CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-306

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review Addendum

NDA: 21-306 (000)
Submission Date: 06/16/10
Product: Buprenorphine Transdermal System (BuTrans™)
Type of Submission: Complete Response Submission – *Biopharm Addendum*
Sponsor: Purdue Pharma L.P.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: In response to the Biopharmaceutics information request (IR) dated February 23, 2010, the sponsor was asked to provide full details of the *in-vivo* studies (Study numbers with data/results) that have been used to generate profiles to determine the impact of changes in *in vitro* dissolution rate, adhesion strength over storage on *in vivo* performance (see original Biopharmaceutics review dated 5/18/2010 in DARRT). In response to that IR letter, the sponsor submitted the following information in their submission dated March 9, 2010.

Study #	Lot#	Date of Manufacture	Study Starting Date	Patch Age, Manufacture to Study Start (days)	Patch Age (yrs)	Mean† AUC [0-168h] (pg.h/mL)	Mean† Cmax [0-168h] (pg/mL)	Study Phase
BP96-0803	7/00499/6	(b) (4)	10/28/1996	242	0.66	14056.47	112.85	1
BP96-0501*	7/00499/6		1/7/1997	313	0.86	21018.00	161.00	1
BP96-0702	7/00499/6		6/9/1997	466	1.28	17200.74	135.52	1
BP98-0201	7/00499/6		4/1/1998	762	2.09	21193.97	170.14	1
BP97-0501	7/00499/6		5/20/1998	811	2.22	21308.63	173.22	1
BP98-1204	7/01081/8B		9/21/1999	475	1.30	20816.35	81.60	1
BUP1009	7/02471/2***		10/21/2002	132	0.37	15008.53	130.48	1
BUP1005**	7/02471/2***		4/29/2003	322	0.88	15086.01	118.46	1

† Values determined from mean concentration vs. time profiles
* Upper chest application site
** Non-US study
*** The corresponding LTS customer lot# is 70142B2 for BTDS 10

The sponsor was also provided with the Agency's following proposed *in vitro* dissolution specification based on the release and stability data they provided.

Time Point	Agency's Proposal
0.5	(b) (4)
2	
8	
24	

Via an e-mail correspondence dated May 26, 2010, the sponsor proposed the following counter proposal as they explained that they can not meet the Agency's specification because several batches will fail either at release or during stability:

Time Point	Agency's Proposal	Purdue's Proposal
0.5		(b) (4)
2		
8		
24		

During the review of the *in vivo* data submitted to justify the sponsor's proposed dissolution specification, it was observed that the *in vivo* plasma concentrations can vary widely. The data demonstrates that from the same lot (7/00499/6) used in five (5) different biostudies, patches at different ages showed approximately seven-fold difference between the minimum and maximum values for both the AUC and Cmax parameters. Therefore, the same lot at different time may not be able to meet the Agency's bioequivalence criteria. The observed *in vivo* variability coupled with great variability in *in vitro* dissolution characteristics (since with time the dissolution rate of the same batch decreases by about 40%) is indicative of an erratic formulation (patch) with inconsistent release characteristics.

In light of these observations, the Office of Clinical Pharmacology (OCP) was consulted and ONDQA and OCP met to discuss the issue. Dr. Suresh Doddapaneni and Dr. Sheetal Agarwal participated in the meeting from OCP. OCP was requested to compare PK of buprenorphine in other dosage forms. OCP submitted the following findings and argued that similar variability in PK is also present in the sublingual strips. Therefore the PK variability may be inherent to the drug molecule.

BUPRENORPHINE PK IN HEALTHY VOLUNTEERS DOSED WITH SUBOXONE SUBLINGUAL STRIPS

	Mean Cmax in ng/mL AUC in ng.h/mL	CV%	Min	Max	Fold
Study 20-250-SA Suboxone SL strips 2 mg n=44 Cmax AUC					
	0.947 7.820	40 35	0.238 4.088	1.82 15.58	7 4
Study 20-273-SA Suboxone SL strips 8 mg n=44 Cmax AUC					
	3.37 28.74	53 45	0.785 10.25	10.6 74.77	13.5 7
Study 20-B20-AU Suboxone SL strips 12 mg n=44 Cmax AUC					
	4.55 40.13	55 36	1.30 16	13.2 72.71	10 4.5
Study 20-A90-AU Suboxone SL strips 16 mg n=44 Cmax AUC					
	5.94 54.35	37 36	1.07 13.29	9.99 98.31	9 7

However, lesser variability from the patch was expected due to avoidance of first pass metabolism from the transdermal route. Nonetheless, the Agency proposed the following dissolution proposal and responded that based on the sponsor's data, few batches may not be able to pass at Level 1 of testing even though it was felt that the sponsor needs to test additional samples to meet the Agency's proposed specifications at Level 2 or Level 3. However, the sponsor had no data to verify that.

