at least three available trough concentrations. Time to achieve steady state was assessed for morphine.
PK parameters: Peak plasma concentration (C_{max}), time to reach peak concentration (t_{max}), the minimum concentration (C_{min}) and time to reach minimum concentration (t_{min}), the area under plasma concentration versus time curves over the steady state day (AUC), the average plasma concentration (C_{avg}), and the percent peak to trough fluctuation (FL), the plasma concentration at the end of the steady state day (C_{last}) and the time of occurrence (t_{last}). In addition, plateau time (T50% and T75%) was calculated following [redacted] administration compared to MS Contin®; T50% (or 75%)

was defined as the total time with plasma concentrations greater than or equal to 50% (or 75%) of the C_{max}.
Efficacy: Number and percentage of patients requiring rescue medication, amount of rescue medication, Visual Analog Scale (VAS) scores of worst pain since rising, and Brief Pain Inventory (BPI) short form.

Analytical Methodology:

Assay Method: [redacted]
Assay Sensitivity, Precision and Accuracy: [redacted]

Statistical methods:

Time to achieve steady state: An iterative assessment starting with the last available three trough concentrations ensured that the time to achieve steady state was that where inclusion of an additional trough value resulted in a positive slope and a statistically significant p value ($p<0.05$).

PK parameters: Analysis of variance was used to test for treatment differences for the untransformed and log-transformed data. The 90% confidence intervals for the dose-normalized log_{10}-transformed data were also calculated. For plateau time analysis, descriptive statistics (mean, standard deviation and coefficient of variation) of the ratio: [redacted]™/MSContin®) for T50% and T75% were generated and reported.

Efficacy: Sign test, Wilcoxon signed rank test, descriptive statistics and paired t-test were used (when appropriate) to evaluate efficacy parameters.

Summary:

Steady state: Analysis of morphine trough plasma concentrations showed that steady state, from [redacted] was achieved in 5 out of the 8 evaluable patients by Day 4 (2 other patients reached at Day 2 and 5, and steady state attainment could not be established for one patient due to highly variable trough data).
Plateau time analysis: The T50% and T75% were approximately 2 times longer for morphine following [redacted]™ administration compared to MS Contin®.

Below are the geometric mean data for morphine, the power of the ANOVA, minimum detectable differences (MDD±) and 90% confidence intervals (CI) for the dose normalized log_{10}-transformed data.

Parameter	MS Contin®	[redacted]™	90% CI	Power	MDD+	MDD-
	Morphine sulfate (data excluding patient 5)					
AUC	1180.37 (1.41)	1186.36 (1.54)	86 - 107	0.90	21.4	17.6
Cmax	100.64 (1.32)	77.69 (1.53)*	63 - 89	0.52	35.1	26.0
Cmin	18.54 (1.83)	31.52 (1.71)*	146 - 193	0.73	27.4	21.5
Clast	28.86 (1.66)	42.99 (1.60)*	123 - 158	0.82	24.4	19.6
Cavg	49.18 (1.41)	49.43 (1.54)	86 - 107	0.90	21.4	17.6
	Morphine sulfate (data including patient 5)					
AUC	1227.73 (1.41)	1156.05 (1.50)	77 - 105	0.64	30.4	23.3
Cmax	107.86 (1.39)	77.76 (1.48)*	57 – 85	0.40	41.4	29.3
Cmin	19.17 (1.77)	29.64 (1.69)*	122 – 189	0.34	45.8	31.4
Clast	28.10 (1.61)	39.65 (1.63)*	117 – 153	0.77	25.9	20.6
Cavg	51.16 (1.41)	48.17 (1.50)	77 - 104	0.64	30.4	23.3

* Statistically significant difference at $p < 0.05$

Efficacy Results: [redacted]™ was similar to MS Contin® in its effect on pain in this chronic, moderate to severe pain population. No clinically or statistically significant differences between treatments were seen in any of the efficacy measurements which included the number and percentage of patients requiring rescue medication, amount of rescue medication, Visual Analog Scale (VAS) scores of worst pain since rising, and Brief Pain Inventory (BPI) short form. All 9 patients required rescue medication during the stabilization period and the [redacted]™ treatment period. The average number of rescue medication requirements was 4.4 for the MS Contin® stabilization period as compared with 4.4 for the [redacted]™ treatment period. Average worst pain since rising on the VAS scale was 52.8 during the stabilization period as compared to 52.9 during the [redacted] treatment period.

