CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-195 & 22-207

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Sayed (Sam) Al Habet, R.Ph., Ph.D**	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**

DATE: **March 12, 2008**	IND No.: Serial No.:	NDA No. **22-195**	DATE OF DOCUMENT **May 16, 2007**	
NAME OF DRUG **Morphine Oral Solution**	INDICATIONS **Relief of Moderate to Severe Pain**		Date of informal/Formal Consult: **000**	Date Received by the Reviewer:

NAME OF THE SPONSOR: **Roxane Laboratories, Columbus, OH**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ **OTHER *(SPECIFY BELOW):*** **[Review Addendum]**
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ Formal Review/Memo (attached) ☐ See comments below ☐ See submission cover letter ☒ OTHER *(SPECIFY BELOW)*: **[Review Addendum]**

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS: This is an addendum to the primary review dated December 21, 2007 for morphine oral solution. This addendum clarifies the role of glycerin as excipient in the two strengths as it relates to the bio-waiver of the 20 mg/5 mL strength.

The conclusion is that the product exists as solution ready for absorption. The difference in the amount of sorbitol and glycerin may be considered minor as both excipients are commonly used in pharmaceutical products.

The literature reports that were reviewed have cited in relation to their effect on PGP, permeability, and gastric empting (e.g., propylene glycol, Tweens, and polysorbates, etc.). Based on its wide use in pharmaceutical products, it is generally believed that glycerin does not affect either the permeability or the PGP activity. b(4)

Based on the historical information available on morphine PK characteristics and the data submitted in both NDAs, there is no reason to suspect that the difference in the amount of glycerin between the 10 mg and 20 mg/5 mL strengths would affect the absorption of morphine. It has been shown that morphine exposure increase proportionally with dose up to 30 mg given as IR tablets.

SIGNATURE OF REVIEWER: _____ **SIGNATURE OF TEAM LEADER:** _____	Date _____ Date _____
CC.: HFD # [580]; Reviewer: (Al Habet); Acting TL: [Zhang]; TL [Doddapaneni] **DD: [Sahjwalla]**	**Project Manager:**_____ **Date** _____

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/s/

Sayed Al-Habet
3/12/2008 02:37:43 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/12/2008 06:45:55 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

NDA: 22-195	**Dates (s) of Submission:** May 16, 2007 November 2, 2007
NDA 22-207	**Date (s) of Submission:** June 7, 2007 November 2, 2007
Generic Name	Morphine Sulfate Oral Solution (**NDA 22-195**) Morphine Sulfate Immediate Release Tablets (**NDA 22-207**)
Brand Name:	**N/A**
Formulations:	Oral Solution (NDA 22-195) Oral Tablets (NDA 22-2007)
Strength:	**Solution:** 10 mg/5 mL and 20 mg/5 mL (NDA 22-195) **Tablet:** 15 and 30 mg (NDA 22-207)
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Route of Administration:	Oral
Indication:	Relief of Moderate to Severe Acute and Chronic Pain
Dosage and Administration:	10 to 20 mg every 4 hours or as directed by a physician
Type of Submission:	Original NDA
Sponsor:	Roxane Laboratories, Columbus, OH
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.

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1.0 Executive Summary

1.1 Recommendation:

From the Clinical Pharmacology perspective, these NDAs are acceptable provided that a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant.

1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no phase 4 commitment is applicable to these NDAs.

1.3 Summary of Important Clinical Pharmacology Findings:

These two NDAs for morphine sulfate oral solution (10 and 20 mg/5 mL) and immediate release tablets (15 mg and 30 mg) were submitted under 505(b)(2) regulations. This is a combined review for both NDAs since the same studies were submitted to both NDAs. These products have been marketed as unapproved products by the sponsor since 1980s under the brand names Morphine Sulfate (Immediate Release) Oral Solution and Morphine Sulfate Immediate Release Tablets.

To support the approval of these formulations, the sponsor conducted three studies using two reference products: morphine sulfate extended-release capsules (Avinza® King Pharms, NDA 21-260) and morphine sulfate injection (Duramorph®, Baxter Healthcare). In addition, nine Clinical Pharmacology and biopharmaceutics related published articles were also submitted. Six of these deal with ethnic differences, gender differences, PK/PD modeling of M-6-G induced analgesia, PK of intradural morphine, PCA-PK, and analgesic plasma concentrations of morphine. These six articles were considered supportive but were not used to determine the acceptability and the approval process of the products. The remaining three articles were submitted to support the biowaiver of the 20 mg/mL solution concentration.

No new Clinical safety and efficacy studies were conducted in support of these NDAs. In addition, no new information related to special populations such as hepatic and renal impairment was submitted by the sponsor. Instead, the sponsor crossed referenced the above products to be used to evaluate the safety and efficacy of morphine in special population and for chronic pain as established for Avinza® and acute pain as established for Duramorph®. As such, the primary support for approval of these products comes from the Clinical Pharmacology studies and the 505 (b) (2) listed drugs (meeting minutes dated September 12, 2006). The following are the brief study designs and summary of the three studies conducted by the sponsor:

Study Designs:

Study # MORP-T30-PLFS-1 (Absolute Bioavailability): This is a crossover single dose study with three treatment arms to investigate the absolute bioavailability of 30mg oral solution and 30 mg immediate release tablets to 10 mg intravenous morphine sulfate (Duramorph®).

Study # MORP-T30-PVFS-2 (Dose Proportionality): This is a single dose, three-period, crossover to investigate the dose proportionality and effect of food on morphine sulfate tablet.

Study # MORP-T30-PVFS-3 (Steady-State, Pivotal Study): This is a crossover multiple-dose/steady-state study with three treatments arms to investigate the relative bioavailability of morphine oral solution, immediate release tablets, and extended release marketed capsules (Avinza®). The tablets and solution were administered at a dose of 30 mg Q6h and Avinza® (extended release capsule) was administered at a dose of 120 mg Q24h for 5 days in 27 healthy subjects.

Summary of Results:

In all these studies the plasma concentrations of the parent drug morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) metabolites were measured.

The first study (#PLFS 1) is considered developmental/pilot with the objective to optimize the study design for the pivotal relative bioavailability study at steady-state. In this study, 17 subjects completed all three arms of the study.

From this study, it appears that the $AUC_{(0-\infty)}$ (0-infinity) for the parent drug morphine after tablet is approximately 40% higher (181±73 ng.h/mL) than after solution (131 ± 23.7 ng.h/mL). However, the $AUC_{(0-t)}$ (from zero to the last time point) after the two formulations are comparable (**Figure 1.3.1 and Table 1.3.1**). It is noteworthy that the same trend of Cmax being higher after tablet (44.8 ± 21.3 ng/mL) than after solution (36.9 ± 12.7 ng/mL) was seen.

Figure 1.3.1. Mean plasma concentrations-Time Profiles of the Parent Drug Morphine

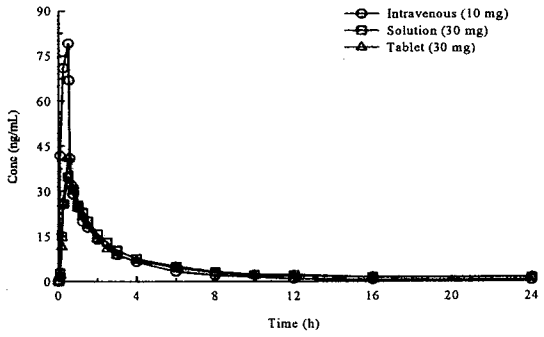

Table 1.3.1. Summary of PK parameters for the Parent Drug Morphine (Study PLFS 1).

Parameter[1]	Intravenous	Solution	Tablet
Cmax (ng/mL)	88.9 ± 32.4 (17)	36.9 ± 12.7 (17)	44.8 ± 21.3 (17)
Tmax (h)	0.50 (17)	0.50 (17)	0.50 (17)
	[0.25 – 0.53]	[0.25 – 0.80]	[0.25 – 1.50]
AUC(0-t) (h•ng/mL)	113 ± 21.3 (17)	117 ± 32.7 (17)	111 ± 35.3 (17)
AUC(inf) (h•ng/mL)	130 ± 34.9 (5)	131 ± 23.7 (4)	181 ± 73.5 (4)
λz (h^{-1})	0.0615 ± 0.0153 (5)	0.0504 ± 0.0175 (4)	0.0403 ± 0.0260 (4)
t½ (h)	11.9 ± 3.07 (5)	15.2 ± 5.90 (4)	30.3 ± 31.04 (4)
Ln(Cmax)	4.43 ± 0.32 (17)	3.55 ± 0.35 (17)	3.70 ± 0.47 (17)
Ln[AUC(0-t)]	4.71 ± 0.17 (17)	4.73 ± 0.26 (17)	4.67 ± 0.31 (17)
Ln[AUC(inf)]	4.84 ± 0.24 (5)	4.86 ± 0.19 (4)	5.13 ± 0.42 (4)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Theoretically, the tablet is expected to have same or lower rate of absorption than solution. The reasons for tablet exhibiting higher rate of absorption is unknown. The typical morphine half life or so called effective half life (clinical half life) is in the range of 2 to 4 hours. The long terminal half life reported in this study could be explained by extended plasma sampling that was not typically done in previous studies. The plasma concentration of morphine associated with these extended plasma sampling is far below the effective level to be considered clinically relevant. Therefore, the clinically useful half life of morphine remains to be between 2 to 4 hours.

Furthermore, due to the variability in the data, there were also few subjects for whom AUC(0-∞) could be calculated to permit a statistical comparison. Therefore, the 90% CI was not reported by the sponsor for AUC(0-∞). Based on this data, the 90% CI for AUC(0-t) was used instead and was within 80-125% for tablet and solution. Relying on AUC(0-t) seems appropriate in light of the half-life discussion in the above paragraph. However, the Cmax was outside the 80-125% (99.03% to 135.55). Therefore, based on this study the two formulations can be considered to be **not bioequivalent (Table 1.3.2).**

Table 1.3.2. Summary of Morphine Bioequivalence Statistical Analysis and 90% CI (Study # PLFS-1)

Parameter	Geometric Mean Ratio (%)[1,2] Estimate	90% Confidence Interval			Within Subject CV (%)
Solution vs. Intravenous					
Cmax	13.93	11.90	→	16.29	27.41
AUC(0-t)	34.26	31.50	→	37.26	14.46
AUC(inf)[3]	55.48				
Tablet vs. Intravenous					
Cmax	16.13	13.79	→	18.88	27.41
AUC(0-t)	31.98	29.40	→	34.78	14.46
AUC(inf)[3]	34.74				
Tablet vs. Solution					
Cmax	115.86	99.03	→	135.55	27.41
AUC(0-t)	93.34	85.83	→	101.51	14.46
AUC(inf)[3]	62.62				

[1]Based on analysis of natural log-transformed data.
[2]Values for the 10 mg intravenous were adjusted to 30 mg before comparison with the oral data.
[3]There were too few subjects for whom AUC(inf) could be calculated to permit a statistical comparison.

In the second study (#PVFS-2), 32 subjects completed the three arms. As in the previous study, the parent drug morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) metabolites were measured in the plasma. The exposure was proportional between 15 and 30 mg doses (**Figure 1.3.2 and Table 1.3.3**).

Figure 1.3.2. Mean plasma concentrations-Time Profiles of Morphine (Study # PVFS-2)

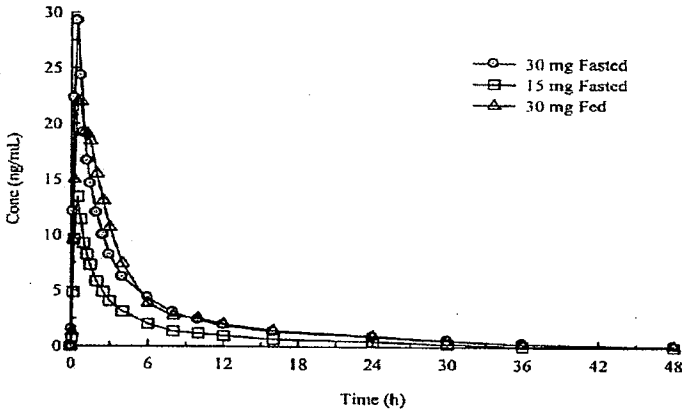

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Table 1.3.3. Summary of PK of Morphine (Study # PVFS-2)

Parameter[1]	30 mg Fasted	15 mg Fasted	30 mg Fed
Cmax (ng/mL)	32.8 ± 13.8 (32)	15.8 ± 7.42 (32)	30.9 ± 21.3 (32)
Tmax (h)	0.50 (32) [0.17 – 0.78]	0.50 (32) [0.17 – 1.50]	0.75 (32) [0.00 – 2.50]
AUC(0-t) (h•ng/mL)	104 ± 32.6 (32)	49.1 ± 14.6 (32)	110 ± 38.0 (32)
AUC(inf) (h•ng/mL)	113 ± 36.9 (22)	54.3 ± 12.7 (21)	125 ± 28.6 (23)
λz (h^{-1})	0.0824 ± 0.0248 (22)	0.0780 ± 0.0366 (21)	0.0801 ± 0.0325 (23)
t½ (h)	9.13 ± 2.65 (22)	12.2 ± 11.77 (21)	10.6 ± 6.52 (23)
Ln(Cmax)	3.40 ± 0.45 (32)	2.64 ± 0.52 (32)	3.31 ± 0.55 (31)
Ln[AUC(0-t)]	4.60 ± 0.30 (32)	3.85 ± 0.30 (32)	4.68 ± 0.34 (31)
Ln[AUC(inf)]	4.68 ± 0.32 (22)	3.97 ± 0.25 (21)	4.80 ± 0.24 (23)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

The presence of food had no apparent effect on the extent of absorption of morphine. However, there is a slight reduction in Cmax and small prolongation in Tmax (**Figures 1.3.2 and Table 1.3.3**). From the bioequivalence perspective, the 90% CI for the Cmax was outside the 80 to 125% (74.58 to 106.17%, **Table 1.3.4**). On a mean basis, there was about 11% reduction in Cmax under fed conditions. This is not expected to be clinically significant and the product can be administered without regard to meals.

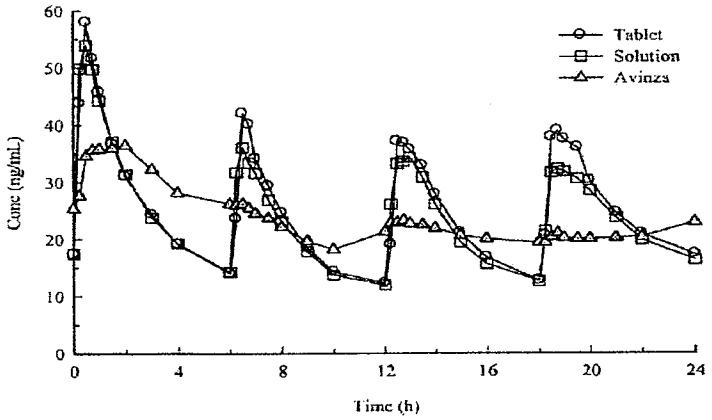
Table 1.3.4. Summary of PK Parameters for Morphine (Study # PVFS-2)

	Geometric Mean Ratio (%)[1,2]			
Parameter	Estimate	90% Confidence Interval		
15 mg Fasted vs. 30 mg Fasted				
Cmax	93.04	78.14	→	110.79
AUC(0-t)	94.95	87.10	→	103.51
AUC(inf)	101.44	94.80	→	108.53
30 mg Fed vs. 30 mg Fasted				
Cmax	88.98	74.58	→	106.17
AUC(0-t)	106.88	97.95	→	116.64
AUC(inf)	114.90	107.97	→	122.28

[1]Based on analysis of natural log-transformed data.
[2]Values for the 15 mg tablet were adjusted to 30 mg before statistical analysis.

The third study (#PVFS-3) is considered **pivotal** since it characterizes the formulations at steady-state and also included Avinza® as a reference product. In this study, 27 subjects completed all three arms. The plasma concentration-time profiles for morphine is typical after Q6h oral dosing of immediate release tablets and solution as well as after Q24h of extended release capsule, Avinza® (**Figure 1.3.3**).

Figure 1.3.3. Mean Plasma Concentration-Time Profiles of Morphine on Day 5 After all Doses (Study # PVFS-3)



Consistent with the observation from the previous two studies (PLFS-1 and PVFS-2), the Cmax after IR tablet appears to be higher by approximately 30 % compared solution (**Table 1.3.5**). Also, the AUC (0-24h) after IR tablet was slightly higher by 10% than after oral solution. Furthermore, the Cmax and AUC for IR tablets were consistently higher after each dose level on Day 5 than after oral solution (**Table 1.3.6**).