:

Time Point	Agency's Proposal	Purdue's Proposal	Agency's Revised Proposal
0.5		(b) (4)	
2			
8			
24			

In response, via an e-mail dated 6/16/2010, the sponsor responded that "*We agree with FDA's revised proposal for specification for the 0.5, 8, and 24 hour time point. After further discussion with the manufacturer and review of data, the tightest range for the 2 hour time point is* (b) (4) *As mentioned in our discussion, two of the batches that would fail release testing at the* (b) (4) *specification are bio batches 7/00499/6, 5 mg and 20 mg, initial values of* (b) (4)*. As discussed, we will revert to L2 and L3 testing as necessary*". They submitted the following proposal:

Time Point	Agency's Revised Proposal	Purdue's Proposal
0.5	(b) (4)	
2		
8		
24		

There was a short t-con with the sponsor on this issue on 6/16/2010, and the sponsor was told that their dissolution specification will be accepted on an interim basis for one year. They will have a post-approval commitment to collect dissolution data from 12 patches and may have to proceed up to Level 3 if necessary, from each post-approval batch and submit after one year to the Agency for review. The sponsor submitted the following amendment via e-mail agreeing with what was discussed:

Post-Approval Commitments

Commitment 1:

Per our discussion on June 16, 2010, we agree to this dissolution specification with a post-approval commitment to collect data from twelve patches for each time point on release and stability. The data with an analysis in relation to the specification will be submitted to FDA June 30, 2011.

Reviewer's Comments: *The sponsor's proposed specifications do not comply with the Agency's IVIVC guidance recommendations because they are more than the maximum 25% range allowed when the dissolution is variable. Moreover, the sponsor was unable to show that these proposed specifications would ensure bioequivalent lots. Nonetheless, these specifications were accepted on an interim basis based on the fact that the sponsor is unable to meet the Agency's proposed tighter specifications and there is a clinical benefit in having this patch in the market. Of note, other buprenorphine product in the market exhibits same degree of variability as observed with this patch though lesser variability from the patch was expected due to avoidance of first pass metabolism from transdermal patch.*

Recommendation: The following dissolution specification is acceptable for one-year on an interim basis using the proposed dissolution test with USP method 6 (rotating cylinder, 50 rpm), whereby 600 ml of 0.9% sodium chloride solution is heated to 32° C. (b) (4) [redacted] The sponsor agreed to a post-approval commitment to collect dissolution data from 12 patches at the beginning and add more samples to proceed further if necessary, from each post-approval batch and submit after one year to the Agency for review.

Time Point	Purdue's Proposal
0.5	(b) (4) [redacted]
2	
8	
24	

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	Butrans (buprenorphine) Transdermal System

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/s/

TAPASH K GHOSH
06/17/2010

PATRICK J MARROUM
06/18/2010

ONDQA (Biopharmaceutics) Review

NDA: 21-306 (000)
Submission Date: 09/25/09
Product: Buprenorphine Transdermal System (BuTrans™)
Type of Submission: Complete Response Submission
Sponsor: Purdue Pharma L.P.
Reviewer: Tapash K. Ghosh, Ph.D.

Background: The sponsor developed the Buprenorphine Transdermal Patch in 3 dosage strengths, 5 mg, 10 mg, and 20 mg and originally submitted NDA 21-306 to the Agency on November 3, 2000 under the proposed trade name of Norspan™. The NDA received the Agency's not approvable (NA) action letter dated August 31, 2001. The current submission dated September 25, 2009, included the Complete Response (CR) to the NA letter. In this CR, the sponsor addressed each of the items cited in the NA letter with their Response to support approval of Buprenorphine Transdermal System (BTDS) under the new proposed trade name BuTrans™ for the indication of relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

In this Biopharmaceutics review, the sponsor's responses only to items 34 and 48 will be addressed. As background, the item descriptions with the original Agency's comments, the sponsor's responses and the Agency's current comments in response to the sponsor's responses are enumerated below.

<u>Item 34</u>:

The Agency's Comment: ***Revise the in vitro release specification as follows:***

a) Tighten the specifications to ensure the proper release profile of the drug product, at release, and through shelf life.

The sponsor's Response: The in vitro release specification has been tightened to ensure the proper release profile of the drug product, at release, and throughout shelf life.

b) Add an intermediate time point, e.g., 8 hours, in the testing.

The sponsor's Response: An additional intermediate time point at 8 hours has been added to the in vitro release testing with limit of NLT (b) (4) % for QC release and the stability testing.

c) Include the USP<724> acceptance criteria of testing through L1, L2, and L3.

The sponsor's Response: The USP<724> acceptance criteria of testing through L1, L2, and L3 stages has been included in the revised BTDS specification 04-413-03-0-00109-01.