Overall Conclusion: In comparison to MS Contin®, [redacted] showed similar AUC, and C_{avg}, lower C_{max} and higher C_{min} and C_{last} (log_{10}-transformed data) in patients who required opioid therapy for treatment of chronic, moderate to severe pain.

Protocol #0197006: A study in healthy volunteers to compare the relative bioavailability at steady state of two elan 60mg once-daily morphine sulphate formulations and oramorph® 10mg oral solution (boehringer) dosed six times daily at four hourly intervals.

Reference: Volume 38 - 39
Investigators:
Study Center:
Bioanalytical Services, Elan Pharm. Technologies, Monksland, Athlone, Ireland.

Formulation:

Treatment	Treatment ID
A	60mg Morphine Sulphate capsule, manufactured by Elan, Athlone, Ireland. Lot No. [redacted]14625
B	60mg Morphine Sulphate capsule, manufactured by Elan Ireland. Lot No. [redacted]14626
C	5ml x Oramorph® (10mg/5ml) oral solution, manufactured by Boehringer Ingelheim, Ltd. Lot No. 690791

Objective: (1) To compare the relative bioavailability at steady state of two Elan 60 mg once-daily morphine sulphate formulations and Oramorph® 10 mg oral solution (Boehringer) dosed six times daily at four hourly intervals (primary). (2) To monitor the subjects adverse events (secondary).

Study Design: The study was an open label, 3 treatment, 3 period, and 6-sequence randomised crossover study with at least a 7-day washout between treatment periods. A total of twelve male subjects were enrolled in the trial, and 11 subjects (mean age of 27.2 years) completed the study. Subjects received treatments randomly A, B and C for 5 days.

Criteria for Evaluation:
PK: Peak plasma concentration (C_{max}), time to peak (t_{max}), the minimum concentration (C_{min}) and time to reach minimum concentration (t_{min}), the area under plasma concentration versus time curves over the steady state day (AUC), the average plasma concentration (C_{avg}), the percent peak to trough fluctuation (%FL), and the plasma concentration at the end of the steady state day (C_{24}).

Blood were collected as follows.
Treatments A and B; predose on days 1, 2, 3, 4, 5 and at the following times post dosing on day 5: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36 hours.
Treatment C; Predose on days 1, 2, 3, 4, 5 and at the following times post dosing on day 5: 0.17, 0.33, 0.50, 0.67, 1, 2, 4, 4.67, 5, 6, 8, 8.33, 8.67, 9, 10, 12, 12.33, 12.67, 13, 14, 16, 16.33, 16.67, 17, 18, 20, 20.33, 20.67, 21, 22, 24, 30, 36 hours

Analytical Methodology:
Assay Method: [redacted]
Assay Sensitivity, Precision and Accuracy:

[redacted]

Statistical methods: An analysis of variance (ANOVA) was performed on C_{max}, AUC, C_{min}, C_{avg}, and C_{24} data transformed to the log base 10 as well as on the non-transformed data. Time to achieve steady state was determined using linear regression analysis of trough concentrations that were obtained prior to the first dose on days 1 – 5 and at the end of the intensively sampled day ($p<0.05$).

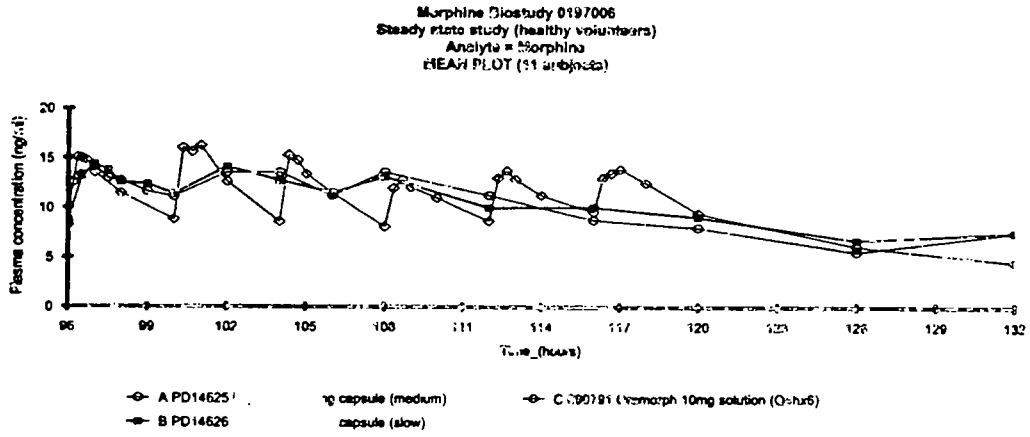
Results: Pharmacokinetic parameters and the 90% confidence intervals following log_{10}-transformation of data for morphine are presented in Table 1. The mean plasma morphine concentrations are shown in Figure 1. The sponsor stated that PK analysis was not performed on the metabolites as the data was considered variable, hence only the parent compound, morphine, was reported.