Table 1.3.5. Summary of Morphine PK Parameters on Day 5 at all Doses (Study # PVFS 3)

Parameter[1,2]	Tablet	Solution	Avinza
Cmax (ng/mL)	78.6 ± 28.5 (27)	58.3 ± 21.2 (27)	41.1 ± 11.2 (27)
Tmax (h)	0.50 (27) [0.25 – 20.1]	0.50 (27) [0.25 – 12.8]	1.50 (27) [0.50 – 3.00]
AUC(24) (h•ng/mL)	581 ± 173 (27)	555 ± 119 (27)	565 ± 145 (27)
Cmin (ng/mL)	10.9 ± 3.83 (27)	11.2 ± 2.76 (27)	16.3 ± 4.82 (27)
Percent Fluctuation	281 ± 84.8 (27)	202 ± 66.8 (27)	107 ± 33.6 (27)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.
[2]Cmax and Cmin are the maximum and minimum concentrations observed over the 24-hour period.

Table 1.3.6. Summary of PK Parameters for Morphine at Each Dose Level on Day 5 (Study # PVFS-3).

	Tablet			Solution		
Dose	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h•ng/mL)	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h•ng/mL)
1st	72.2 ± 27.8 (27)	1 (27)	166 ± 50.3 (27)	58.2 ± 21.3 (27)	1 (27)	166 ± 38.7 (27)
2nd	47.4 ± 19.3 (27)	7 (27)	126 ± 34.1 (27)	37.7 ± 10.9 (27)	7 (27)	120 ± 23.7 (27)
3rd	46.4 ± 21.0 (27)	13 (27)	135 ± 41.4 (27)	36.8 ± 9.55 (27)	13 (27)	128 ± 28.2 (27)
4th	44.4 ± 24.2 (27)	19 (27)	154 ± 59.7 (27)	36.0 ± 12.1 (27)	19 (27)	141 ± 36.7 (27)

[1]Arithmetic mean ± standard deviation (N).
[2]Median (N)

From the bioequivalence perspective, the 90% CI for Cmax was outside the boundary limits of 80 % and 125% (**Table 1.3.7**). However, the AUC was within the 80 to 125%. Therefore, in principle the two formulations are **not bioequivalent.**

Table 1.3.7. Summary of Statistical Analysis of Morphine PK Data (Study # PVFS-3)

Parameter	Geometric Mean Ratio (%)[1,2]			
	Estimate	90% Confidence Interval		
Solution vs. Avinza				
Cmax	72.02	65.42	→	79.29
AUC(0-24)	100.50	96.99	→	104.14
Tablet vs. Avinza				
Cmax	53.84	48.90	→	59.29
AUC(0-24)	97.28	93.87	→	100.81
Tablet vs. Solution				
Cmax	133.75	121.49	→	147.25
AUC(0-24)	103.31	99.70	→	107.05

[1]Based on analysis of natural log-transformed data.

In comparison to the extended release (ER) formulation, Avinza, the AUC (0-24) are comparable to both Roxane IR formulations (**Table 1.3.5**). The 90 % CI following the three treatments was within 80 to 125% (**Table 1.3.7**). Since the Cmax after IR is expected to be higher than after ER formulation, then the two Roxane's formulations are considered comparable to Avinza, **but not bioequivalent to each other.**

Special Population:

No formal studies were conducted in special population in this NDA. However, based on historical data, clinical experience, and the well know metabolic and excretion pathways of morphine and its metabolites, the sponsor included in the draft labeling a language similar to that already in Avinza approved label to caution the use of morphine in patients with hepatic or renal insufficiency. (see also QBR section).

Pediatric Indication:

Based on the pre-IND meeting held in September 12, 2006 (IND # 75,041), the sponsor was advised that the literature and/or the PK information alone are unlikely to provide sufficient, evidence-based pediatric dosing information to adequately address the requirements of PREA and that they may request a deferral of pediatric studies at the time of marketing application (see meeting minutes dated September 12, 2007, IND # 74,041).

Overall Summary and Conclusions:

- Based on the pilot study (#PFLS-1) and the pivotal study (#PVFS-3), the bioavailability of tablets and solution are comparable, but **not bioequivalent** due to the difference in Cmax.

- The clinically relevant or the so called effective half life of morphine range from 2 to 4 hours. The reported half life in the range of 10 to 30 hours represents the terminal elimination phase (half life) that may not be of clinically relevant due to the low concentration range in the terminal phase.

- The exposure to morphine and its metabolite, M3G and M6G, is dose proportional after 15 mg and 30 mg tablets.

- Food appears to slightly delay the Tmax and reduce the Cmax by approximately 10%. Even though, from a bioequivalence perspective, the two treatments (fed vs fasted) are **not bioequivalent,** the small reduction in Cmax under fed conditions is not expected to be clinically significant.

- Steady-state was achieved after 5 days of treatments at Q6H regimen for Roxane IR formulation and Q24h of the reference product, extended release capsule Avinza®.

- The total exposure as measured by AUC (0-24) following IR formulation after Q6h treatment and Avinza, Q24h treatment, were comparable. The 90% CI for AUC (0-24h) fall within 80-125%. Based on this data, the two formulations are considered comparable, but **not bioequivalent** due to the differences in Cmax..

- The AUC (0-24h) for IR table and solution falls within 80-125%. However, the Cmax after IR tablets was consistently higher than after solution. The 90% CI for the Cmax was outside 80-125%. Therefore, it can be concluded that the two formulations are **not bioequivalent.**

- No PK data is available on the highest oral solution strength of 20 mg/5 mL. All studies were conducted using the lower strength of 10 mg/5 mL. In addition, the composition of the two formulation are comparable, but **not the same.** However, since this is a solution and the drug is highly soluble and dose proportional the availability of a PK data for the 20 mg/5 mL strength would be useful, but may not hold the approval. In addition, from the clinical perspective, the drug would be titrated to the nearest dose to achieve the optimal analgesia within a reasonable safety margin. It should be noted that on November 2, 2007, the sponsor provided justification for the change in formulation accompanied with literature articles. The information submitted by the sponsor indicates that the differences in the formulation may not substantially affect the absorption and bioavailability of morphine solution (see the biopharmaceutics section of this review for more detailed discussion on the bio-waiver for the 20 mg/5 mL strength).

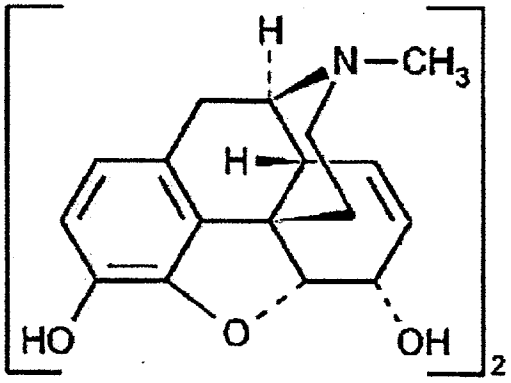
Overall, the two products (IR tablets and solution) are comparable to each other with respect AUC (overall exposure) and to the reference Avinza®, but they are **not bioequivalent at the Cmax .** However, since they have equivalent exposure at equivalent total daily doses and the Cmax values are higher as expected, the two products would be expected to be efficacious. If anything, the higher Cmax values relative to that of Avinza may present safety issues from a theoretical point of view. However, based on available data from previously approved products, such differences are typical of IR to MR switch of morphine and are therefore not expected to cause undue safety concern.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Morphine is an old drug with fully characterized physico-chemical characteristics. It is insoluble in water and slightly soluble in alcohol. It has a pKa of 7.9. The structural formula is shown below:



• H_2SO_4 • $5H_2O$

The sponsor is proposing to use suppliers of morphine sulfate substances/API, b(4)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Morphine is a pure opioid agonist relatively selective for the mu receptor. It is mainly used as analgesic to control moderate to severe pain.

Indications:

The primary indication of tablets and solutions is for relief of moderate to severe acute and chronic pain.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The tablet and solution are proposed to be administered at dose ranging from 15 to 30 mg every 4 hours or as directed by the physician.

However, morphine should be administrated with caution in patients with hepatic or renal insufficiency.

2.1.4 What are the Core Studies Submitted in this NDA?

In this NDA, three studies were submitted. The first study is a pilot/developmental study to determine the absolute bioavailability of immediate release (IR) tablet and oral solution comparing to intravenous (IV) morphine. The second objective is to optimize the study design for the pivotal bioequivalence (BE) study (Study # MORP-T30-PLFS-1).

The second study was to investigate the dose proportionality between 15 mg and 30 mg IR tablets and the effect of food on the PK of morphine after 30 mg IR tablets (Study # MORP-T30-PLF-2).

The third was a pivotal study that was conducted to characterize the PK of morphine at steady state following tablet and solution and to establish their relative bioavailability to the marketed extended release capsule, Avinza®. The DSI inspection reports dated October 11, 2007 of this study concluded that the inspectional findings should not have significant impact on the acceptability of study findings (See review dated October 11, 2007 for details of the inspection report).

In addition, the sponsor submitted sixteen published articles in support to the utilization of morphine specific clinical settings and patients population. Several of these articles were not directly relevant to the approval process of these products. They are mainly related to the control of analgesia in different ethnic and gender groups as well as post operative pain. Other articles were related to excretion of morphine in breast milk, the PK of intradural morphine in post surgery, PK/PD of M6G, and the utilization of IV of morphine in Chinese patients. Three articles supported the sponsor's rationale for a biowaiver of the 20 mg/mL solution concentration.

No new clinical studies were conducted by the sponsor in support of these two products. The approval of these products relies on the bioavailability comparisons between these products and the approved Duramorph and Avinza products and the historical data.

2.2 General Clinical Pharmacology

Based on the data from the studies submitted in this NDA and the historical data, the PK of morphine is summarized below.

Morphine undergoes extensive pre-systemic metabolism. The oral bioavailability of morphine is <40% with high inter-subject variability. Morphine is widely distributed in the body and in most vital organs, primarily CNS. The metabolism of morphine is well characterized. It is mainly undergoes conjugation with either D-glucuronic acid or sulfuric acid. The primary two metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The latter appears to have more analgesic activity than the former.

Morphine excreted mainly in urine as M3G and M6G. Approximately 10% of morphine dose is excreted unchanged in urine and another 10% in feces. The half life of morphine after IV administration is short. It is approximately 2 hours (effective half life). However, depending on the assay sensitivity and duration of sampling, the terminal half life may be longer, especially after oral administration. Nevertheless, at this point, the blood concentration is too low to be considered significant to control analgesia.

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was used in this NDA. All data in this NDA were presented as comparative PK.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

All data were based on measurement of the parent drug, morphine and its two metabolites, M3G and M6G. As stated earlier, morphine undergoes extensive pre-systemic (first pass metabolism) after oral administration. Therefore, it is excreted mainly as metabolites in urine and approximately 20% excreted as unchanged in feces and urine.

2.2.3 Exposure Response
2.2.3.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and response/efficacy. In other words, the focus of this NDA is on the comparative bioavailability for the tablet and oral solution relative to the marketed product, Avinza®. Therefore, no PK/PD analysis was performed in these submissions to establish the relationship between morphine dose and efficacy.

2.2.3.2 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety.

2.2.3.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of morphine on QTc.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of morphine and its metabolites? How do the PK parameters change with time following chronic dosing?

The sponsor conducted three studies, two after a single dose and one after a multiple dose of 30 mg IR tablet or solution on a regimen of Q6h for 5 days and Q24h also for 5 days for 120 mg extended release (ER) marketed formulation, Avinza® (Study # MORP-T30-PVFS-3). The main objective of the study is to compare the PK and determine the relative bioavailability of 30 mg IR formulation to 120 mg ER capsule. The data from this study is summarized in **Figure 2.2.4.1 and Tables 2.2.4.1.1-3.**

Figure 2.2.4.1.1 Mean Plasma Concentration-Time Profiles of Morphine (Study # PVFS-3)

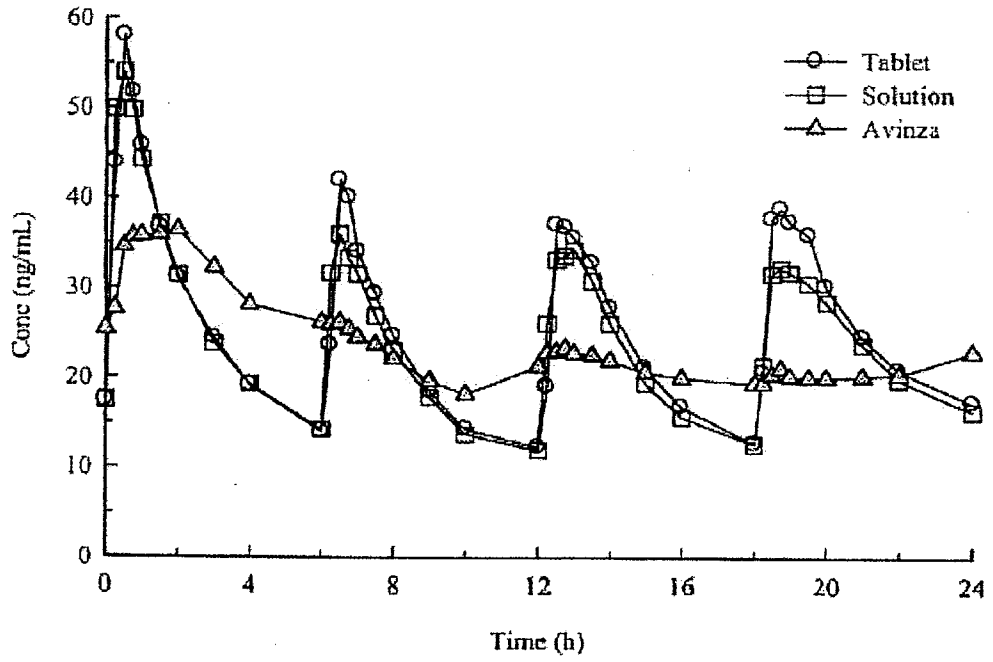


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Table 2.2.4.1.1. Summary of Morphine PK Parameters (Study # PVFS 3)

Parameter[1,2]	Tablet	Solution	Avinza
Cmax (ng/mL)	78.6 ± 28.5 (27)	58.3 ± 21.2 (27)	41.1 ± 11.2 (27)
Tmax (h)	0.50 (27) [0.25 – 20.1]	0.50 (27) [0.25 – 12.8]	1.50 (27) [0.50 – 3.00]
AUC(24) (h•ng/mL)	581 ± 173 (27)	555 ± 119 (27)	565 ± 145 (27)
Cmin (ng/mL)	10.9 ± 3.83 (27)	11.2 ± 2.76 (27)	16.3 ± 4.82 (27)
Percent Fluctuation	281 ± 84.8 (27)	202 ± 66.8 (27)	107 ± 33.6 (27)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.
[2]Cmax and Cmin are the maximum and minimum concentrations observed over the 24-hour period.

Summary (Study # PVSF-3):

From this study, the data can be summarized as follows:

- The plasma concentration-time profiles for morphine was typical for Q6h dosing of immediate release tablets and solution as well as for Q24h dosing for extended release capsule Avinza® (**Figure 2.2.4.1.1**).

- The Cmax after IR tablet appears to be higher by approximately 25 % than after solution (**Table 2.2.4.1.1**). However, the AUC (0-24h) after IR tablet was slightly higher by 10% than oral solution.

- In comparison to the extended release (ER) formulation, Avinza, the AUC (0-24) are comparable to both Roxane IR formulations (**Table 2.2.4.1.1**).

- The plasma concentration-time profiles of the two metabolites, M3G and M6G followed similar patterns as the parent drug, morphine (**For more details, see individual study review**).

Conclusions (Study # PVSF-3):

Based on this study, the exposure (AUC) following the three products is comparable. The Cmax tends to decrease with time on Day 5 of the study. However, no additional PK information is available with the proposed formulations after chronic administration.

2.2.4.2 Are the PK of Morphine and its metabolites linear and dose-proportional?

The sponsor conducted one study to determine the dose proportionality between 15 mg and 30 mg tablet after a single dose in healthy subjects (Study # MORP-T30-PVFS-2).