Reviewer's Commenst:

In vitro release specifications have been tightened. The updated in vitro release specifications include the addition of an intermediate sampling point at 8 hours. Updated drug product specifications, provided under "BTDS specification 0.4-413-03-0-00109-01", are listed in the following Table .

Table 19. Revised BTDS In Vitro Release Specifications		
Time Point (hr)	*Current Acceptance Criteria*	*Previous Acceptance Criteria*
0.5	(b) (4)	
2		
8		
24		

However, based on the dissolution profiles of the batches kept at proposed storage condition at release and at 12 mo, 18 mo and 24 months, the reviewer recommends the following specifications:

Proposed BTDS In Vitro Release Specifications			
Time Point (hr)	*Previous Acceptance Criteria*	*Current Sponsor's Proposed Acceptance Criteria*	***The Agency's Proposed Acceptance Criteria***
0.5			(b) (4)
2			
8			
16			

<u>Item 48</u>:

The Agency's Comment:

A significant decrease is observed in dissolution (drug release) for the drug product on stability.

a) Provide tightened dissolution specifications, and a shorter expiration dating period (you have proposed (b) (4)), to ensure acceptable performance of the drug product through its expiration dating period.

The sponsor's Response: The tightened dissolution specification has been set as presented in response to Item 34a. The tightened specification supports the (b) (4)

expiration dating. In consideration of the new specification, the (b) (4) shelf life is now fully justified by the real time stability results taken together with PK and clinical study results.

b) Provide the results of an investigation into the factors (e.g., raw materials, manufacturing, packaging, etc.) which may have caused the observed wide variability in stability for drug dissolution of the drug product.

The sponsor's Response: The factors of raw materials, manufacturing and packaging were examined. Based on the 14 years (1995 – present) of manufacturing experience of BTDS, there is no evidence showing that those factors contributed to the wide variation of the drug dissolution in stability. The trend of decrease in drug dissolution stability showed the same wide variation across the strengths throughout the product development history.

Such a decrease in the *in vitro* release rate is a common phenomenon of matrix type transdermal delivery systems. The matrix of BTDS is actually a (b) (4) . Therefore, (b) (4) affects the short term "extractability" of buprenorphine from the transdermal delivery system and results in increased variability of the dissolution rate for the 2 hour time point but to a lesser extent at the 24 hour time point.

The sponsor investigated several factors that could contribute to the observed drug dissolution variability, specifically dissolution media pH, potential agglomeration of oleyl oleate on the patch surface, and differences in exposed edges of active and inactive patch surface areas. Results from these experiments did not provide a direct cause and effect explanation to the drug dissolution variability in BTDS.

In addition, the Mass Balance Study on BTDS, LTS 04-300-40-1-00001-00 (NDA 21-306, Vol 6, p130) indicates that (b) (4) which makes it more hydrophobic. The ability of the matrix to be hydrated by the aqueous dissolution medium (0.9 % NaCl) will therefore result in more variable in vitro release at the early time points, but to a lesser extent at the later (24 hr) time point when the matrix has been fully hydrated.

As noted, there are changes in the in vitro release profile of all strengths of BTDS during storage –particularly at the 2 hour sampling time. However, as discussed in Section 2.1.3 of the Pharmaceutical Development Report for Buprenorphine Transdermal Delivery Systems, these changes in the *in vitro* release profile were not accompanied by any changes in the clinical pharmacokinetic performance as indicated by peak exposure (C_{max}) or total exposure (AUC_{168}) during the 168-hour dosing period by BTDS application.

Reviewer's Comment:

*Dissolution specifications have been tightened (see Item **34**) though not acceptable by the reviewer. The Agency also does not concur with the sponsor's proposed expiry period based on available data. The Agency's proposed dissolution specification and shelf-life have been described above in response to Item 34.*

Regarding the observed variability in the dissolution data, several factors that could contribute to the observed drug dissolution variability, specifically dissolution media pH, potential agglomeration of oleyl oleate on the patch surface, and differences in exposed edges of active and inactive patch surface areas, were investigated by the sponsor. However, the results from these experiments did not provide a direct cause and effect explanation to the drug dissolution variability in BTDS. All dissolution data are within the sponsor's proposed specifications, and more importantly these changes in the in vitro release profile were not accompanied by any changes in the clinical pharmacokinetic performance as indicated by peak exposure (C_{max}) or total exposure (AUC_{168}) during the 168-hour (1 week) dosing period by BTDS application.

However, the amount of buprenorphine delivered after the recommended usage of 7 days is shown in Table P.1-2.