Table 1. Log_{10}-transformed PK data for morphine: Geometric Mean (gsd), n = 11

Parameter	Treatment A	Treatment B	Treatment C	90% CI comparison	
				A:C	B:C
$AUC_{ss, 0\text{-}36h}$ (ng/ml.h)	263.6 (1.32)	270.3 (1.24)	272.6 (1.26)	86 – 108	88 - 111
C_{max} (ng/ml)	17.6 (1.43)	16.5 (1.38)	19.4 (1.27)	73 – 109	69 - 103
C_{min} (ng/ml)	6.6 (1.47)	7.3 (1.46)*	6.3 (1.38)	94 – 116	105 – 130
C_{24} (ng/ml)	7.4 (1.49)	8.3 (1.57)	9.1 (1.37)	68 – 102	76 - 114
C_{avg} (ng/ml)	11.0 (1.32)	11.3 (1.24)	11.4 (1.26)	86 – 108	88 – 111
%FL[a]	106.4 ± 78.1	87.6 ± 76.2	116.2 ± 26.7		

*P<0.025 (Bonferroni adjusted p-value to keep overall level of significance at 5%), statistically significant compared to Oramorph. [a]Arithmatic Mean ± SD

Figure 1. Mean plasma Morphine concentration versus time graphs



Summary:

Based on analysis with trough concentrations all subjects reached steady state by day 3 with treatment —14625 and eight evaluable subjects were at steady state by day 5 with treatment —14626. Both ——————™ formulations were bioequivalent to Oramorph® in terms of log_{10}-transformed AUC with 90% confidence intervals for —14625 and —14626 of 86 – 108% and 88 – 111% respectively. The log_{10}-transformed C_{max}, C_{min}, C_{24} and C_{avg} for —14625 were similar to Oramorph®. Similar results were obtained for —14626 with the exception of a significantly higher C_{min} compared to Oramorph®. The %FL for —14625 (106%) and —14626 (88%) were similar to the oral solution (116%).

Comments: The results of analytical data for morphine metabolites were less than satisfactory (i.e., > 15%CV).

The sponsor provided the following synopsis:

Title of Study:	A Multicenter, Randomized, Incomplete Block, Double-Blind, Double-Dummy, 2-Period Crossover Study Comparing the Pharmacokinetic-Pharmacodynamic Relationships of Once-Daily [redacted]™ (morphine sulfate oral sustained release capsules) and Twice Daily MS Contin® in Patients with Chronic, Moderate to Severe Pain of Non-Malignant Origin.
Study Center:	Multicenter
Reference	Volume 31 - 37
Phase of development:	II/III
Objectives:	The primary objective of this study was to establish a pharmacokinetic-pharmacodynamic (PK-PD) relationship for [redacted]™ and MS Contin® in patients with chronic, moderate to severe pain of non-malignant origin. A secondary objective was to compare the Morphine PK-PD relationship between [redacted] and MS Contin®.
Methodology:	Patients were admitted to the study after satisfying entry criteria and completing screening and baseline evaluations. Patients were initially stabilized on MS Contin® for a minimum of 3 days. The rescue medication dose during this period was prescribed as the equivalent of 10% of the total daily dose of morphine and was given as MSIR® every two hours as needed. After stabilization patients were randomized to receive two of three study treatments. All patients received 100% equivalent total daily morphine stabilization dose as [redacted]™ in one study period and either 100% equivalent total daily morphine stabilization dose as MS Contin® or 50% equivalent total daily morphine stabilization dose as [redacted]™ in the other study period. On day 7 of each study period, frequent blood samples were collected from patients for PK analysis. Patients recorded PD measures in a daily dairy throughout the study.
Number of Subjects (planned and analyzed):	Planned = 42 Analyzed = 32 (PK and PK-PD); 34 (Safety during blinded study period)
Diagnosis and main criteria for inclusion:	Chronic moderate to severe pain of non-malignant origin requiring treatment with a minimum of 60 mg and a maximum of 1000 mg oral morphine equivalents daily.