From this study the exposure between 15 mg and 30 mg was dose proportional with respect to both Cmax and AUC (**Table 2.2.4.2.1 and Figure 2.2.4.2.1**). The same trend

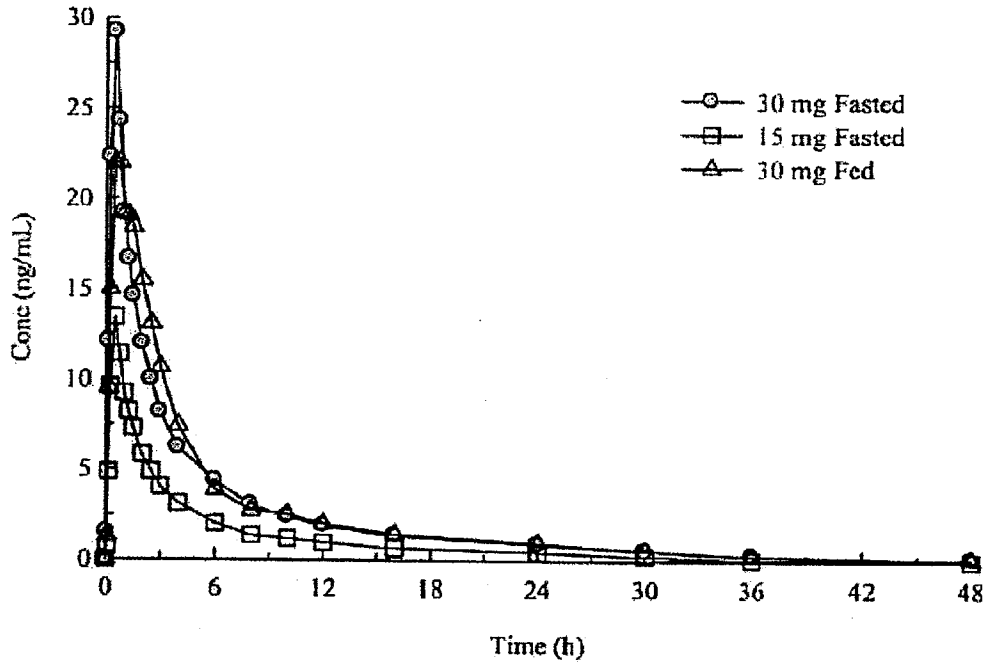
was observed for morphine metabolites, M3G and M6G (for more details, see individual study review).

Table 2.2.4.2.1. Summary of PK of Morphine (Study # PVFS-2)

Parameter[1]	30 mg Fasted	15 mg Fasted	30 mg Fed
Cmax (ng/mL)	32.8 ± 13.8 (32)	15.8 ± 7.42 (32)	30.9 ± 21.3 (32)
Tmax (h)	0.50 (32) [0.17 – 0.78]	0.50 (32) [0.17 – 1.50]	0.75 (32) [0.00 – 2.50]
AUC(0-t) (h*ng/mL)	104 ± 32.6 (32)	49.1 ± 14.6 (32)	110 ± 38.0 (32)
AUC(inf) (h*ng/mL)	113 ± 36.9 (22)	54.3 ± 12.7 (21)	125 ± 28.6 (23)
$\lambda z (h^{-1})$	0.0824 ± 0.0248 (22)	0.0780 ± 0.0366 (21)	0.0801 ± 0.0325 (23)
t½ (h)	9.13 ± 2.65 (22)	12.2 ± 11.77 (21)	10.6 ± 6.52 (23)
Ln(Cmax)	3.40 ± 0.45 (32)	2.64 ± 0.52 (32)	3.31 ± 0.55 (31)
Ln[AUC(0-t)]	4.60 ± 0.30 (32)	3.85 ± 0.30 (32)	4.68 ± 0.34 (31)
Ln[AUC(inf)]	4.68 ± 0.32 (22)	3.97 ± 0.25 (21)	4.80 ± 0.24 (23)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Figure 2.2.4.2.1: Mean plasma concentrations-Time Profiles of Morphine (Study # PVFS-2)



The half life was approximately 10 hours, irrespective of dose. The long half life value for morphine should be interpreted with caution as they do not reflect the so called **"effective half-life' but the terminal elimination half life. The effective half life of** morphine is approximately 2-4 hours. The terminal half life is reflective of the assay sensitivity and the duration of blood sampling time.

2.2.4.3 What is the Extent of Systemic Exposure After Morphine Administration?

As stated previously, only one study was conducted in this NDA to establish the PK and relative bioavailability after multiple dose administration of IR formulation (30 mg at Q6h) and 120 mg ER capsule (Q24h) for only 5 days (Study # PVFS-3). The dose proportionality study, however, was conducted after a single dose of 15 mg and 30 mg IR tablets (Study # PVFS-2). As stated earlier, the exposure after multiple dose were comparable after IR and ER.

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal studies were conducted in special population in this NDA. However, based on known metabolic and excretion pathways of morphine and its metabolites, the sponsor proposed in the draft labeling that caution should be exercised when administering morphine in patients with hepatic or renal insufficiency. Based on some literature reports, morphine clearance decreases in patients with hepatic and renal impairment as well as the AUC ratios of M3G and M6G to morphine AUC.

Furthermore, the sponsor included a language in the proposed label similar to that already in Avinza label to reflect the following:

- The sensitivity to morphine increase in elderly patients over 65 years of age. Therefore, dosing should be carefully selected.
- Women are more sensitive to morphine than men.
- The clearance of morphine appears to be faster in Chinese subjects compared to Caucasians.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol on morphine use were not evaluated.

No specific studies were conducted to investigate the effect of extrinsic factors on the disposition of morphine. However, based on the clinical experience other CNS depressant drugs such as alcohol, other opioids or illicit drugs may have additive effect on morphine.

However, the sponsor conducted specific study to investigate the effect of food on the PK of IR tablet. This will be discussed in the next section below.

2.5 General Biopharmaceutics

The DSI inspection report dated October 11, 2007 for both tablets and oral solutions concluded that the inspectional findings should not have significant impact on the study outcome (See review dated October 11, 2007 for details of the inspection report).

2.5.1 What is the BCS Class classification for Morphine?

This information was not provided by the sponsor in this NDA.

However, as stated earlier, morphine is highly soluble, is dose proportional, with oral bioavailability of approximately 40%. No data on the permeability was provided by the sponsor to classify morphine under BCS with certainty. The classification of morphine is relevant to the approvability of the 20 mg/5 mL solution strength.

Based on the sponsor justification dated November 2, 2007, the drug is highly soluble and is already in solution. The differences in the formulation between 10 mg/5 ml and 20 mg/5 mL solution strengths may have no substantial impact on the absorption and bioavailability of morphine.

Based on this as well as the extensive clinical experience with morphine, the 20 mg/5 ml should be approved along with the 10 mg/5 mL strength.

2.5.2 What is the effect of food on the BA of Morphine?

The sponsor conducted one study to investigate the effect of food after 30 mg IR tablet (Study # MORP-T30-PVFS-2). This study was part of the dose proportionality study in 32 healthy subjects as three treatments in crossover design as follows:

Treatment A (15 mg fasting): 15 mg tablets after overnight fasting

Treatment B (30 mg fasting): 30 mg tablet after overnight fasting.

Treatment C (30 mg fed): 30 mg tablet after high fat standard breakfast.

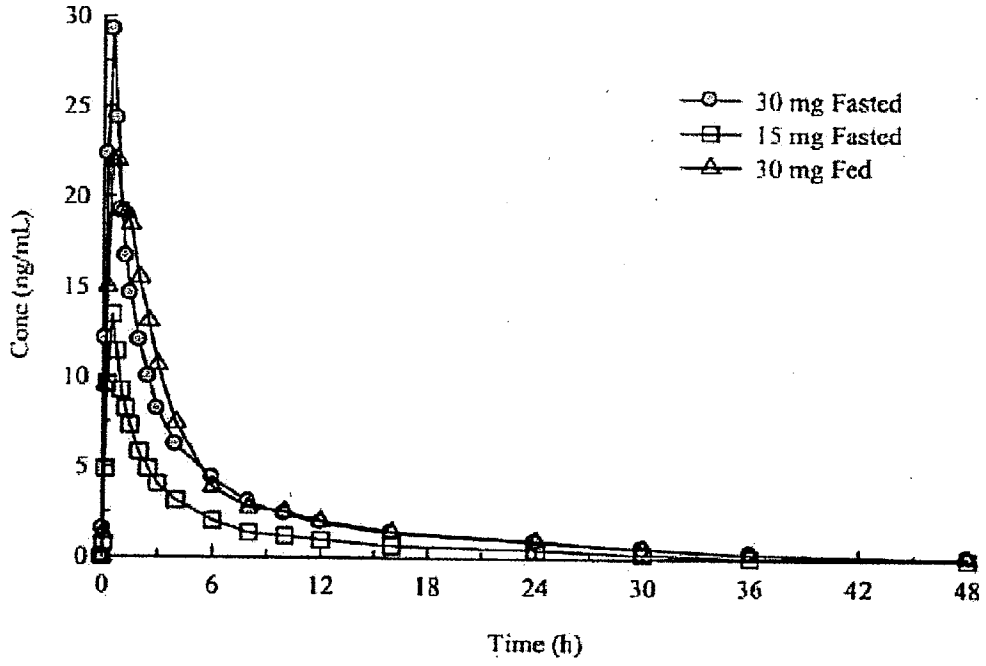
- Based on this study it can be concluded that food appears to slightly reduce the Cmax and prolong Tmax of morphine (**Table 2.5.2.1 and Figure 2.5.2.1**). The same trend was seen for morphine metabolite, M3G and M6G (See individual study review for details).

Table 2.5.2.1. Summary of PK of Morphine (Study PVFS-2)

Parameter[1]	30 mg Fasted	15 mg Fasted	30 mg Fed
Cmax (ng/mL)	32.8 ± 13.8 (32)	15.8 ± 7.42 (32)	30.9 ± 21.3 (32)
Tmax (h)	0.50 (32) [0.17 – 0.78]	0.50 (32) [0.17 – 1.50]	0.75 (32) [0.00 – 2.50]
AUC(0-t) (h*ng/mL)	104 ± 32.6 (32)	49.1 ± 14.6 (32)	110 ± 38.0 (32)
AUC(inf) (h*ng/mL)	113 ± 36.9 (22)	54.3 ± 12.7 (21)	125 ± 28.6 (23)
λz (h^{-1})	0.0824 ± 0.0248 (22)	0.0780 ± 0.0366 (21)	0.0801 ± 0.0325 (23)
t½ (h)	9.13 ± 2.65 (22)	12.2 ± 11.77 (21)	10.6 ± 6.52 (23)
Ln(Cmax)	3.40 ± 0.45 (32)	2.64 ± 0.52 (32)	3.31 ± 0.55 (31)
Ln[AUC(0-t)]	4.60 ± 0.30 (32)	3.85 ± 0.30 (32)	4.68 ± 0.34 (31)
Ln[AUC(inf)]	4.68 ± 0.32 (22)	3.97 ± 0.25 (21)	4.80 ± 0.24 (23)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Figure 2.5.2.1. Mean plasma concentrations-Time Profiles of Morphine



Conclusion:

Food appears to slightly delay the absorption of morphine and/or the formation of the metabolites as characterized by Tmax and rate of absorption. The Cmax of morphine was reduced by approximately 10% and for the metabolites was reduced by approximately 25-32%. However, the overall exposure (AUC) was comparable in fed or fasting states (for details, see individual study review).

2.5.3 Was the to-be-marketed formulation used in the PK/Clinical trials?

Yes.

For tablets, according to the sponsor, all lots were manufactured using the same formula, manufacturing site, equipment and process. There are no differences in the manufacturing process or equipment between the commercial/registration lots used in the biostudies. The same applies for oral solution, except that the 20 mg/5 mL strength was scaled up to 3800 L.

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

The formulation composition for tablets and oral solution are shown in **Tables 2.5.4.1 and 2.5.4.2).**

It should be noted that the 15 mg and 30 mg tablets are compositionally proportional in all ingredients (**Table 2.5.4.1**). Also, there were no differences in the manufacturing process or equipment between the commercial/registration lots used in the biostudies and the historical commercial lots.

For oral solution, the two strengths are different from each other in terms of composition (**Tables 2.5.4.2**). No explanation was provided by the sponsor for the difference. Also, no PK data were provided by the sponsor for 20 mg/5 mL solution strength.

Table 2.5.4.1. Morphine Formulation Composition For 15 mg and 30 mg Tablets

Ingredients	Purpose	Quality Standard	Amount (mg per tablet)	
			15 mg tablets	30 mg tablets
Morphine Sulfate, USP	Active Ingredient		15.15 mg	30.3 mg
Microcrystalline Cellulose, NF		NF		
Pregelatinized Starch, NF		NF		
Corn Starch, NF		NF		
Colloidal Silicon Dioxide, NF		NF		
Stearic Acid, NF		NF		
Theoretical Tablet Weight	-	-	100 mg	200 mg

b(4)

Table 2.5.4.2. Morphine Formulation Composition for Oral Solutions (10 mg/5 mL and 20 mg/5 mL)

Ingredient	Amount per 5 mL		Amount (%)	
	Strength 1 (10 mg/5 mL)	Strength 2 (20 mg/ 5mL)	Strength 1 (10 mg/5 mL)	Strength 2 (20 mg/ 5mL)
Morphine Sulfate, USP	10 mg	20.0 mg	0.20%	0.40%
Sorbitol USP				
Glycerin, USP				
Citric Acid, USP				
Sodium Benzoate, NF				
Disodium Edetate, USP				
FD & C Green No. 3 Certified (Fast Green)				
Water, USP				
Methylparaben, NF				
Propylparaben, NF				

b(4)

Justification For Bio-waiver for 20 mg/5 mL Strength:

As stated earlier there were no PK data with 20 mg/5 mL. All the available data is with 10 mg/5 mL. On November 2, 2007 the sponsor provided justification with supporting literature articles indicating that the change in the formulation will have no significant implication the absorption and bioavailability of the solution. Morphine is highly soluble drug and its PK is dose proportional. The product is formulated as a solution . However, no information is available on the permeability of morphine. The bioavailability of oral morphine is approximately 40%. From the clinical perspective, the dose of morphine will be titrated to a dose that will provide optimal pain relief with minimal adverse events.

The major difference between the 10 and 20 mg/5 mL strengths is the amount of glycerin and sorbitol. b(4)

Based on the literature reports, sorbitol in a dose dependent fashion may significantly reduce the absorption of low permeability drugs such as ranitidine (reference 2) but to lesser extent high permeability drugs such as metoprolol (reference 3).

If morphine is assumed to be a low permeability drug and based on the difference in the amount of sorbitol between the two formulations, the reduction in morphine absorption, if any, would be associated with decreased efficacy. From the clinical respective, the drug will be titrated as need for pain.

Furthermore, the absorption of morphine is enhanced by P-glycoprotein (PGP) blocker such as quinidine (3). However, no information is available to indicate that glycerin or sorbitol affects the PGP activity.

Since there are insufficient information about the permeability of morphine, the following is additional justification to grant the bio waiver for the 20 mg/5 mL strength.

The 10 mg/5 mL strength contains — sorbitol and — glycerin and the 20 mg /5mL strength contains sorbitol and ~ glycerin. Therefore, the % of each component in 5 ml is as follows: b(4)

	10 mg/5mL	20 mg/5mL	20 mg Dose (using 10 mg/5mL)
Glycerin			
Sorbitol			b(4)

The above table shows that the amount of glycerin in 5 mL is only , higher in the 20 mg/5 mL strength than in the 10 mg/5 mL strength. However, the amount of sorbitol, which appears to be more important than glycerin, based on the above discussion, is lower in the highest strength than the lowest strength. For doses of 20 mg or higher, the amount of sorbitol and glycerin will be lower with the 20 mg/5 mL strength when compared to the 10 mg/5 mL strength.

Therefore, from the safety and efficacy perspective, this difference is negligible. Furthermore, the availability of the 20 mg/5 mL strength is beneficial should a higher dose of morphine such as 40 or 60 mg is need. In this case the amount of sorbitol will be lower using the 20 mg/5 mL strength than using the 10 mg/5 mL strength (third column).

Therefore, based on the overall assessment of the physiochemical characteristics of the morphine, the PK profiles, the amount of each inactive components, no additional PK data is necessary for the 20 mg/5 mL strength.

References:

1) Preechagoon, D. et al . Formulation development and stability testing of oral morphine solution utilizing reformulation approach. J. Pharm. Pharmacuti. Sci, 8 (2):362-369 (2005).
2) Chen, M.L., et al: A modern view of excipient effects on bioequivalence: Case study of sorbitol. Pharm. Res, 24(1):73-80 (2007).
3) Kharasch, E.D. et al. Role of P-glycoprotein in the intestinal absorption and clinical effects of morphine. Clin Pharmacol. Ther 74 (6):543-554 (2003).