Table P.1-2. Amount Delivered After recommended Usage

Strength (Total amount)	*Active Surface Area*	*Delivery rate*	*Duration*	*Amount Delivered*	*% Used*
5 mg	6.25 mm^2	5 µg/h	7 days	(b) (4)	
10 mg	12.5 mm^2	10 µg/h	7 days		
20 mg	25 mm^2	20 µg/h	7 days		

The data reveals that more than (b) (4) *of the original amount of buprenorphine remains in the patch after recommended usage period. Also, the Content Uniformity specification of the Drug Product is "No unit outside* (b) (4) *%" which suggests that even 75% of the current loading may be capable of delivering the required amount of buprenorphine consistently over 7-day period. Overall, the data also suggests that loading dose in the patches can be reduced while still maintaining the required flux over the 7-day usage period. The sponsor is advised to continue development work in this line following initial approval of the product. This is in line with the Agency's current thinking of promoting further development work on transdermal products with the intention to minimize the residual drug amount. The goal of this venture is to minimize the potential for abuse of the drug substance following the recommended usage period.*

Overall Comments:

1. *Based on the dissolution profiles of the batches kept at proposed storage condition at release and at 12 mo, 18 mo and 24 months, the reviewer recommends the following specifications:*

Proposed BTDS In Vitro Release Specifications			
Time Point (hr)	*Previous Acceptance Criteria*	*Current Sponsor's Proposed Acceptance Criteria*	***The Agency's Proposed Acceptance Criteria***
0.5	(b) (4)		
2			
8			
16			

2. *The permeability study was conducted up to 72 hours (3 days). The patch's usage period can be up to 7 days. No in-vitro permeation data up to 7 days is available from patches. Therefore, assurance of the patch performance continuously for 7 days based on in-vitro permeation data at release and/or at later time points is not possible.*

3. *Based on the results and the sponsor's analysis of the in-vitro permeation, the sponsor concluded that that the permeability of the three-year old batches is equivalent to that of the freshly made batches. However, patches of the same batches at manufacture and at 3 years of age were not used. Therefore conclusion of the study is based on pooled data from various batches (Cross-study analysis).*

4. *The interaction analysis of buprenorphine with a multiple regression model using the individual subject values (N= 109) for $C_{max(0-168)}$ and for $AUC_{(0-168)}$ with terms for patch lot#, patch age supports the conclusion that differences in patch age are not associated with in vivo pharmacokinetic performance differences.*

5. *The sponsor's evaluations conclude that patch age accompanied by the observed decrease in in vitro dissolution along with the decrease in both adhesion strength and release strength does not affect the clinical performance of the BTDS. However, after usage more than* (b) (4) *of the buprenorphine remains in the patch. Therefore, it may be possible to reduce the loading dose of buprenorphine in the patch while still maintaining the required flux. The sponsor is advised to continue development work in this line following initial approval of the product. This is in line with the Agency's current thinking of promoting further development work on transdermal products with the intention to minimize the residual drug amount. The goal of this venture is to minimize the potential for abuse of the drug substance following the recommended usage period.*

Comments for the Clinical Division:

The sponsor reported that further information on the in vivo performance of the BTDS during the storage period is discussed in the following two reports.

The first report, Assessment of Patch Age and Efficacy, provides information on the batches used in the Phase 3 studies including BUP.CLIN0001, a pivotal clinical study. This report also evaluated the patch performance during the long term clinical study where patients continued treatment for more than 21 months.

The second report, Analysis of Impact of the BTDS Release Rate on Clinical Efficacy, provides an analysis of the impact of age of BTDS on clinical efficacy across five studies performed in the USA. A detailed statistical analysis of data from 421 subjects by stepwise multiple regression examined the effect of the fractional 2 hour in vitro release rate on in vivo clinical efficacy. The report concludes that the change in release rate with age, up to 2 years, did not have impact on clinical efficacy of BTDS.

Both evaluations conclude that patch age accompanied by the observed decrease in in vitro dissolution along with the decrease in both adhesion strength and release strength, does not affect the clinical performance of the BTDS.

The above mentioned reports need to be reviewed by the clinical division to accept the sponsor's conclusion.

Recommendation: *Based on the dissolution profiles of the batches kept at proposed storage condition at release and at 12 mo, 18 mo and 24 months, the reviewer recommends the following specifications:*

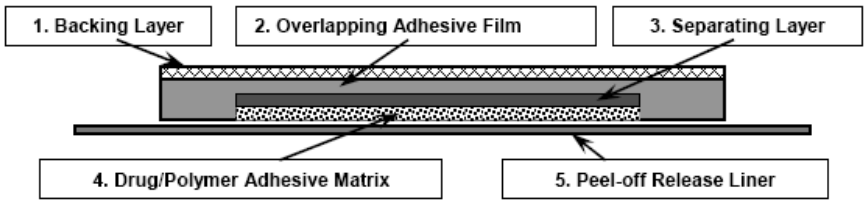
Proposed BTDS In Vitro Release Specifications			
Time Point (hr)	*Previous Acceptance Criteria*	*Current Sponsor's Proposed Acceptance Criteria*	***The Agency's Proposed Acceptance Criteria*** (b) (4)
0.5	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