Test product, dose, duration, and mode of administration, batch number: After stabilization patients were randomized into one of four treatment groups as follows:

	PERIOD	
Group	1	2
1	A	B
2	B	A
3	A	C
4	C	A

where: Treatment A = 100% equivalent daily morphine stabilization dose of once daily [redacted] 100%); Treatment B = 100% equivalent daily morphine stabilization dose of twice daily MS Contin® (MS Contin 100%) and Treatment C = 50% equivalent daily morphine stabilization dose of once daily [redacted]™ ([redacted]; 50%).

PK-PD: A significant concentration-response relationship that is independent of formulation was demonstrated in the analysis using VAS score as the measure of effect. In the course of developing the model, M6G appeared to be the best predictor of effect although the improvement over morphine and M3G was marginal. The inhibitory E_{max} model with baseline effect resulted in a better fit to these data when compared to the linear model. Only one significant covariate-parameter relationship was identified. Study baseline VAS score (measured on day one of stabilization) was a significant predictor of E0.

Although the best model fit was obtained when M6G concentrations were used as the independent variable, morphine concentration was a significant predictor of response. This can be explained by the high degree of correlation observed between the two analytes. When the final model was run using morphine as the predictor, parameter estimates were similar to estimates obtained from the final model with M6G as a predictor, except for the estimate of EC50, which was different because of differences in observed concentrations between morphine and M6G. This indicates that both morphine and M6G are good predictors of the concentration-effect relationship.

In the time-to-rescue analysis, a concentration-response relationship describing a decreased probability of taking rescue medication as a function of morphine or M6G concentration was not demonstrated.

PD Data Summary: When the daily least-squares mean estimates of the various PD measurements were plotted over time, there were no apparent differences observed when [redacted]100% was compared with MS Contin 100%. There was a trend for daily VAS, PDS and quality of sleep scores to be higher for [redacted]50% compared with [redacted]100%. There were no differences in the PD measurements averaged over days 5 to 7 when [redacted]100% was compared with MS Contin 100%. When [redacted]100% was compared with [redacted]50%, there was a trend for all measures to be greater for [redacted]50%. The number of patients requiring less than four doses of rescue medication on either treatment were similar across treatments. However the number of individuals requiring more than four doses of rescue medication on both treatments was higher for the [redacted]100% /[redacted]50% group than for the [redacted]100%/ MS Contin 100% group, 7 versus 3, respectively.

OVERALL SUMMARY AND CONCLUSIONS:

Population PK modeling was carried out to determine the PK parameters for morphine, M6G and M3G in patients and to establish a means for linking dose to response in this trial. Final models were obtained for each analyte and the individual predicted plasma concentrations obtained from fitting the models to the data were used to develop the PK-PD models. Two PK-PD analyses were conducted using the data from this trial. In the first analysis, the continuous PD measurement, VAS score, was modeled as a function of drug concentration. The second analysis was a time-to-event analysis where an event was defined as the time a rescue medication dose was taken, or the censoring time if no rescue dose was taken. In both analyses, the individual predicted analyte concentrations, derived from the fit of the final PK models to the data, were included as potential predictors of the effect.

A concentration-effect relationship was established using VAS scores as the PD endpoint. The data were best described by an inhibitory E_{max} model, but within the range of observed concentrations the relationship was approximately linear. This concentration-effect relationship was independent of formulation ([redacted]™ or MS Contin®). All analytes were found to be good predictors of effect, however M6G was a marginally better predictor of effect than parent morphine concentrations, based on statistical significance. Incorporation of the baseline VAS score as a covariate on the E0 parameter (which represented the response in the absence of drug) resulted in an improved fit of the model and explained some of the random inter-individual variability in the data. In the second PK-PD analysis (the time-to-rescue analysis), no significant concentration-effect relationship was established for the analgesic effects of morphine or M6G. Across the study population, individual rescue dosing behavior was positively correlated with M6G concentration, but this was most likely reflective of the tendency for those patients

with higher stabilization doses to use more rescue medication.

Overall, the study medication (——— ™ and MS Contin®) was well tolerated. The majority of adverse events reported by the 34 patients who received study medication were adverse events that are known to be associated with opioid analgesic use. There were no clinically significant changes in laboratory values, vital signs, or physical exams related to administration of study medication.

Population PK-PD Analysis:

Population PK models were built using a non-linear mixed-effect population modeling approach with the ———software (Version V, Level 1.1).