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2.5.5 Are the method and dissolution specifications supported by the data provided by the sponsor?

This section is not applicable for oral solutions. For the 15 mg and 30 mg tablets the drug release was over —— at 15 minutes. The method used for both tablet strengths was: b(4)

Apparatus: 2 (Paddles)
Media: 900 ml DI Water
Speed: 50 RPM
Time: 10, 15, 20 min

For detail discussion and recommendation related to dissolution specs and method acceptability see CMC review.

2.6 Analytical Section

The plasma concentrations of morphine, and its two major metabolites, M3G and M6G, were determined by a validated LC-MS-MS method ——> b(4)
——. The limit of quantitation of the assay is 0.2, 3.5, and 1 ng/mL for morphine, M3G, and M6G, respectively. The assay precession (% CV) ranges from approximately 1.1 to 8.5% for the three components (**Table 2.6.1**). Overall, the assay validation data are satisfactory.

Table 2.6.1. Assay Precision (% CV)

Analyte	Within-Run CV		Bias	
	From	To	From	To
Morphine (Table 4)	1.1%	8.5%	-3.9%	2.8%
Morphine-3β-glucuronide (Table 5)	1.2%	2.9%	-7.1%	4.6%
Morphine-6β-glucuronide (Table 6)	2.0%	7.5%	-2.0%	3.0%

3.0 Labeling Comments

The labeling comments will be incorporated directly into the sponsor's proposed label after discussion with the review team. Here is the highlight of the labeling comments which are subject to change at the time of approval of the NDA.

7. DRUG INTERACTIONS

b(4)

38 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling b(4)

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.2 **Individual Study Review:**

4.2.1. Study # MORP-T30-PLFS-1 (Pilot BE Study)

Objective:
The primary objective of this pilot study was to determine the absolute bioavailability of the immediate release tablet and oral solution by comparing them to intravenous morphine. The second objective is to optimize the study design for the pivotal BE study.

Study Design:

This was a single dose, 3 periods, 3 treatments, crossover design in 17 healthy subjects as follows:

Treatment A (Reference, IV): Single 10 mg intravenous morphine dose infused over 30 min (Duramorph®, Baxter Healthcare, NDA 18-565).

Treatment B (Test 1, Solution 10 mg/5 mL: 30 mg (15 mL) single oral dose of morphine oral solution (Roxane)

Treatment C (Test 2, Tablet): 30 mg single oral dose of immediate release table (Roxane)

Products Administration:

All treatments were conducted after overnight fasting. Each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of morphine at 12 hours and 1 hour before receiving morphine and then 12 hours after receiving morphine doses. Blood samples for the determination of parent drug morphine and its two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were collected at appropriate time intervals over 24 hours.

Results:

- It appears that the $AUC_{(0-\infty)}$ (0-infinity) for the parent drug morphine after tablet is approximately 40% higher (181±73 ng.h/mL) than after solution (131 ± 23.7 ng.h/mL). However, the $AUC_{(0-t)}$ (zero to the last time point) after the two formulations are comparable (**Table 4.2.1.1 and Figure 4.2.1.1**). It is noteworthy that the same trend of Cmax being higher after tablet (44.8 ± 21.3 ng/mL) than after solution (36.9 ± 12.7 ng/mL) was seen.

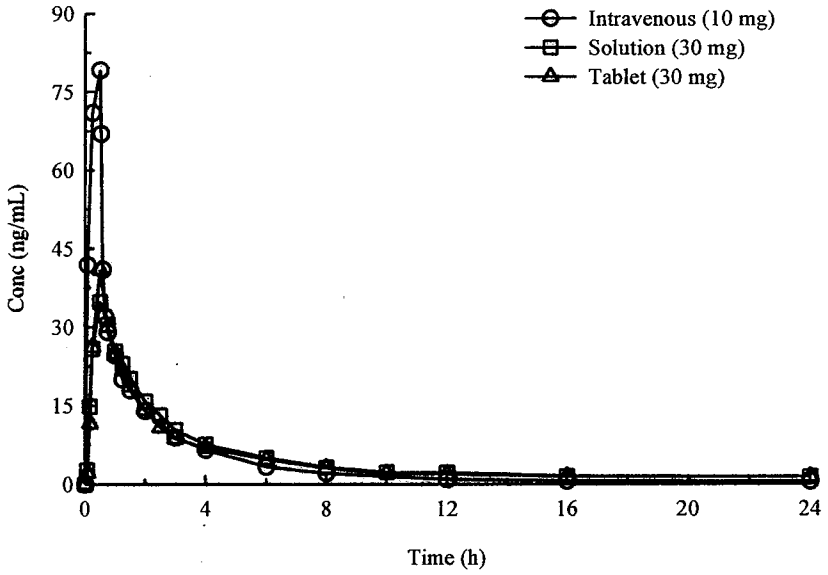
- Due to multiple factors including high variability, long terminal elimination phase, and assay issues, the mean half life of morphine ranged from approximately 12 to 30 h. Due to these issues, the half life was determined for only 4 or 5 subjects in each arm of the study (**Table 4.2.1.1**).

Table 4.2.1.1. Summary of PK parameters for the Parent Drug Morphine (Study PLFS 1).

Parameter[1]	Intravenous	Solution	Tablet
Cmax (ng/mL)	88.9 ± 32.4 (17)	36.9 ± 12.7 (17)	44.8 ± 21.3 (17)
Tmax (h)	0.50 (17)	0.50 (17)	0.50 (17)
	[0.25 – 0.53]	[0.25 – 0.80]	[0.25 – 1.50]
AUC(0-t) (h•ng/mL)	113 ± 21.3 (17)	117 ± 32.7 (17)	111 ± 35.3 (17)
AUC(inf) (h•ng/mL)	130 ± 34.9 (5)	131 ± 23.7 (4)	181 ± 73.5 (4)
λz (h^{-1})	0.0615 ± 0.0153 (5)	0.0504 ± 0.0175 (4)	0.0403 ± 0.0260 (4)
t½ (h)	11.9 ± 3.07 (5)	15.2 ± 5.90 (4)	30.3 ± 31.04 (4)
Ln(Cmax)	4.43 ± 0.32 (17)	3.55 ± 0.35 (17)	3.70 ± 0.47 (17)
Ln[AUC(0-t)]	4.71 ± 0.17 (17)	4.73 ± 0.26 (17)	4.67 ± 0.31 (17)
Ln[AUC(inf)]	4.84 ± 0.24 (5)	4.86 ± 0.19 (4)	5.13 ± 0.42 (4)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Figure 4.2.1.1 Mean plasma concentrations-Time Profiles of the Parent Drug Morphine



- The effective half lifet used to determine dosing frequency of morphine ranges from 2 to 4 hours. Therefore, appropriate language will be included in the label to reflect the effective half life, not the long (as reflected by longer sampling duration) terminal elimination half life.

- Due to the variability in the data, there were few subjects for whom AUC(0-∞) could be calculated to permit a statistical comparison. Therefore, the 90% CI based on AUC(0-∞) is considered unreliable to determine the bioequivalence between the two formulations.

- Based on this data, the 90% CI for AUC(0-t) was used instead of AUC (0-∞) for assessment of bioequivalence. From this data analysis, the 90% CI for AUC was within 80-125% for the tablet and solution. However, the Cmax was outside the 80-125% (99.03% to 135.55). Therefore, the two formulations are considered **not bioequivalent (Table 4.2.1.2).**

Table 4.2.1.2. Summary of Morphine Bioequivalence Statistical Analysis and 90% CI (Study # PLFS-1)

Parameter	Geometric Mean Ratio (%)[1,2] Estimate	90% Confidence Interval			Within Subject CV (%)
Solution vs. Intravenous					
Cmax	13.93	11.90	→	16.29	27.41
AUC(0-t)	34.26	31.50	→	37.26	14.46
AUC(inf)[3]	55.48				
Tablet vs. Intravenous					
Cmax	16.13	13.79	→	18.88	27.41
AUC(0-t)	31.98	29.40	→	34.78	14.46
AUC(inf)[3]	34.74				
Tablet vs. Solution					
Cmax	115.86	99.03	→	135.55	27.41
AUC(0-t)	93.34	85.83	→	101.51	14.46
AUC(inf)[3]	62.62				

[1]Based on analysis of natural log-transformed data.
[2]Values for the 10 mg intravenous were adjusted to 30 mg before comparison with the oral data.
[3]There were too few subjects for whom AUC(inf) could be calculated to permit a statistical comparison.

- Based on this study and using AUC (0-t), the absolute bioavailability was 32% and 34% for the tablet and solution, respectively.

- The higher Cmax seen with the tablet compared to the solution is contrary to the general expection of either the same or slower rate of release with tablets compared to the solution. The reasons for this findings is unknown.

- As expected due to the first pass effect, the formation of the metabolite was higher after oral than after IV administration (**Tables 4.2.1.3 and 4.2.1.4 and Figures 4.2.1.2 and Figure 4.2.1.3**).

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Table 4.2.1.3. Summary of PK Parameters for Morphine-3-Glucuronide (M3G) After Oral.

Parameter[1]	Intravenous	Solution	Tablet
Cmax (ng/mL)	212 ± 34.0 (17)	874 ± 117 (17)	926 ± 173 (17)
Tmax (h)	0.75 (17)	1.00 (17)	1.00 (17)
	[0.57 – 1.25]	[0.75 – 2.00]	[0.50 – 2.00]
AUC(0-t) (h•ng/mL)	1,233 ± 207 (17)	4,461 ± 652 (17)	4,149 ± 595 (17)
AUC(inf) (h•ng/mL)	1,373 ± 216 (15)	5,099 ± 643 (12)	4,676 ± 618 (13)
λz (h^{-1})	0.0940 ± 0.0121 (15)	0.0845 ± 0.0229 (12)	0.0874 ± 0.0169 (13)
t½ (h)	7.49 ± 0.95 (15)	8.79 ± 2.43 (12)	8.21 ± 1.59 (13)
Ln(Cmax)	5.34 ± 0.16 (17)	6.76 ± 0.13 (17)	6.82 ± 0.18 (17)
Ln[AUC(0-t)]	7.10 ± 0.16 (17)	8.39 ± 0.14 (17)	8.32 ± 0.13 (17)
Ln[AUC(inf)]	7.21 ± 0.15 (15)	8.53 ± 0.12 (12)	8.44 ± 0.12 (13)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Table 4.2.1.4 Summary of PK Parameters for Morphine-6-Glucuronide

Parameter[1]	Intravenous	Solution	Tablet
Cmax (ng/mL)	35.4 ± 5.62 (17)	154 ± 22.0 (17)	159 ± 29.7 (17)
Tmax (h)	1.00 (17)	1.25 (17)	1.25 (17)
	[0.75 – 1.50]	[1.00 – 2.00]	[0.75 – 2.00]
AUC(0-t) (h•ng/mL)	178 ± 27.9 (17)	665 ± 78.5 (17)	613 ± 70.7 (17)
AUC(inf) (h•ng/mL)	191 ± 25.8 (11)	747 ± 96.0 (9)	675 ± 67.7 (12)
λz (h^{-1})	0.0909 ± 0.0239 (11)	0.0760 ± 0.0258 (9)	0.0794 ± 0.0257 (12)
t½ (h)	8.09 ± 2.06 (11)	10.9 ± 6.71 (9)	10.5 ± 6.92 (12)
Ln(Cmax)	3.55 ± 0.16 (17)	5.03 ± 0.14 (17)	5.05 ± 0.19 (17)
Ln[AUC(0-t)]	5.17 ± 0.16 (17)	6.49 ± 0.12 (17)	6.41 ± 0.12 (17)
Ln[AUC(inf)]	5.24 ± 0.15 (11)	6.61 ± 0.13 (9)	6.51 ± 0.10 (12)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Figure 4.2.1.2. Mean plasma concentrations-Time Profiles for Morphine-3-Glucuronide.

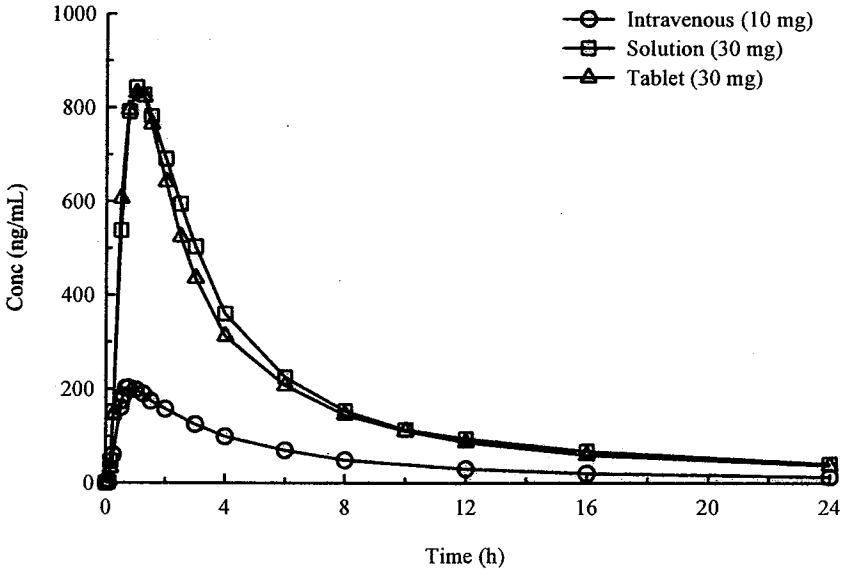
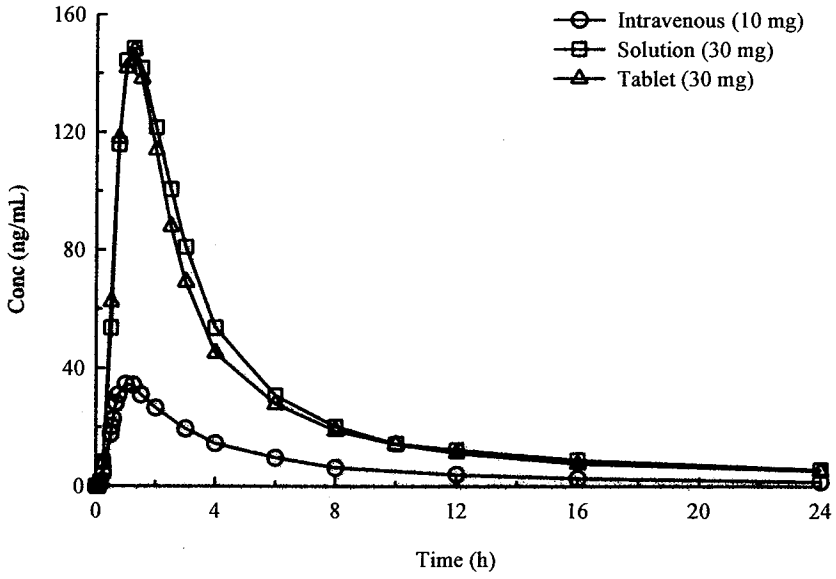


Figure 4.2.1.3. Mean Plasma Concentrations-Time Profiles of Morphine-6-Glucuronide (Study # PLFS-1).



- The 90% CI for Cmax and AUC of both M3G and M6G metabolites after oral solution and tablets were within 80-125% (**Tables 4.2.1.5 and 4.2.1.6**).

4.2.1.5. Summary of Bioequivalence Data for Morphine-3-Glucuronide (Study # PLFS-1).

Parameter	Geometric Mean Ratio (%)[1,2] Estimate	90% Confidence Interval			Within Subject CV (%)
Solution vs. Intravenous					
Cmax	138.20	130.33	→	146.55	10.08
AUC(0-t)	121.08	116.58	→	125.76	6.50
AUC(inf)	124.54	118.43	→	130.97	7.18
Tablet vs. Intravenous					
Cmax	145.53	137.24	→	154.32	10.08
AUC(0-t)	112.55	108.36	→	116.89	6.50
AUC(inf)	114.36	108.71	→	120.30	7.18
Tablet vs. Solution					
Cmax	105.30	99.30	→	111.66	10.08
AUC(0-t)	92.95	89.49	→	96.54	6.50
AUC(inf)	91.82	86.83	→	97.11	7.18

[1]Based on analysis of natural log-transformed data.
[2]Values for the 10 mg intravenous were adjusted to 30 mg before comparison with the oral data.