Drug Product

The buprenorphine transdermal delivery system (BTDS) is a rectangular or square beige-colored transdermal patch with rounded corners that is formulated to provide a controlled release of buprenorphine for a period of seven (7) days for the amelioration of chronic pain. The BTDS is a matrix system in which the drug is dissolved in the polymer matrix. The rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the stratum corneum of the epidermis. The BTDS consists of a backing layer to prevent the buprenorphine-free adhesive matrix layer from sticking to clothing. The buprenorphine-free adhesive matrix allows the BTDS to adhere to the skin. A separating foil is present to prevent diffusion of the buprenorphine into the buprenorphine-free adhesive matrix during storage. The drug containing adhesive matrix contains the buprenorphine drug substance and is in direct contact with the skin. A (b) (4) release liner is used for easy removal prior to application. A cross section of the BTDS is shown below.



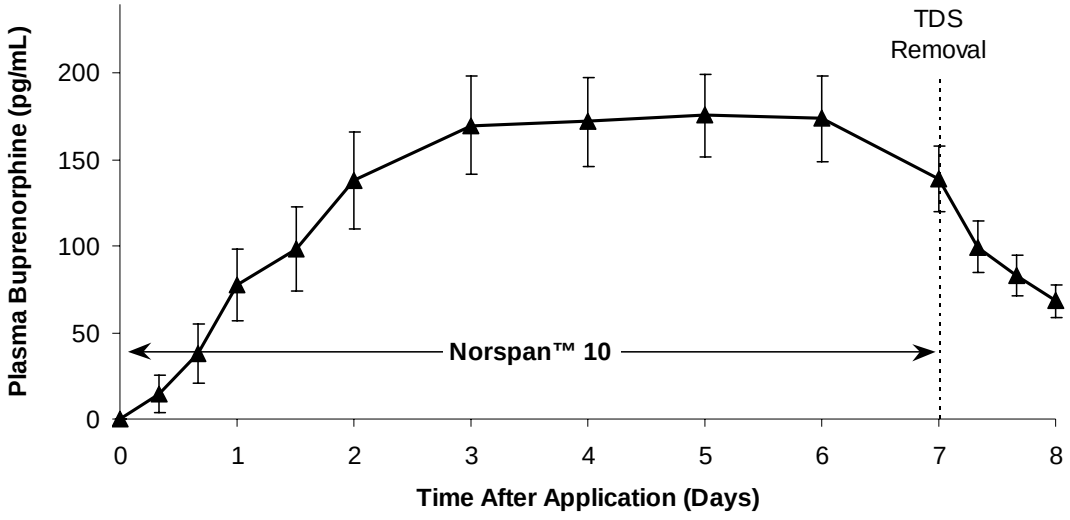
Cross Section Diagram of BuTrans (not to scale).

In addition to the active component buprenorphine, the drug-containing adhesive matrix contains levulinic acid, povidone, oleyl oleate, and the polymer Duro-Tak® (b) (4)

BTDS 5 mg, 10 mg, and 20 mg are designed for systemic delivery of buprenorphine for up to 7 days (usage time) with normal rates of 5 µg/h, 10 µg/h, and 20 µg/h, respectively. After usage more than (b) (4) of the buprenorphine remains in the patch. Therefore, deviations of the recommended usage and disposal are prone to misuse and/or abuse of this potential addictive drug. The patient is instructed to adequately dispose of the remaining patch.

BuTrans™ is intended to be used for the continual transdermal release of buprenorphine over a period of 7 days per system in patients with moderate to severe pain requiring continuous, around-the-clock opioid treatment for up to 7 days as shown in the following

figure.



Description and Composition of the Drug Product

The composition of the BTDS remains unchanged (Table P.1-1) from the original submission:

Table P.1-1. Drug Product Composition

Component	*5 mg*	*10 mg*	*20 mg*
Buprenorphine	5	10	20
Levulinic acid	(b) (4)		
Oleyl oleate			
Povidone (PVP), USP			
Polyacrylate (b) (4) (b) (4)			
Aluminum acetylacetonate (cross linking agent)	***	***	***

(b) (4)

The 5 mg, 10 mg and 20 mg strengths are designed for systemic delivery of buprenorphine continually for up to 7 days with normal rates of 5 µg/h, 10 µg/h and 20 µg/h, respectively (recommended usage). The amount of buprenorphine delivered after the recommended usage of 7 days is shown in Table P.1-2.

Table P.1-2. Amount Delivered After recommended Usage

Strength (Total amount)	*Active Surface Area*	*Delivery rate*	*Duration*	*Amount Delivered*	*% Used*
5 mg	6.25 mm^2	5 µg/h	7 days	(b) (4)	
10 mg	12.5 mm^2	10 µg/h	7 days		
20 mg	25 mm^2	20 µg/h	7 days		

More than (b) (4) of the original amount of buprenorphine remains in the patch after recommended usage period which has the potential for abuse.