The following briefly outlines the steps used to build the (pop) PK model:

1. Define a base model (one-compartment model with first-order absorption and elimination).
2. Empirical Bayesian estimates of individual model parameters were generated using the POSTHOC subroutine in ———.
3. The statistical significance of each covariate-parameter relationship was tested individually in a stepwise parameter addition method in ———The covariate resulting in the most significant improvement in the objective function was incorporated into a model and this model then served as the base model for the next building step. This process was repeated until no more significant covariate-parameter relationships were found. Significance during model building was defined as a change in the objective function value when comparing two hierarchical models of at least 3.84 units ($p<0.05$) for the addition of one parameter (1 df).
4. "Final" model: After the full model was defined (the model resulting at the end of the building process is known as the "full" ——— model), the statistical significance of each covariate-parameter relationship was tested individually in a stepwise deletion method at the $p<0.005$ level (increase in objective function value of at least 7.88 units for 1 df). The required p-value is decreased during model reduction to account for the multiple comparisons that are made; this is standard practice for population mixed-effect modeling. This process was repeated until only significant parameters remained in the model.

Results:
Population PK are summarized in the table below (inactive metabolite, M3G is not shown).

Table 1. Morphine and M6G Final Model Parameter Estimates

Final Model Parameter Estimates - FO Method Structural Model and Inter-individual Variance Parameters				
Parameter	**Morphine**		**M6G**	
	Typical Value (%RSE*)	**Inter-individual %CV (%RSE*)**	**Typical Value (%RSE*)**	**Inter-individual %CV (%RSE*)**
ka (hr^{-1}) - [redacted]	0.0175 (27%)	NE	0.0291 (22%)	47% (43%)
ka (hr^{-1}) - MS Contin	0.108 (27%)	NE	0.0796 (29%)	73% (44%)
ka (hr^{-1}) - MSIR	6 fixed	NE	0.130 (13%)	NE
CL/F (L/hr)	$\theta 4 + \theta 8$*(WT-84.09)	37% (60%)	$\theta 4 + \theta 11$*(WT-84.09)	31%(23%)
$\theta 4_{INT}$	278 (11%)	-	62.9 (7%)	-
$\theta 8_{WT}$	2.33 (36%)	-	-	-
$\theta 11_{WT}$		-	0.594 (19%)	-
V/F (L)	841 fixed	85% (72%)	87.0 (13%)	106%(50%)
ALAG (hr) - [redacted]	-		0.180 (3%)	NE
ALAG (hr) - MS Contin	-		0.655 (15%)	NE
ALAG (hr) - MSIR	-		0.517 (45%)	NE
F - MS Contin	1.47 (12%)	41% (55%)	1.20 (12%)	44% (52%)
F - MSIR	0.559 (21%)	72% (62%)	1.09 (23%)	57% (34%)
Parameter	**Intra-individual, Residual Error Estimate (%RSE*)**		**Intra-individual, Residual Error Estimate (%RSE*)**	
$\sigma^2 1_{prop}$	%CV=34% (19%)		%CV=24% (18%)	
$\sigma^2 2_{add}$	SD=1.86 (51%)		0 fixed	

* %RSE: percent relative standard error of the estimate = SE/parameter estimate*100
Abbreviations: FO = first order, ka = absorption rate constant, CL/F = oral clearance, V/F = oral volume of distribution, Relative F = Bioavailability relative to the reference formulation [redacted], $\sigma^2 1_{prop}$ = proportional component of the residual error model, $\sigma^2 2_{add}$ = additive component of the residual error model, NE = Not Estimated.

Figure 1. Plasma Morphine (left) and M6G (right) concentrations versus time after dose (all patients).

[redacted]

Figure 2. Population (left) or Individual (right) Mean Prediction versus Observed Plasma Morphine Concentrations (Final Model):