4.2.1.5. Summary of Bioequivalence Data for Morphine-6-Glucuronide (Study # PLFS-1).

Parameter	Geometric Mean Ratio (%)[1,2] Estimate	90% Confidence Interval			Within Subject CV (%)
Solution vs. Intravenous					
Cmax	145.80	135.83	→	156.50	12.19
AUC(0-t)	125.28	120.39	→	130.37	6.84
AUC(inf)	131.50	123.39	→	140.15	7.15
Tablet vs. Intravenous					
Cmax	149.36	139.15	→	160.32	12.19
AUC(0-t)	115.38	110.88	→	120.06	6.84
AUC(inf)	115.50	108.70	→	122.72	7.15
Tablet vs. Solution					
Cmax	102.44	95.44	→	109.96	12.19
AUC(0-t)	92.10	88.50	→	95.84	6.84
AUC(inf)	87.83	82.34	→	93.68	7.15

[1]Based on analysis of natural log-transformed data.
[2]Values for the 10 mg intravenous were adjusted to 30 mg before comparison with the oral data.

Reviewer's Comments:

This is a pilot study to determine the absolute bioavailability of morphine and its major metabolites, M3G and M6G following single dose oral solution or immediate release tablets in healthy subjects (n=17). The study design seems adequate to address the stated objectives. However, the interpretation of the data is a little complex.

The accurate estimation of the $AUC_{(0-\infty)}$ was not possible in many subjects due to many factors including assay issues and the prolonged elimination phase that was used to extrapolate the last portion of the curve to infinity. Therefore, the AUC(0-t) appears to be most reliable to be used for the comparing bioavailability between the two formulations and the determination of the absolute bioavailability.

Therefore, based on AUC (0-∞) morphine exposure after tablet was approximately 40% higher (181±73 ng.h/mL) than after solution (131 ± 23.7 ng.h/mL). However, the exposure based on $AUC_{(0-t)}$ after the two formulations are comparable. It is noteworthy that the same trend of Cmax being higher after tablet (44.8 ± 21.3 ng/mL) than after solution (36.9 ± 12.7 ng/mL) was seen. In the reverse order of the parent drug morphine and as expected, the formation of both M3G and M6G was slightly lower after tablets compared to solution.

Generally it is expected that the absorption from the solution is either the same or faster than after tablets. In this study, the reverse was true. The reason for this phenomenon is not clear.
For bioequivalence analysis, AUC(0-t) and AUC (0-∞) are generally used. However, due to the variability in the data, the AUC(0-∞) was reported only in a few subjects to permit

a statistical comparison. Therefore, the 90% CI was reported based on AUC(0-t) which fell within 80-125% for tablet and solution. However, the Cmax was outside the limits (99.03% to 135.55). Therefore, the two formulations are considered **not bioequivalent** (**Table 4.2.1.2**).

Conclusions:

From this pilot study the following conclusions can be made:

1) The bioavailability is comparable for tablets and solution.
2) The two formulations are **not bioequivalent** as the 90% CI for Cmax is outside the BE limits of 80-125%.
3) The absolute bioavailability for the parent drug morphine is approximately 30-35% for tablets and solution.

Overall, the two formulations are comparable, **but not bioequivalent.**

4.2.2. Study # MORP-T30-PVFS-2 (Dose Proportionality and Effect of Food)

Objective:

The primary objective of this study is to establish the dose proportionality between 15 mg and 30 mg tablets. The secondary objective is to investigate the effect of food on the PK of morphine following 30 mg tablet.

Study Design:

This was a single dose, 3 periods, 3 treatments, crossover design in 32 healthy subjects as follows:

Treatment A (15 mg fasting): 15 mg tablets after overnight fasting

Treatment B (30 mg fasting): 30 mg tablet after overnight fasting.

Treatment C (30 mg fed): 30 mg tablet after high fat standard breakfast.

Products Administration:

All treatments were conducted after overnight fasting except the fed arm. As in the pilot study, each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of morphine at 12 hours and 1 hour before receiving morphine and then 12 hours after receiving morphine doses.

Blood samples for the determination of parent drug morphine and its two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were collected at appropriate time intervals over 48 hours.

Results:

- From the dose proportionality perspective, the exposure between 15 mg and 30 mg was dose proportional with respect to both Cmax and AUC (**Table 4.2.2.1 and Figure 4.2.2.1**).

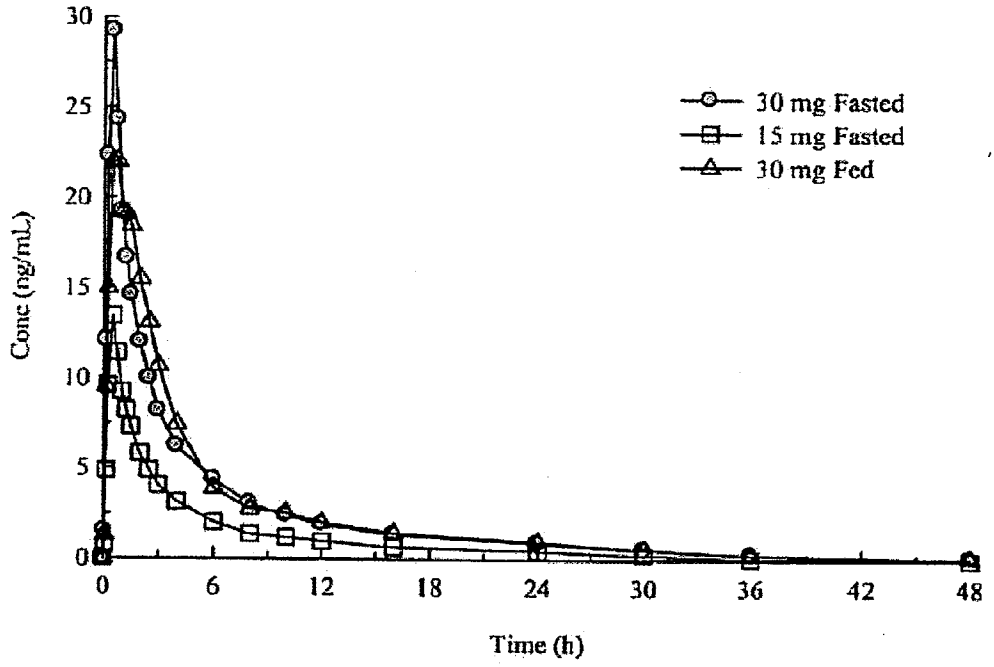
- As observed in the previous study (#PLFS-1), the half life is approximately 10 hours, irrespective of dose (**Table 4.2.2.1**). Also, as discussed in the previous study, these half lives values should be interpreted with caution as they do not reflect the so called **"effective half-life'**.

Table 4.2.2.1. Summary of PK of Morphine (Study # PVFS-2)

Parameter[1]	30 mg Fasted	15 mg Fasted	30 mg Fed
Cmax (ng/mL)	32.8 ± 13.8 (32)	15.8 ± 7.42 (32)	30.9 ± 21.3 (32)
Tmax (h)	0.50 (32) [0.17 – 0.78]	0.50 (32) [0.17 – 1.50]	0.75 (32) [0.00 – 2.50]
AUC(0-t) (h*ng/mL)	104 ± 32.6 (32)	49.1 ± 14.6 (32)	110 ± 38.0 (32)
AUC(inf) (h*ng/mL)	113 ± 36.9 (22)	54.3 ± 12.7 (21)	125 ± 28.6 (23)
$\lambda z (h^{-1})$	0.0824 ± 0.0248 (22)	0.0780 ± 0.0366 (21)	0.0801 ± 0.0325 (23)
t½ (h)	9.13 ± 2.65 (22)	12.2 ± 11.77 (21)	10.6 ± 6.52 (23)
Ln(Cmax)	3.40 ± 0.45 (32)	2.64 ± 0.52 (32)	3.31 ± 0.55 (31)
Ln[AUC(0-t)]	4.60 ± 0.30 (32)	3.85 ± 0.30 (32)	4.68 ± 0.34 (31)
Ln[AUC(inf)]	4.68 ± 0.32 (22)	3.97 ± 0.25 (21)	4.80 ± 0.24 (23)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Figure 4.2.2.1: Mean plasma concentrations-Time Profiles of Morphine (Study # PVFS-2)



- The 90% CI for Cmax after fed and fasted treatments of 30 mg tablets were outside 80-125%.(**Table 4.2.2.2**). However, the 90% CI for AUC (0-t) and (0-∞) were within 80-125% . From this study it can be concluded that food appears to slightly reduce the Cmax and prolong Tmax of morphine.

Table 4.2.2.2. Summary of PK Parameters for Morphine (Study # PVFS-2)

Parameter	Geometric Mean Ratio (%)[1,2] Estimate	90% Confidence Interval
15 mg Fasted vs. 30 mg Fasted		
Cmax	93.04	78.14 → 110.79
AUC(0-t)	94.95	87.10 → 103.51
AUC(inf)	101.44	94.80 → 108.53
30 mg Fed vs. 30 mg Fasted		
Cmax	88.98	74.58 → 106.17
AUC(0-t)	106.88	97.95 → 116.64
AUC(inf)	114.90	107.97 → 122.28

[1]Based on analysis of natural log-transformed data.
[2]Values for the 15 mg tablet were adjusted to 30 mg before statistical analysis.

- The formation of both morphine glucuronidated metabolites, M3G and M6G was also dose proportional between 15 mg and 30 mg (**Tables 4.2.2.3 and 4.2.2.4 and Figures 4.2.2.2 and 4.2.2.3**). Consistent with the effect on morphine, food also slightly reduced the exposure, specifically the Cmax, of both M3G and M6G.

Table 4.2.2.3. Summary of PK Parameters for Morphine-3-Glucuronide (Study # PVFS-2)

Parameter[1]	30 mg Fasted	15 mg Fasted	30 mg Fed
Cmax (ng/mL)	919 ± 215 (32)	466 ± 95.8 (32)	714 ± 220 (32)
Tmax (h)	1.00 (32) [0.50 – 1.50]	1.00 (32) [0.50 – 2.00]	1.50 (32) [0.50 – 3.00]
AUC(0-t) (h•ng/mL)	4,794 ± 766 (32)	2,450 ± 443 (32)	4,397 ± 1,218 (32)
AUC(inf) (h•ng/mL)	4,964 ± 813 (28)	2,505 ± 468 (26)	4,775 ± 783 (28)
λz (h^{-1})	0.0854 ± 0.0259 (28)	0.0931 ± 0.0253 (26)	0.0890 ± 0.0345 (28)
t½ (h)	9.01 ± 3.54 (28)	8.02 ± 2.32 (26)	8.77 ± 2.84 (28)
Ln(Cmax)	6.80 ± 0.22 (32)	6.12 ± 0.21 (32)	6.42 ± 0.92 (32)
Ln[AUC(0-t)]	8.46 ± 0.15 (32)	7.79 ± 0.17 (32)	8.17 ± 1.28 (32)
Ln[AUC(inf)]	8.50 ± 0.15 (28)	7.81 ± 0.17 (26)	8.46 ± 0.15 (28)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Table 4.2.2.4. Summary of PK Parameters for Morphine-6-Glucuronide (Study # PVFS-2)

Parameter[1]	30 mg Fasted	15 mg Fasted	30 mg Fed
Cmax (ng/mL)	136 ± 24.1 (32)	66.8 ± 12.4 (32)	100 ± 30.3 (32)
Tmax (h)	1.00 (32)	1.25 (32)	1.50 (32)
	[0.75 – 2.00]	[0.75 – 2.00]	[0.00 – 3.00]
AUC(0-t) (h•ng/mL)	583 ± 93.4 (32)	281 ± 54.1 (32)	518 ± 144 (32)
AUC(inf) (h•ng/mL)	624 ± 94.9 (23)	309 ± 50.1 (22)	570 ± 114 (25)
λz (h^{-1})	0.0892 ± 0.0310 (23)	0.0843 ± 0.0288 (22)	0.0916 ± 0.0270 (25)
t½ (h)	8.96 ± 3.90 (23)	9.02 ± 2.68 (22)	8.28 ± 2.62 (25)
Ln(Cmax)	4.90 ± 0.18 (32)	4.18 ± 0.19 (32)	4.61 ± 0.26 (31)
Ln[AUC(0-t)]	6.36 ± 0.16 (32)	5.62 ± 0.19 (32)	6.26 ± 0.25 (31)
Ln[AUC(inf)]	6.43 ± 0.15 (23)	5.72 ± 0.16 (22)	6.32 ± 0.25 (25)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.

Figure 4.2.2.2. Mean Plasma Concentrations-Time Profiles of M3G (Study # PVFS-2)

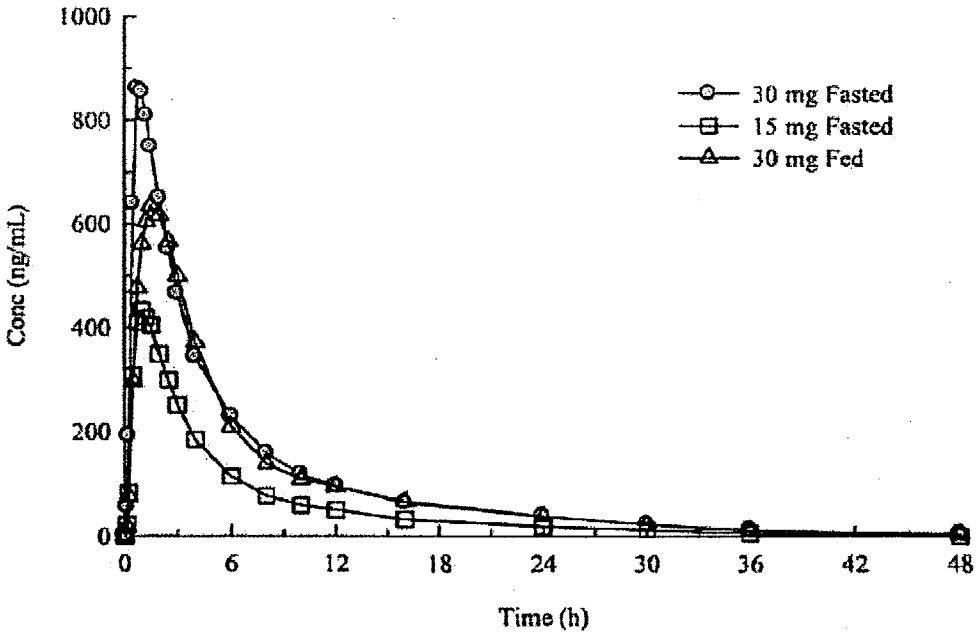


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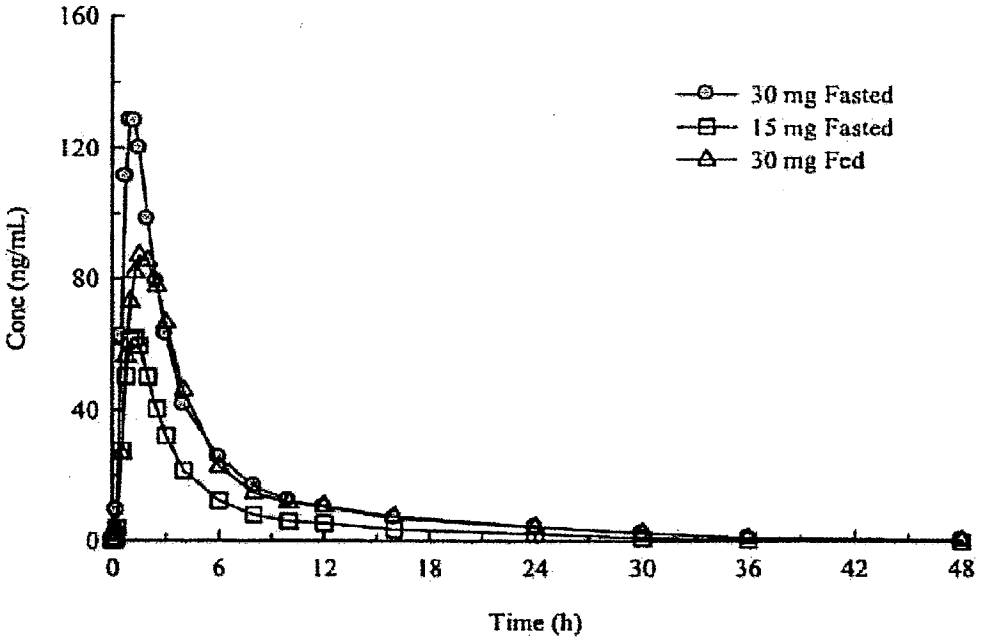
Figure 4.2.2.3: Mean Plasma Concentrations-Time Profiles of M6G (Study # PVFS-2)



- The 90% CI for the M3G were outside 80 to 125% for Cmax and AUC (**Table 4.2.2.5 and 4.2.2.6**). However, for M6G it was below 80% for Cmax relative to food.