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Figure 1. Skin Permeation Profiles by Batch

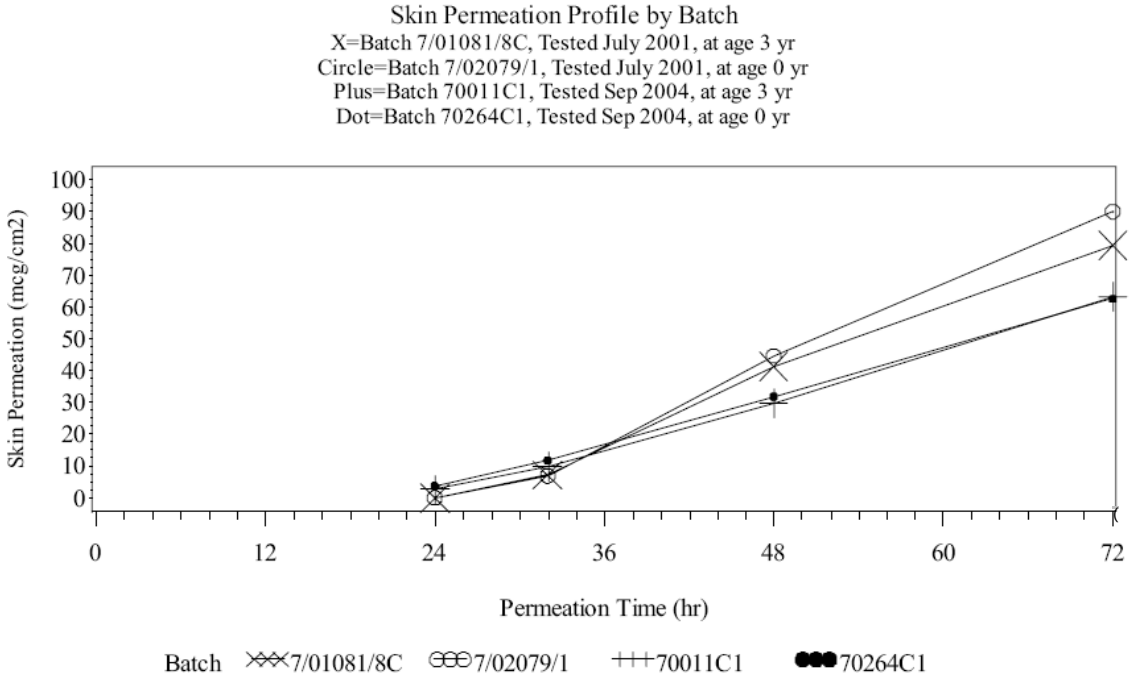
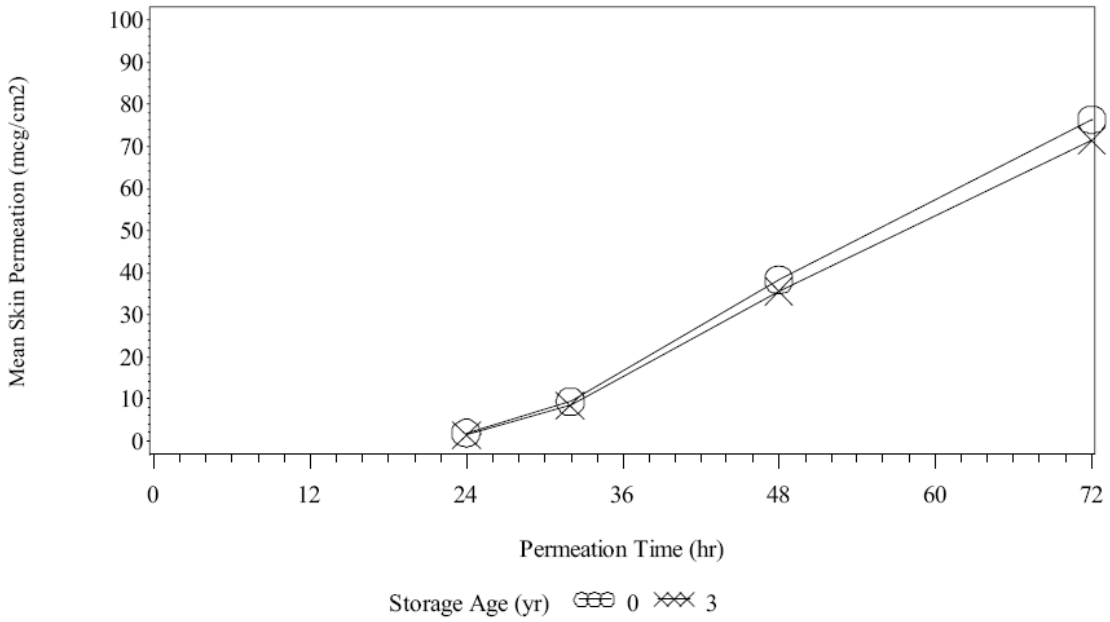