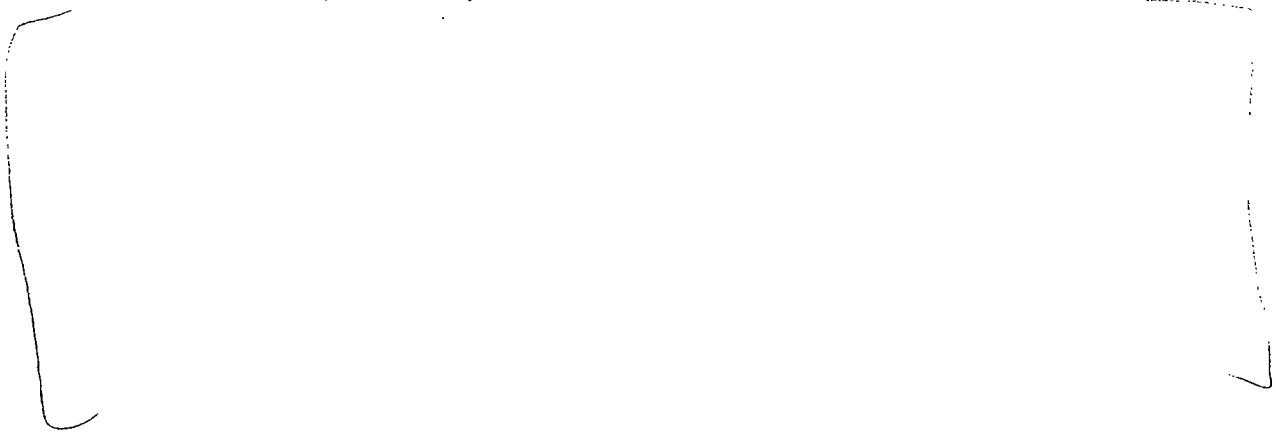


Figure 3. Population (left) or Individual (right) mean prediction versus observed plasma M6G Concentrations (Final Model):

PK-PD RELATIONSHIPS

PK-PD analysis using VAS (Continuous Data):

Data: (1) the predicted plasma concentrations (using the final population PK model parameter values) for each analyte, (2) VAS measurements, (3) covariates such as age, weight and sex for each individuals, (4) baseline mean VAS scores, and (5) formulation ([redacted]versus MS Contin®).

Models: The following mixed-effects models were investigated in this analysis;

1. the baseline effect model with no drug effect
2. the linear PD model with baseline effect included
3. the inhibitory E_{max} model with baseline effect included

Results and Discussion: The results of these model fits are shown in Table 2.

Table 2. Summary of selection of the PD model and independent variable

Run No.	Model Description	Predictor	OFV	ΔOF[a]
102	Baseline Effect Only	N/A	7565.352	N/A
101	Linear model with baseline effect	Morphine	7536.759	-28.593[c]
152	E_{max} Model with baseline effect	Morphine	7527.358	-37.994[c]
106	Linear model with baseline effect	M6G	7520.535	-44.817[c]
153[b]	E_{max} Model with baseline effect	M6G	7505.957	-59.395[c]
111	Linear model with baseline effect	M3G	7536.700	-28.652[c]
154	E_{max} Model with baseline effect	M3G	7519.046	-46.306[c]

Abbreviations: M3G = morphine-3-β-D-glucuronide , M6G = morphine-6-β-D-glucuronide, OFV = Objective Function Value, ΔOF = Change in Objective Function, N/A = not applicable

[a] change in objective function when PD model compared with a model which contained only a baseline effect

[b] model used as the base model for PK-PD modeling [c] significant ($p<0.005$)

The significant decrease in the objective function for all models (29 to 59 points) when compared with the baseline-only model indicated that incorporation of a drug effect is important irrespective of which analyte is used as the predictor or which PD model is used. Taking the linear models first, M6G proved to be a better predictor of effect than morphine or M3G with observed decreases in the objective function of 45, 29 and 29, respectively when compared with the baseline-only model. When M6G was used as the predictor, the (inhibitory) E_{max} model (run 153) resulted in a further drop in the objective function, 45 versus 59 for the linear and E_{max} models, respectively. However, the model (i.e., run 153) predicted E0 and EC50 were 51 mm and 1050 ng/ml, respectively. In addition, both parameters were associated with large inter-individual variability, 64 %CV and 215 %CV for E0 and EC50, respectively. In corporation of the baseline VAS score as a covariate on the E0 parameter (which represented the response in the absence of drug) resulted in an improved fit of the model and explained some of the random inter-individual variability in the data as shown in Table 3.

Table 3. Parameter estimates of the final PD model using morphine or M6G as the independent variable.

Structural Model and Inter-individual Variance Parameters				
	Morphine		M6G	
Parameter	Typical Value (%RSE[b])	Inter-individual %CV[a] (%RSE[b])		Inter-individual %CV[a] (%RSE[b])
E0	θ1 + θ3*(BASE-68)	58% (44%)	θ1 + θ3*(BASE-68)	43% (32%)
θ1	52.2 (11%)	-	58.8 (10%)	-
θ3	0.72 (15%)	-	0.823 (13%)	-
EC50	161 (49%)	137% (41%)	1110 (64%)	239% (49%)
Residual Error				
Parameter	**Estimate (%RSE[b])**		**Estimate (%RSE[b])**	
σ^2_{add}	SD=13.27 (17%)		SD=13.11 (17%)	

[a] approximate %CV

%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100

θ1 = typical population parameter for the intercept of the linear effect of Base on E0

θ3 = typical population parameter for the slope of the linear effect of Base on E0

The inhibitory E_{max} model resulted in a better fit to the observed data when compared to the linear model. However, the population typical value for EC50 (1050 ng/ml by base model; 1110 ng/ml final

model) was much higher than the maximum observed M6G concentration of approximately 550 ng/mL. This indicated that the observed data were primarily in the linear range of the inhibitory E_{max} PD model, therefore, extrapolation of this model beyond the range of observed data is not appropriate (i.e., any sufficient information to precisely estimate parameter values such as EC_{50}).