Table 4.2.2.5: Statistical Comparison of Pharmacokinetic Parameters for M3G (Study # PVFS-2)

Parameter	Geometric Mean Ratio (%)[1,2]			
	Estimate	90% Confidence Interval		
15 mg Fasted vs. 30 mg Fasted				
Cmax	102.08	81.83	→	127.35
AUC(0-t)	102.69	75.17	→	140.29
AUC(inf)	100.95	98.48	→	103.48
30 mg Fed vs. 30 mg Fasted				
Cmax	68.36	54.80	→	85.28
AUC(0-t)	75.29	55.11	→	102.85
AUC(inf)	97.17	94.83	→	99.57

[1]Based on analysis of natural log-transformed data.
[2]Values for the 15 mg tablet were adjusted to 30 mg before statistical analysis.

Table 4.2.2.6: Statistical Comparison of PK Parameters for M6G (Study # PVFS-2)

Parameter	Geometric Mean Ratio (%)[1,2]			
	Estimate	90% Confidence Interval		
15 mg Fasted vs. 30 mg Fasted				
Cmax	97.75	90.26	→	105.86
AUC(0-t)	96.27	90.04	→	102.92
AUC(inf)	98.61	90.37	→	107.60
30 mg Fed vs. 30 mg Fasted				
Cmax	74.55	68.78	→	80.81
AUC(0-t)	90.57	84.65	→	96.90
AUC(inf)	89.96	82.68	→	97.88

[1]Based on analysis of natural log-transformed data.
[2]Values for the 15 mg tablet were adjusted to 30 mg before statistical analysis.

Reviewer's Comments:

- This study provided information on the dose proportionality between 15 mg and 30 mg. The data was consistent for the parent drug, morphine, and its two major metabolites, M3G and M6G.

- Food appears to slightly delay the absorption of morphine. The Cmax of morphine was reduced by approximately 10%. However, the overall exposure (AUC) was comparable in fed or fasting states.

- Since the 90% CI for Cmax after fed and fasted conditions was outside the 80-125% boundary, the two treatments are considered **not bioequivalent.**

Conclusions:

From this study the following conclusions can be made:

- The exposure to morphine and its metabolite, M3G and M6G, is dose proportional after 15 mg and 30 mg tablets.
- Food appears to slightly delayed the Tmax and reduce the Cmax by approximately 10%. However, the Cmax for the metabolites reduced by approximately 25-32%.
- From the bioequivalence perspective, the two treatments (fed vs fasted) are **not bioequivalent.**

4.2.3. Study # MORP-T30-PVFS-3 (Steady-State-Pivotal Study)

Objective:

The primary objective of this study was to characterize the PK of morphine at steady state following oral administration of Roxane immediate release tablets and solution. The secondary objective was to compare the PK of oral tablets and solution at steady state administered as 30 mg Q6h x 5 days extended release capsule, Avinza 120 mg QD.

Study Design:

This was a single dose, 3 periods, 3 treatments, crossover design in 27 healthy subjects as follows:

Treatment A (Oral solution 10mg/5 mL): 30 mg (15 mL) Q6H of Roxane oral solution at 0800, 1400, 2000, and 0200 hours **x 5 days**

Treatment B (Oral Tablet): 30 mg Q6h of Roxane tablet at 0800, 1400, 2000, and 0200 hours **x 5 days.**

Treatment C (Reference, Avinza):120 mg QD of Avinza extended release capsule (Ligand Pharmaceuticals, Inc.,) **x 5 days.** This acts as a Reference Listed Drug (RLD).

Since the study was conducted at steady state, no washout period was allowed between treatments.

Products Administration:

All treatments were conducted after overnight fasting. As in the previous studies, each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of morphine at 12 hours before the first dose and continuing through 24 hours after the last dose of period 3.

Blood samples for the determination of parent drug morphine and its two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were collected at appropriate time intervals as follows:

Day 1 before first dose at 0800 hour (Baseline)
Day 3 before 0800 dose (For Cmin)
Day 4 before 0800 dose (For Cmin)
Day 5 before 0800 dose and through 24 hours (for full PK profile over 24 hours given as 6 hour dosing)

Results:

- The plasma concentration-time profiles for morphine was typical for Q6h dosing of immediate release tablets and solution as well as for Q24h dosing for extended release capsule Avinza® (**Figure 4.2.3.1**).

- Consistent with the observation from the previous two studies (PLFS-1 and PLFS-2), the Cmax after IR tablet appears to be higher by approximately 25 % than after solution (**Table 4.2.3.1**). However, the AUC (0-24h) after IR tablet was slightly higher by 10% than oral solution. Furthermore, the Cmax and AUC for IR tablets were consistently higher after each dose level on Day 5 than after oral solution (**Table 4.2.3.2**).

- The percent of fluctuation was also higher after IR tablet (281 ± 84.8) and oral solution (202 ± 66.8). The degree of fluctuation after Avinza was lower compared to both IR tablet and solution (**Table 4.2.3.1**).

Figure 4.2.3.1 Mean Plasma Concentration-Time Profiles of Morphine (Study # PVFS-3)

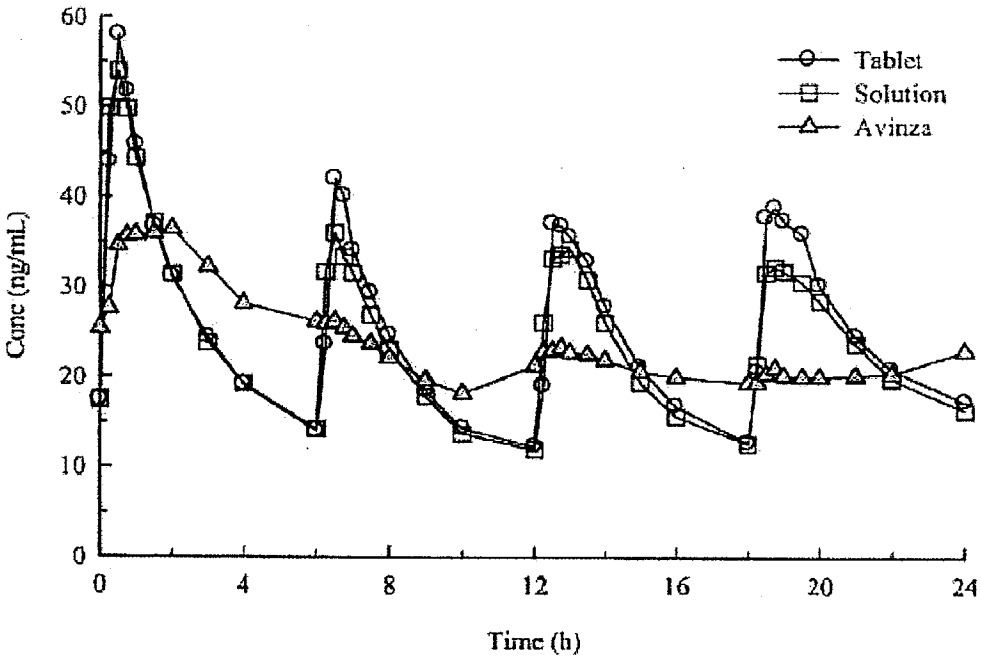


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Table 4.2.3.1. Summary of Morphine PK Parameters (Study # PVFS 3)

Parameter[1,2]	Tablet	Solution	Avinza
Cmax (ng/mL)	78.6 ± 28.5 (27)	58.3 ± 21.2 (27)	41.1 ± 11.2 (27)
Tmax (h)	0.50 (27) [0.25 – 20.1]	0.50 (27) [0.25 – 12.8]	1.50 (27) [0.50 – 3.00]
AUC(24) (h·ng/mL)	581 ± 173 (27)	555 ± 119 (27)	565 ± 145 (27)
Cmin (ng/mL)	10.9 ± 3.83 (27)	11.2 ± 2.76 (27)	16.3 ± 4.82 (27)
Percent Fluctuation	281 ± 84.8 (27)	202 ± 66.8 (27)	107 ± 33.6 (27)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.
[2]Cmax and Cmin are the maximum and minimum concentrations observed over the 24-hour period.

Table 4.2.3.2 Summary of PK Parameters for Morphine at Each Dose Level (Study # PVFS-3).

	Tablet			Solution		
Dose	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h·ng/mL)	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h·ng/mL)
1st	72.2 ± 27.8 (27)	1 (27)	166 ± 50.3 (27)	58.2 ± 21.3 (27)	1 (27)	166 ± 38.7 (27)
2nd	47.4 ± 19.3 (27)	7 (27)	126 ± 34.1 (27)	37.7 ± 10.9 (27)	7 (27)	120 ± 23.7 (27)
3rd	46.4 ± 21.0 (27)	13 (27)	135 ± 41.4 (27)	36.8 ± 9.55 (27)	13 (27)	128 ± 28.2 (27)
4th	44.4 ± 24.2 (27)	19 (27)	154 ± 59.7 (27)	36.0 ± 12.1 (27)	19 (27)	141 ± 36.7 (27)

[1]Arithmetic mean ± standard deviation (N).
[2]Median (N)

- In terms of bioequivalence, the 90% CI for Cmax was outside the 80 % and 125% (**Table 4.2.3.3**). However, for AUC it was within the 80 to 125%. Therefore, in principle the two formulations are **not bioequivalent.**

Table 4.2.3.3. Summary of Statistical Analysis of Morphine PK Data (Study # PVFS-3)

Parameter	Geometric Mean Ratio (%)[1,2]			
	Estimate	90% Confidence Interval		
Solution vs. Avinza				
Cmax	72.02	65.42	→	79.29
AUC(0-24)	100.50	96.99	→	104.14
Tablet vs. Avinza				
Cmax	53.84	48.90	→	59.29
AUC(0-24)	97.28	93.87	→	100.81
Tablet vs. Solution				
Cmax	133.75	121.49	→	147.25
AUC(0-24)	103.31	99.70	→	107.05

[1]Based on analysis of natural log-transformed data.

- In comparison to the extended release (ER) formulation, Avinza, the AUC (0-24) are comparable to both Roxane IR formulations (**Table 4.2.3.1**). The 90 % CI following the three treatments was within 80 to 125% (**Table 4.2.3.3**). Since the Cmax after IR formulations (tablets or solution) is expected to be higher than after ER formulation, then the two Roxane's formulations are considered comparable to Avinza, **but not bioequivalent** to each other.

- The plasma concentration-time profiles for M3G and M6G followed the same patterns as of the parent drug, morphine (**Figures 4.2.3.2 and 4.2.3.3**). As expected, the Cmax was higher for tablets than solution, but the AUCs were comparable for both metabolites, M3G and M6G (**Tables 4.2.3.4 and 4.2.3.5**).

Figure 4.2.3.2. Plasma Concentration-Time Morphine Profiles of M3G (Study # PVFS-3)

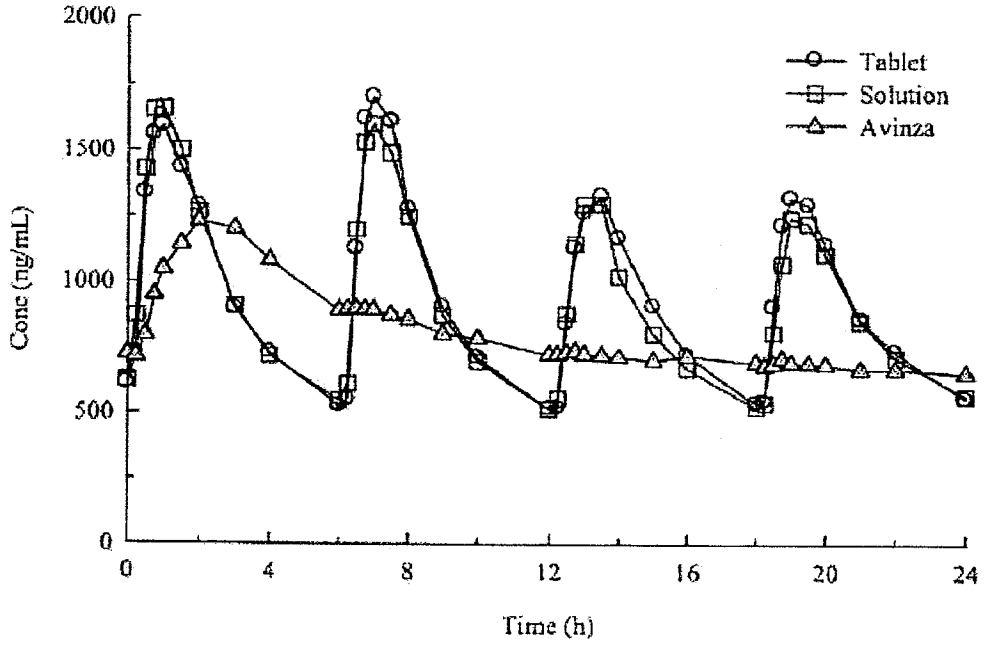

Figure 4.2.3.3. Plasma Concentration-Time Morphine Profiles of M6G (Study # PVFS-3)

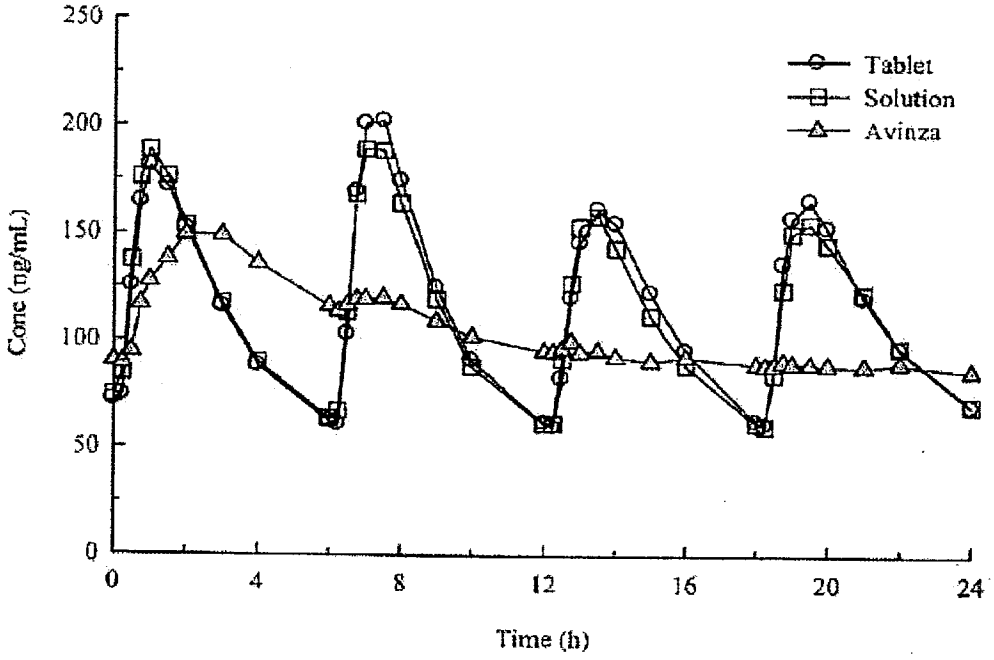

Table 4.2.3.4. Summary of PK Parameters for M3G (Study PVFS-3)

Parameter[1,2]	Tablet	Solution	Avinza
Cmax (ng/mL)	1,960 ± 315 (27)	1,770 ± 307 (27)	1,322 ± 251 (27)
Tmax (h)	6.75 (27)	1.00 (27)	2.00 (27)
	[0.50 – 19.5]	[0.50 – 7.50]	[0.75 – 4.00]
AUC(24) (h•ng/mL)	22,060 ± 2,839 (27)	21,580 ± 3,238 (27)	19,556 ± 2,965 (27)
Cmin (ng/mL)	462 ± 105 (27)	480 ± 079 (27)	582 ± 118 (27)
Percent Fluctuation	166 ± 45.6 (27)	144 ± 30.4 (27)	90.9 ± 21.0 (27)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.
[2]Cmax and Cmin are the maximum and minimum concentrations observed over the 24-hour period.