Figure S2. Mean Skin Permeation Profile by Storage Age

Skin Permeation Mean Profile by Age



A statistical analysis was conducted to determine whether there was a statistically significant difference which could be attributed to storage age, i.e. which could be attributed to the slower dissolution at 3 years than at initial. Table 4 summarizes the LSMeans comparing the results of the freshly made batches to the results of the 3 year old batches, and indicates that the average permeability of the three year old batches

was 88.2% of the permeability of the freshly made batches, with a 90% confidence interval (81.0%, 96.0%). Thus the 90% confidence interval for the ratio of 3 year old to freshly made is within the bioequivalence criteria of (80.0%, 125.0%), and it is concluded that the permeability of the three-year old batches is equivalent to that of the freshly made batches.

Table 4. Skin Permeability LSMeans, Compare Recent Manufactured to 3 yr

Statistic	Recently Manufactured Batches	3 yr Old Batches	DIfference 3 yr-Recent LSMeans, or Ratio 3 yr/Recent Exponentiated LSMeans (90% Confidence Interval)
LSMean(a)	2.3201	2.1943	-0.1258 (-0.211217, -0.040432)
Exponentiated LSMean(b)	10.18	8.974	88.2% (81.0%, 96.0%)

(a) Natural log transformed data were analyzed
(b) Corresponds to geometric mean of permeation data

Reviewer's Comment:

Based on the results and the sponsor's analysis, the sponsor concluded that that the permeability of the three-year old batches is equivalent to that of the freshly made batches. However, patches of the same batches at manufacture and at 3 years of age were not used. Therefore conclusion of the study is based on pooled data from various batches (Cross-study analysis).

Both the batches 70011C1 and 7/02079/1 were manufactured on (b) (4) *While data from batch 7/02079/1 tested in July, 2001 has been presented, it is not clear why the same batch was not tested in 2004 to have a direct comparison from the same batch after 3 years. The same way, it is not clear why initial permeation data from batch 70011C1 is not available. In absence of direct comparison from the same batches, validation of results is difficult especially in light of wide variation of "24 hours" data among the batches. .*

The permeability study was conducted up to 72 hours (3 days). The patch's usage period can be up to 7 days. No in-vitro permeation data up to 7 days is available from patches which are either freshly made or 2 years or older in age.

Impact of Changes in In Vitro Release, Adhesion Strength and Release Strength over Storage on In Vivo Performance

There is a trend of decline in the in vitro release, adhesion strength and release strength for all strengths of BTDS during storage. For example, the mean amount of buprenorphine released from batch 7/00499/6 10 mg patches at 2 hours declined from (b) (4)% initially to (b) (4)% at 24 months and (b) (4)% at 36 months. However, according to the sponsor, this trend of decrease in the above mentioned attributes was not accompanied by

any changes in the in vivo absorption as measured by peak exposure (C_{max}) (Figure 7) or total exposure during the 168 hour period of BTDS application (AUC_{168}) (Figure 8).

Figure 7: *In Vivo* Absorption as Measured by Peak Exposure (C_{max})
BTDS 10 Cmax vs. Patch Age by Lot