Figure 4. Prediction versus Observed Visual Analogue Scale Scores (Base (left) and final (right) Model): The line of unity (solid) is included as a reference.

Figure 5. Individual Prediction versus Observed Visual Analogue Scale Scores (Base (left) and final (right) Model): A loess (local regression method) smooth of the data (dotted line) and the line of unity (solid) is included as a reference.

Figure 6. Observed and Predicted VAS Scores versus Plasma M6G Concentrations (Base (left) and final (right) Model): A loess (local regression method) smooth of the data (dotted line) and the line of unity (solid) is included as a reference.

PK-PD analysis using Time-to-Rescue

Data: The data set included the following; (1) individual predictions of plasma morphine and M6G concentrations at the times of rescue or censoring, (2) covariates (age, weight, sex), (3) baseline VAS, (4) treatment, and (5) total daily stabilized dose. An exponential constant hazard model was used to describe the time-to-rescue data [*i.e.*, base model = $\theta_1 \bullet \exp(\eta_1)$]. The model was fitted to the data by maximizing the likelihood of the probability density function for the event (or rescue) when a rescue occurred, or by maximizing the probability of the survival function when a censoring event occurred. A censoring event occurred when a patient did not take a rescue dose over the entire observational day and therefore "survived".

Results and Discussion: A concentration-response relationship describing a decreased probability of taking rescue medication as a function of morphine or M6G concentration was not demonstrated for the time-to-rescue PD endpoint (these findings are consistent with observations). However during model building process, it was shown that M6G concentrations was a predictor of time-to-rescue (i.e., objective function decreased (barely) statistically significant). However, the sponsor suspected this was most likely reflective of the tendency for those patients with higher stabilization doses to use more rescue medication (i.e., individuals who required a higher total daily stabilization dose (and had higher concentrations) experienced more pain and were more likely to use rescue medication).

Labeling claims:
The sponsor proposed use the following text for labeling based on the results of this PK-PD modeling:

[redacted]

The following is provide by the sponsor in support of IVIVC:

SYNOPSIS

TITLE: A single dose study in healthy volunteers to compare the relative bioavailability of four Elan 60 mg once-daily morphine sulphate formulations with a range of in-vitro dissolution profiles

INVESTIGATO: [redacted]

STUDY SITE: [redacted]

PHASE: Phase I (Clinical Pharmacology)

OBJECTIVES: Primary- To develop and validate an IVIVC for Elan's 60mg morphine sulphate extended release capsule formulation.
Secondary - To monitor the volunteers for adverse events.

STUDY MEDICATION: 60 mg morphine sulphate capsule (Elan): Treatment A: Lot # [redacted]14044 (very fast), Treatment B: Lot # [redacted]14623 (fast), Treatment C: Lot # [redacted]14625 (medium), Treatment D: Lot # [redacted]14626 (slow).
Treatment E: 10 mg Oramorph Solution (10mg/5ml)-Boehringer- Lot # [redacted] 690448.

DOSE LEVEL: A total daily oral dose of 10 mg or 60 mg morphine sulphate was administered at each treatment period.

DESIGN: Open label, five treatments, five period crossover study with at least a seven day washout between dosing days.

STUDY POPULATION: Fifteen (15) healthy male volunteers aged between 18 and 40 years.

DATA SOURCE: This study was an open label, single dose, five treatment, five periods, balanced randomized crossover. Fifteen healthy male volunteers were recruited to the study. Twelve subjects completed all five-treatment periods; subjects 13,14, and 15 tested positive for cannabis after completing the first treatment period and were discontinued from the study.
TREATMENTS:

A 60 mg morphine sulphate capsule (Elan) Lot # [redacted]14044 – very fast
B 60 mg morphine sulphate capsule (Elan) Lot # [redacted]14623 – fast
C 60 mg morphine sulphate capsule (Elan) Lot # [redacted]14625 – medium
D 60 mg morphine sulphate capsule (Elan) Lot # [redacted] 14626 – slow
E 10 mg Oramorph solution (10 mg/5ml) – Boehringer Lot # [redacted] 690448