Table 4.2.3.5. Summary of PK Parameters for M6G (Study PVFS-3)

Parameter[1,2]	Tablet	Solution	Avinza
Cmax (ng/mL)	225 ± 32.6 (27)	206 ± 33.7 (27)	160 ± 30.5 (27)
Tmax (h)	7.00 (27)	7.00 (27)	3.00 (27)
	[0.75 – 13.0]	[0.75 – 13.5]	[1.00 – 7.50]
AUC(24) (h•ng/mL)	2,724 ± 417 (27)	2,687 ± 417 (27)	2,530 ± 471 (27)
Cmin (ng/mL)	52.7 ± 14.7 (27)	54.8 ± 11.5 (27)	73.0 ± 20.1 (27)
Percent Fluctuation	156 ± 41.0 (27)	136 ± 21.5 (27)	84.8 ± 27.6 (27)

[1]Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported.
[2]Cmax and Cmin are the maximum and minimum concentrations observed over the 24-hour period.

- As for the parent drug, morphine, the degree of fluctuation was also higher for IR tablets compared to solution and Avinza (**Tables 4.2.3.4 and 4.2.3.5**).

- The 90% CI for AUC (0-24) for both metabolites was within 80-125% equivalency limits after the three treatments (**Tables 4.2.3.6 and 4.2.3.7**). The 90% CI for the Cmax for both metabolites after IR tablet and solution was within 80-125%. However, as observed with the parent drug, the Cmax was consistently higher after IR tablet than solution at all doses (**Tables 4.2.3.8 and 4.2.3.9**).

Table 4.2.3.6. Summary of Statistical Analysis of M3G on the last day of dosing (Study # PVFS-3)

Parameter	Estimate	90% Confidence Interval		
Solution vs. Avinza				
Cmax	74.41	69.43	→	79.74
AUC(0-24)	90.57	87.38	→	93.88
Tablet vs. Avinza				
Cmax	66.92	62.44	→	71.72
AUC(0-24)	88.35	85.23	→	91.58
Tablet vs. Solution				
Cmax	111.19	103.76	→	119.16
AUC(0-24)	102.51	98.90	→	106.26

[1]Based on analysis of natural log-transformed data.

Table 4.2.3.7. Summary of Statistical Analysis of M6G on the last day of dosing (Study # PVFS-3)

Parameter	Geometric Mean Ratio (%)[1,2]			
	Estimate	90% Confidence Interval		
Solution vs. Avinza				
Cmax	77.63	73.35	→	82.15
AUC(0-24)	93.54	90.54	→	96.64
Tablet vs. Avinza				
Cmax	70.74	66.84	→	74.87
AUC(0-24)	92.14	89.19	→	95.20
Tablet vs. Solution				
Cmax	109.73	103.69	→	116.12
AUC(0-24)	101.51	98.26	→	104.87

[1]Based on analysis of natural log-transformed data.

Table 4.2.3.8. Summary of PK Parameters of M3G At Individual on the last day of dosing (Study # PVFS-3)

	Tablet			Solution		
Dose	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h*ng/mL)	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h*ng/mL)
1st	201 ± 43.3 (27)	1 (27)	678 ± 135 (27)	195 ± 32.2 (27)	1 (27)	700 ± 109 (27)
2nd	217 ± 33.7 (27)	7 (27)	723 ± 112 (27)	197 ± 35.4 (27)	8 (27)	698 ± 109 (27)
3rd	183 ± 36.1 (27)	14 (27)	656 ± 965 (27)	163 ± 30.3 (27)	14 (27)	631 ± 103 (27)
4th	178 ± 35.8 (27)	20 (27)	667 ± 113 (27)	160 ± 34.3 (27)	20 (27)	658 ± 118 (27)

[1]Arithmetic mean ± standard deviation (N).
[2]Median (N)

Table 4.2.3.9. Summary of PK Parameters of M6G At Individual on the last day of dosing (Study # PVFS-3)

Dose	Tablet			Solution		
	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h*ng/mL)	Cmax[1] (ng/mL)	Tmax[2] (h)	AUC(0-6)[1] (h*ng/mL)
1st	1,780 ± 432 (27)	1 (27)	5,777 ± 1,035 (27)	1,730 ± 316 (27)	1 (27)	5,925 ± 868 (27)
2nd	1,828 ± 305 (27)	7 (27)	5,781 ± 761 (27)	1,632 ± 350 (27)	7 (27)	5,625 ± 933 (27)
3rd	1,532 ± 369 (27)	14 (27)	5,231 ± 769 (27)	1,356 ± 359 (27)	13 (27)	4,951 ± 799 (27)
4th	1,473 ± 355 (27)	19 (27)	5,271 ± 838 (27)	1,305 ± 369 (27)	19 (27)	5,079 ± 887 (27)

[1]Arithmetic mean ± standard deviation (N).
[2]Median (N)

- It should be noted that morphine Cmax after the last dose on the last day of dosing is lower than the first dose administered in the morning The same trend appears to be similar with M3G (**Figure 4.2.3.2**) and M6G (**Figure 4.2.3.3**).

Reviewer's Comments:

- This is a pivotal study to establish the comparability in exposure between Roxane IR tablets and solution relative to Reference Listed Drug (RLD) extended release capsule, Avinza® at steady state.

- The steady state was achieved after 5 days of administration of Roxane IR formulations at Q6h regimen and at Q24h regimen for Avinza.

- The pattern and magnitude of Cmax after IR tablets relative to solution has been consistent throughout the study for the parent drug morphine and its two metabolites, M3G and M6G. In other words, the Cmax was consistently higher after tablets than solution. This pattern has also been demonstrated consistently among the three studies submitted in this NDA. Although the reverse trend is expected for the solution, the reason for the faster rate of absorption after IR tablet compared to solution is unknown.

- **The 90% CI for morphine's Cmax after** IR table and solution was outside the bioequivalence limit of 80% to 125%. However, it was within these limits for both metabolites, M3G and M6G.

- As expected, the Cmax after ER capsule, Avinza, was lower than after Roxane IR formulations. However, the total exposure on Day 5 as characterized by AUC (0-24) was comparable after Avinza when administered as Q24h to IR formulations administered as Q6h. The data was consistent among the three analytes, the parent drug morphine and its two metabolites M3G and M6G.

Conclusions:

Based on this study, the following conclusions can be made;

- Steady-state was achieved after 5 days of treatments at Q6H regimen for Roxane IR formulation and Q24h of the RLD, extended release capsule Avinza.

- The total exposure as measured by AUC (0-24) following IR formulation after Q6h treatment and Avinza, Q24h treatment, were comparable. The 90% CI for AUC (0-24h) fall within 80-125%. Based on this data, the two formulations are considered comparable, but **not bioequivalent to each other** due to the differences in Cmax..

- The AUC (0-24h) for IR table and solution falls within 80-125%. However, the Cmax after IR tablets was consistently higher than after solution. The 90% CI for the Cmax was outside 80-125%. Therefore, it can be concluded that the two formulations are **not bioequivalent.**

Across Studies Analysis:

For IR formulation, the plasma concentration-time profiles following 30 mg solution and tablets were comparable in studies PLFS-1 and PVFS-2 (**Figure 1**). The level following 15 mg tablets was almost 50% of that after 30 mg tablets, suggesting dose proportionality. In study # PLFS-1, the Cmax and AUC after tablet were higher than after solution (**Figure 2 and 3**). The same trend was seen at steady state in study # PVFS-3 in which the Cmax after tablets was approximately 30 to 40% higher than after solution (**Figures 4 and 5**).

Figure 1. Mean Plasma Concentration-Time Profiles of Morphine in Studies PLFS-1 and PVFS-2.

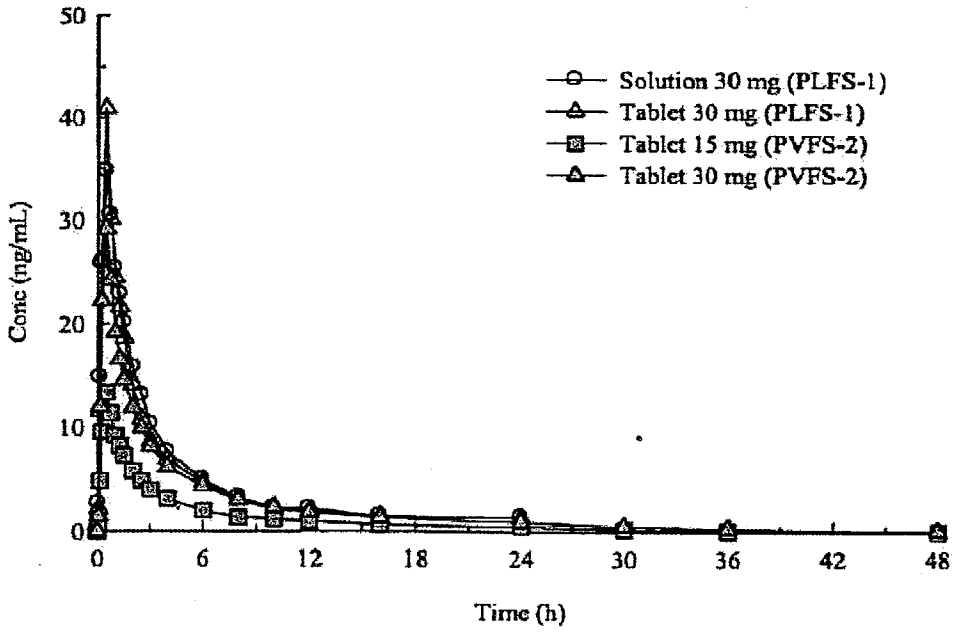

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Figure 2. Mean (±SD) of Morphine Cmax Across Studies