RESULTS: There is a clear rank order in the data with the slowest dissolution corresponding to the minimum C_{max} and AUC and the fastest dissolution corresponding to the maximum C_{max} and AUC. The linear mean-based convolution-based model, incorporating time-shift and time-scaling, met 9 out of 10 FDA predictability criteria. Specifically, AUC absolute percent prediction errors (|%PE|) for treatments —14044,—14623,—14625 and—14626 were equal to 12.86, 8.39, 3.78, and 10.19%, respectively with AUC mean |%PE| equal to 8.80%. C_{max} |%PE| were equal to 6.25, 16.71, 6.65, and 9.98%, respectively with C_{max} mean |%PE| equal to 9.90%. The only parameter outside the allowable limits was C_{max} |%PE| for the —14623 treatment, which was underestimated by 16.71% (exceeding the FDA internal validation limit of 15% by 1.71%). Attempts to use an individual convolution-based approach, or individual or mean deconvolution-based linear and non-linear models, did not improve the fit.

CONCLUSIONS: A Level A IVIVC linear convolution-based model, with time-shift and time-scaling, applied to the mean concentration time data provided the best predictions. The model met the required internal validation criteria limits (|%PE| < 15%, mean |%PE| < 10%), except for C_{max} for the —14623 treatment, which is underestimated by 16.71%, exceeding the FDA limit by 1.71%. Therefore, the model can not and will not be used for setting dissolution specifications and biowaivers at this time.

The mean morphine sulphate concentration-time profiles following each treatment and the mean *in vitro* dissolution profiles are shown in Figure 1. PK parameters of morphine sulphate are presented in Table 1.

Figure 1. Mean plasma morphine concentration-time curves (left), and the mean *in vitro* dissolution profiles (right).

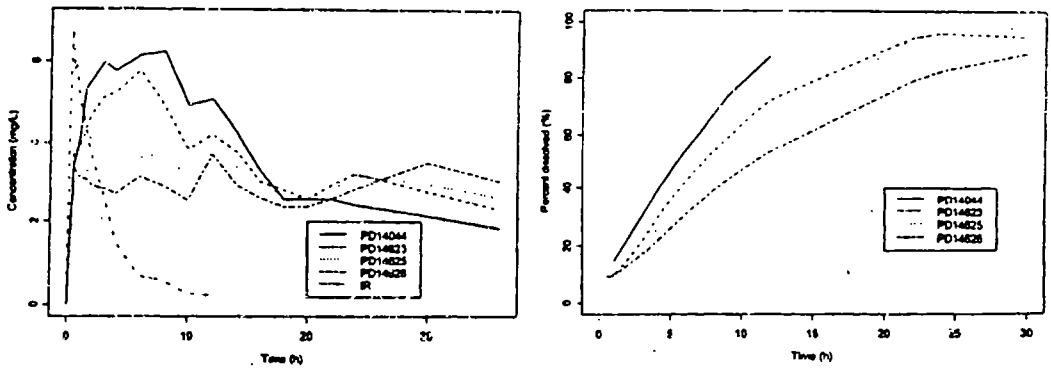


Table 1: Summary of Pharmacokinetic Parameters (Mean ± SD)

	Treatment A PD14044	Treatment B PD14623	Treatment C PD14625	Treatment D PD14626	Treatment E Oramorph Solution (Lot BN690448)
C_{max} (ng/ml)	7.21 ± 1.78	6.32 ± 1.26	4.83 ± 1.44	4.93 ± 1.44	7.11 ± 1.95
T_{max} (h)	5.59 ± 3.31	7.96 ± 6.18	11.30 ± 8.84	14.38 ± 11.02	0.42 ± 0.15
AUC_{last} (ng.h/ml)	128.02 ± 25.50	125.93 ± 25.41	109.16 ± 24.00	104.53 ± 14.55	19.23 ± 4.46
AUC_{all} (ng.h/ml)	128.02 ± 25.50	125.93 ± 25.41	109.16 ± 24.00	104.53 ± 14.55	19.60 ± 4.24
$AUC_{0-infinity}$ (ng.h/ml)	-*	-*	-*	-*	22.20 ± 5.44
$T_{1/2}$ (h)	-*	-*	-*	-*	3.50 ± 2.53

* Lambda_z not estimable

Comment: The sponsor's conclusion is acceptable.

APPEARS THIS WAY
ON ORIGINAL

/s/

Shinja Kim
3/6/01 02:37:17 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/6/01 02:42:06 PM
BIOPHARMACEUTICS