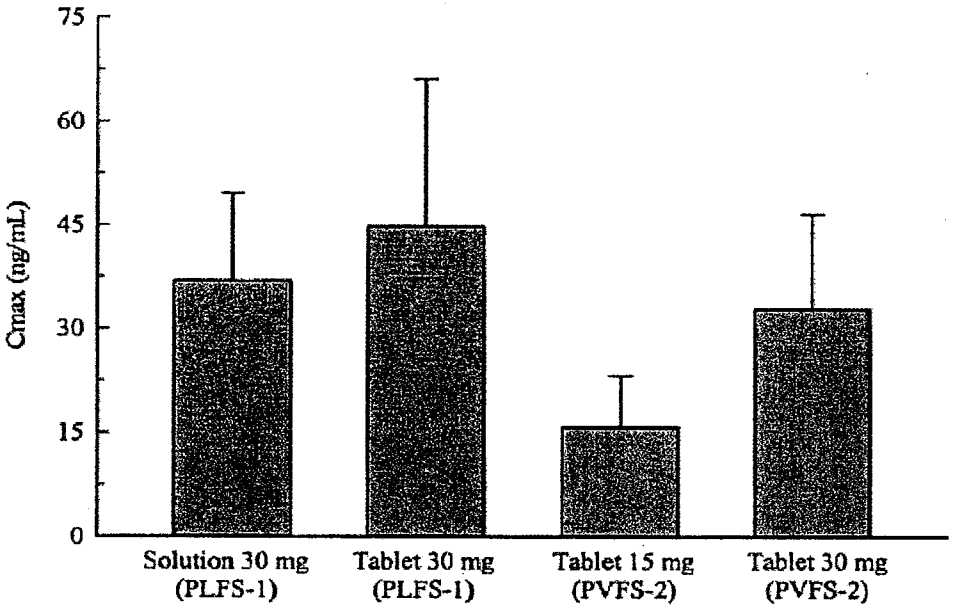

Figure 3. Mean (±SD) of Morphine AUC (0-24) Across Studies

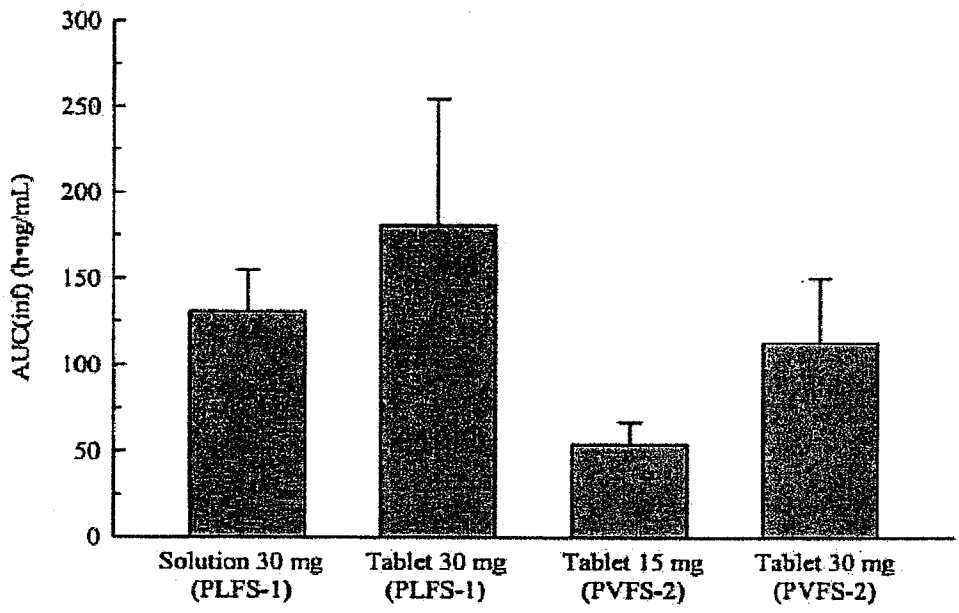

Figure 4. Mean Morphine Cmax at Steady State in Study PVFS-3

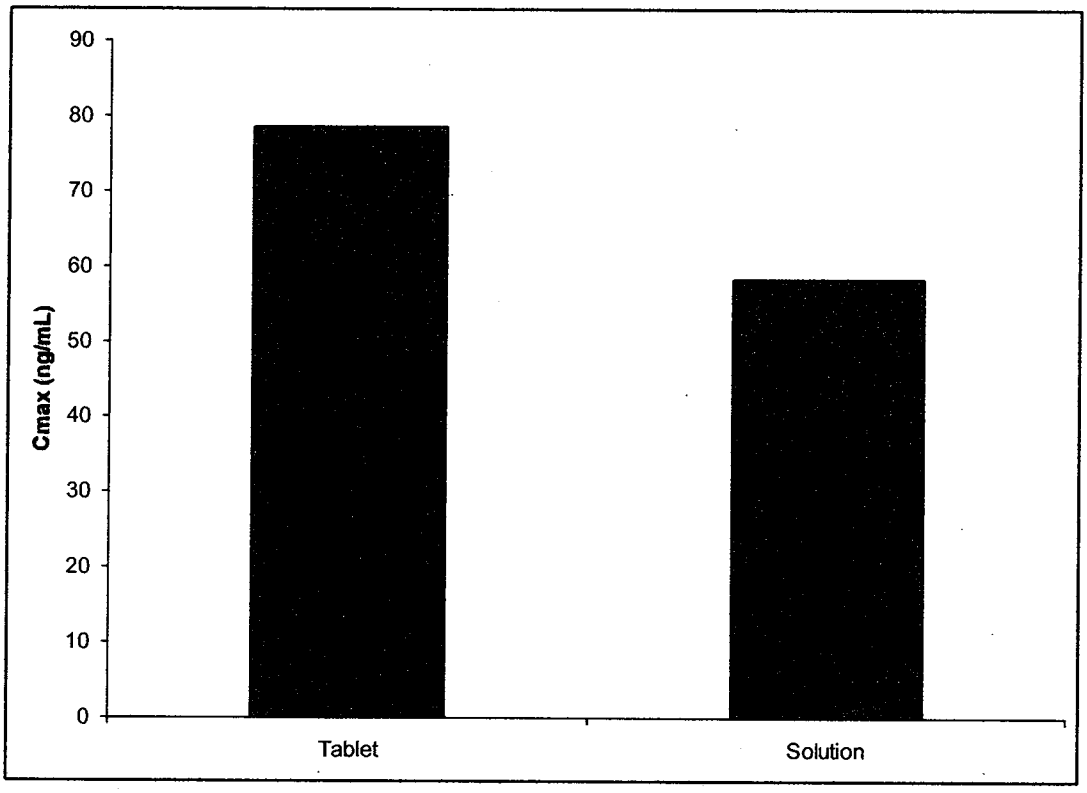

Figure 5. Mean Morphine AUC (0-24) at Steady State in Study PVFS-3

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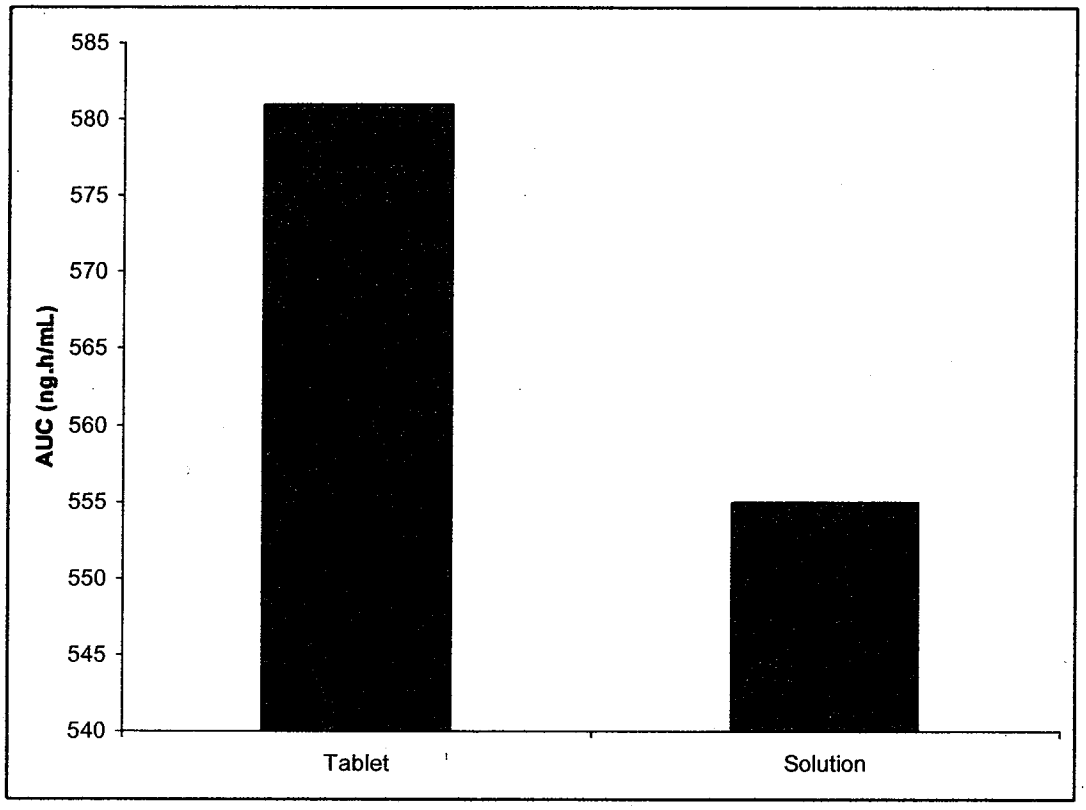

The formation of the two metabolites, M3G and M6G, was higher after oral administration of 30 mg IR tablet or solution compared to 10 mg intravenous administration of Duramorph®. This suggests a high first pass metabolism.

At steady state, the AUC of morphine and its two metabolites, M3G and M6G, following oral tablets or solution where comparable to that after extended release product, Avinza **(Figures 6, 7, and 8)**.

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Figure 7. Mean (±SD) of Morphine AUC After a Single Dose and at Steady State (Studies # PLFS-1, PVFS-2, and PVFS-3)

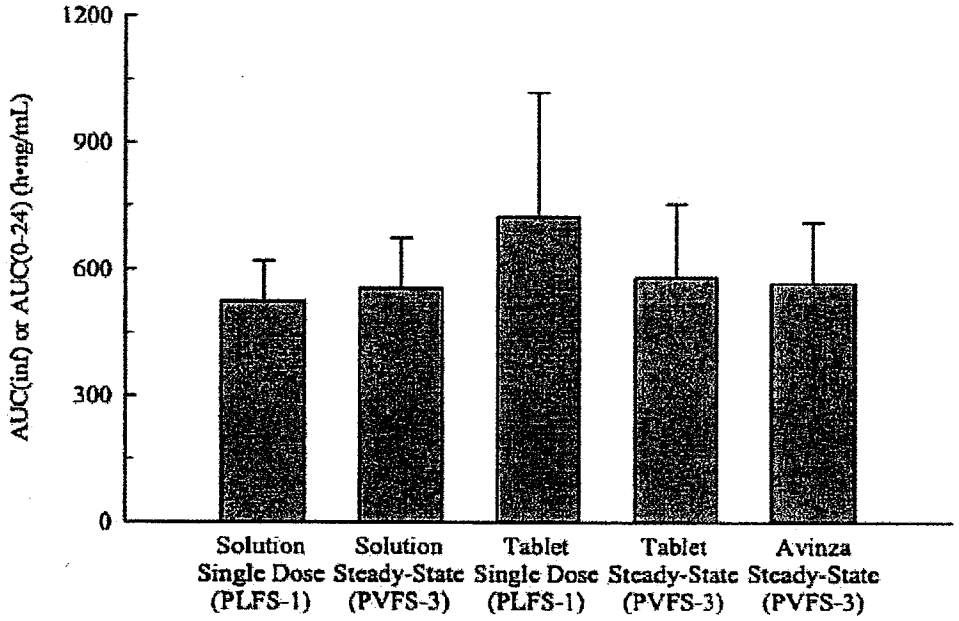


Figure 8. Mean (±SD) of M3G AUC After a Single Dose and at Steady State (Studies # PLFS-1, PVFS-2, and PVFS-3)

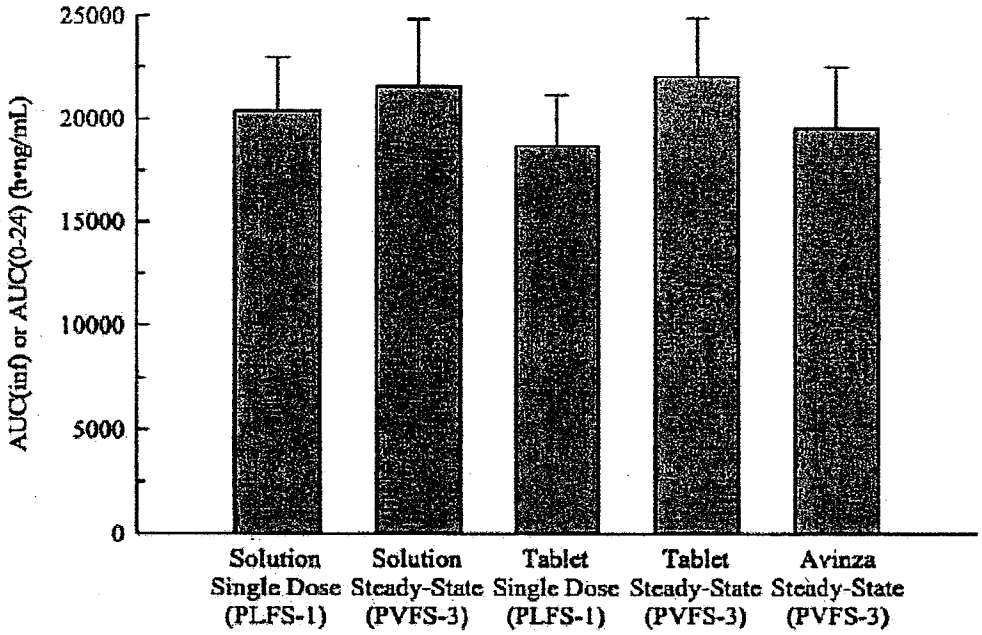
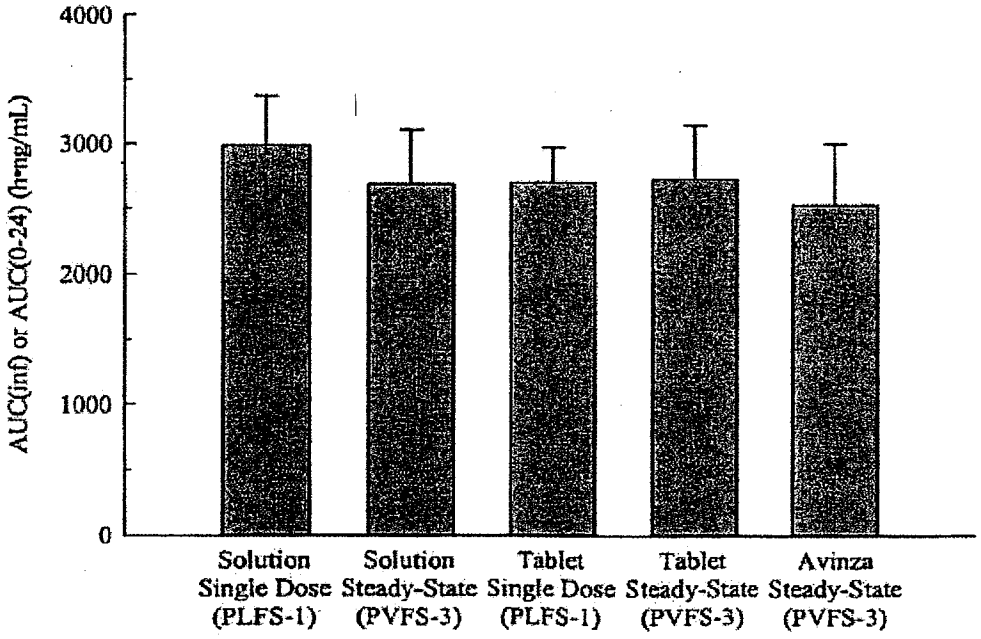


Figure 9. Mean (±SD) of M6G AUC After a Single Dose and at Steady State (Studies # PLFS-1, PVFS-2, and PVFS-3)



Overall Conclusions:

From this across studies comparison, the following conclusions can be made:

- The Cmax is consistently higher after tablets compared to solutions.
- The exposure after the two IR formulations, oral solution and tablet is comparable. However, due to the Cmax differences, the two formulations are **not bioequivalent.**
- At steady-state, the AUC after IR formulations (tablets and solution) of 30 mg dose at Q6h regimen was comparable to that of extended release Avinza® capsule when given as Q24h at a dose of 120 mg for 5 days. As expected, the Cmax after IR tablets or solution was lower than that of Avinza®. However, the Cmax was 30% to 40 % higher after tablets than solution. Therefore, the tablet and solution are not bioequivalent to each other.
- The exposure characteristics observed for the parent drug, morphine, can also be translated to its two metabolites, M3G and M6G.

4.3 Consult Review (Pharmacometric Review)

No pharmacometric consult was needed for this NDA.

4.4 Filing Memos:

Morphine Sulfate Solutions (NDA 22-195):

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-195	Brand Name	
OCP Division (I, II, III, IV, V)	II	Generic Name	Morphine Sulfate Solution
Medical Division	Anesthesia, Analgesia, and Rheumatology Products	Drug Class	Opioid Analgesic
OCP Reviewer	Sayed Al-Habet	Indication(s)	Relief of moderate to severe acute and chronic pain
OCP Team Leader	Suresh Doddapaneni	Dosage Form	Solution
		Dosing Regimen	Titrated to effect
Date of Submission	5/16/07	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Roxane Labs
PDUFA Due Date		Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			MORP-T30-PLFS-1 Morphine sulfate injection, solution , and tablets relative bioavailability

multiple dose:	X			MORP-T30-PVFS-3 Morphine Sulfate solution and IR tablets 30 mg Q6h and Avinza 120 mg QD
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			MORP-T30-PVFS-2- IR Tablets and Duramorph (IV); MORP-T30-PVFS-3- IR tablets and Avinza (extended release capsules)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		MORP-T30-PVFS-2 Dose-proportionality of 15 mg and 30 mg morphine IR tablets; food effect on 30 mg tablet
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				

Literature References	X	9		Ethnic differences; gender differences PK/PD modeling of M-6-G induced analgesia; PK of intradural morphine; PCA-PK and analgesic plasma concentrations of morphine; effect of sorbitol on permeability; effect of quinidine on morphine; formulation development of morphine
Total Number of Studies		12	5	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Bioavailability studies formulation and to be marketed formulation is the same
Comments sent to firm ?	X	There are no Information requests at time of filing
QBR questions (key issues to be considered)		(1) What is the absolute bioavailability of the solution? Note: sponsor is relying on the findings of efficacy and safety through 505 (b) (2) route of Duramorph brand of parenteral morphine formulation (2) What is the bioavailability of the solution relative to the tablets? Note: for dose-proportionality and food effect, sponsor is relying on the data acquired with morphine sulfate tablets (3) What is the relative bioavailability of the solution with respect to Avinza brand of morphine sulfate extended release tablets? Note: sponsor is relying on the findings of efficacy and safety through 505 (b) (2) route of Avinza brand of extended release morphine formulation (4) Does timing of drug administration need to be standardized relative to food consumption? (5) Is there dose-proportionality across the two strengths of 10 mg/5 mL and 20 mg/mL? (6) Is there significant accumulation upon multiple dosing?
Other comments or information not included above		-Meeting with Roxane held on 9/12/06 to discuss the adequacy of this program -Morphine Sulfate Solution has been marketed by Roxane Labs since the 1980s without and NDA. An NDA for this formulation is now submitted in an effort to bring the product into compliance of applicable laws. Only Bioavailability studies were conducted with this product in support of the NDA. The clinical efficacy and safety findings of Avinza and Duramorph (RLDs) are being relied upon by Roxane in lieu of conducting their own Clinical studies. -Study MORP-730-PVFS-3 will need to be inspected by DSI as this will constitute a pivotal BE study.
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Morphine Sulfate Tablets (NDA 22-207):

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-207	Brand Name	
OCP Division (I, II, III, IV, V)	II	Generic Name	Morphine Sulfate tablets
Medical Division	Anesthesia, Analgesia, and Rheumatology Products	Drug Class	Opioid Analgesic
OCP Reviewer	Sayed Al-Habet	Indication(s)	Relief of moderate to severe acute and chronic pain
OCP Team Leader	Suresh Doddapaneni	Dosage Form	15 mg and 30 mg tablets
		Dosing Regimen	Titrated to effect
Date of Submission	6/7/2007	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Roxane Labs
PDUFA Due Date	4/8/2008	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			MORP-T30-PLFS-1 Morphine sulfate Injection, solution , and tablets relative bioavailability
multiple dose:	X			MORP-T30-PVFS-3 Morphine Sulfate solution and IR tablets 30 mg Q6h and Avinza 120 mg QD
Patients-				
single dose:				
multiple dose:				

Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			MORP-T30-PVFS-2- IR Tablets and Duramorph (IV); MORP-T30-PVFS-3- IR tablets and Avinza (extended release capsules)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		MORP-T30-PVFS-2 Dose-proportionality of 15 mg and 30 mg morphine IR tablets; food effect on 30 mg tablet
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				Is requesting a deferral; will conduct studies post marketing
Literature References	X	9		Ethnic differences; gender differences PK/PD modeling of M-6-G induced analgesia; PK of intradural morphine; PCA-PK and analgesic plasma concentrations of morphine; effect of sorbitol on permeability; effect of quinidine on morphine; formulation development of morphine
Total Number of Studies		12	5	
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	Bioavailability studies formulation and to be marketed formulation is the same
Comments sent to firm ?	X	There are no Information requests at time of filing
QBR questions (key issues to be considered)	(1) What is the absolute bioavailability of the tablet? Note: sponsor is relying on the findings of efficacy and safety through 505 (b) (2) route of Duramorph brand of parenteral morphine formulation (2) What is the relative bioavailability of the tablet with respect to Avinza brand of morphine sulfate extended release tablets? Note: sponsor is relying on the findings of efficacy and safety through 505 (b) (2) route of Avinza brand of extended release morphine formulation (3) Does timing of drug administration need to be standardized relative to food consumption? (4) Is there dose-proportionality across the two strengths of 15 mg and 30 mg? (5) Is there significant accumulation upon multiple dosing?	
Other comments or information not included above	-Meeting with Roxane held on 9/12/06 to discuss the adequacy of this program -Morphine Sulfate tablets has been marketed by Roxane Labs since the 1980s without and NDA. An NDA for this formulation is now submitted in an effort to bring the product into compliance of applicable laws. Only Bioavailability studies were conducted with this product in support of the NDA. The clinical efficacy and safety findings of Avinza and Duramorph (RLDs) are being relied upon by Roxane in lieu of conducting their own Clinical studies. -Study MORP-730-PVFS-3 will need to be inspected by DSI as this will constitute a pivotal BE study. -Pediatric deferral is requested (Roxane is proposing to conduct pediatric studies as a PMC). Note: since the database is common to both solution (NDA 22-195) and tablets (this NDA), both NDA's will be handled together from Clin Pharm point of view.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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/s/

Sayed Al-Habet
12/21/2007 02:33:01 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
12/21/2007 02:45:13 PM
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