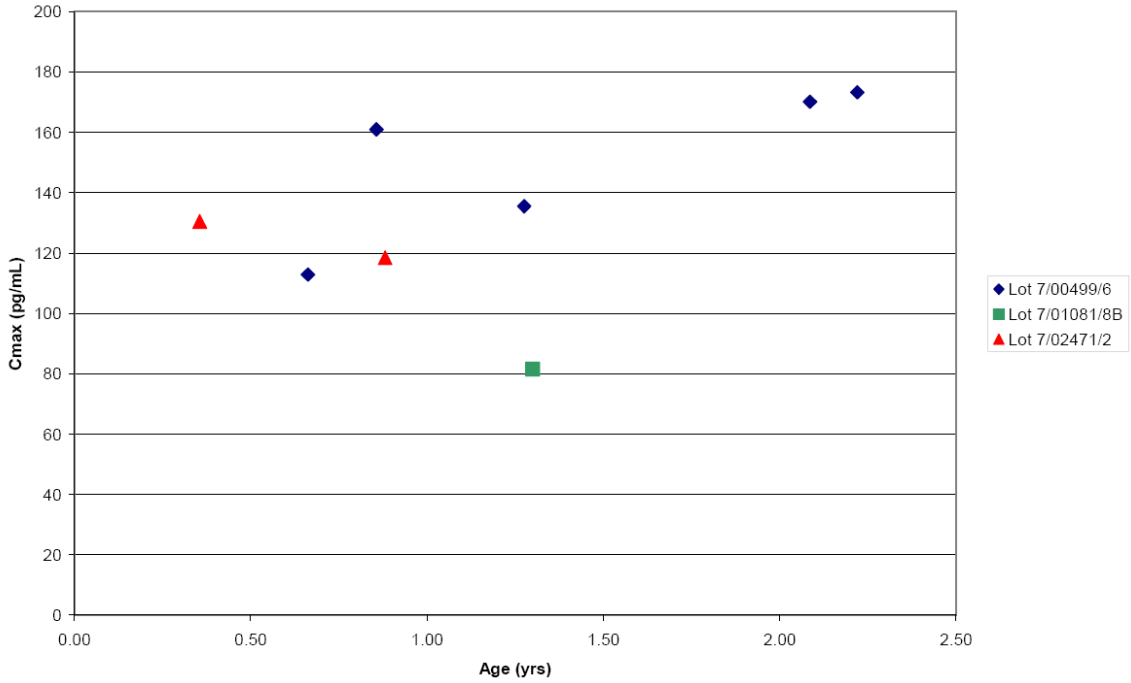
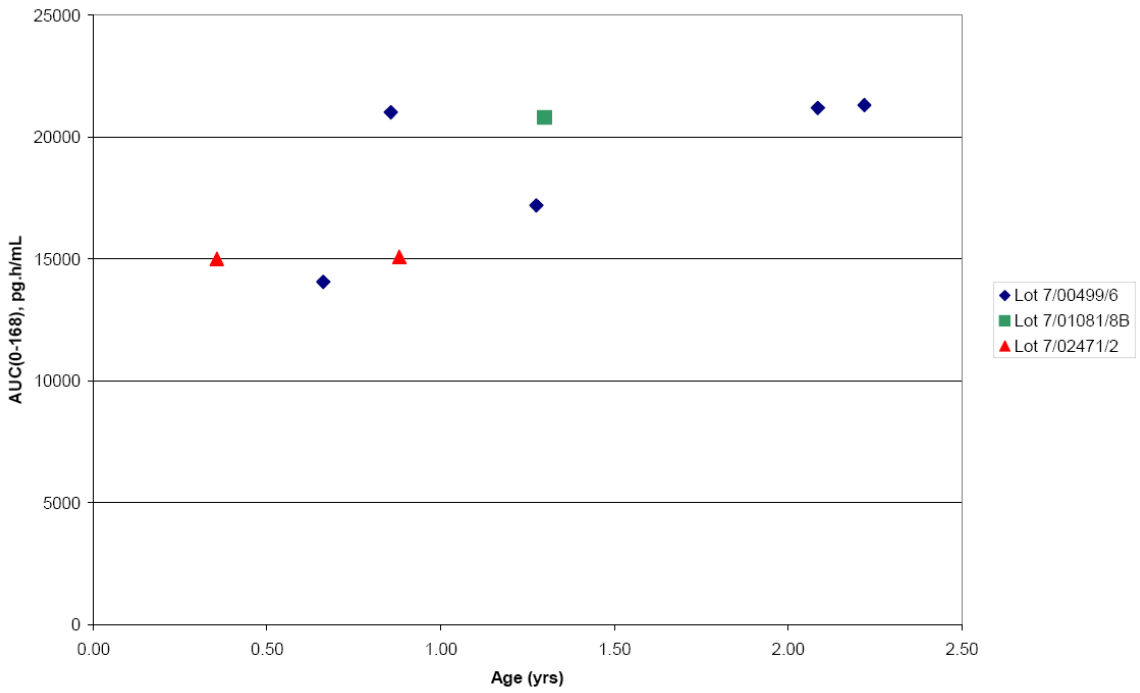


Figure 8: Total Exposure During the 168 Hour Period of BTDS Application (AUC_{168})
BTDS 10 AUC(0-168) vs. Patch Age by Lot



Upon review of the above study results, the following information request was made via an email through Matthew Sullivan, M.S., Regulatory Project Manager on February 23, 2010.

FDA Request:

The following information has been submitted in the original submission:

> **Impact of Changes in In Vitro Release, Adhesion Strength and Release Strength over Storage on In Vivo Performance**

There is a trend of decline in the in vitro release, adhesion strength and release strength for all strengths of BTDS during storage. For example, the mean amount of buprenorphine released from batch 7/00499/6 10 mg patches at 2 hours declined from (b)(4)% initially to (b)(4)% at 24 months and (b)(4)% at 36 months. However, this trend of decrease in the above mentioned attributes was not accompanied by any changes in the in vivo absorption as measured by peak exposure (Cmax) (Figure 7) or total exposure during the 168 hour period of BTDS application (AUC168) (Figure 8).

Please provide full details of the in-vivo studies (Study numbers with data/results) that have been used to generate the above profiles. Also, confirm that the lots used are of clinical batches.

The Sponsor's response:

Table 1, below, contains the data that were used to generate Figures 7 & 8 of the BTDS Pharmaceutical Development Report submitted on September 30, 2009. The corresponding study reports for the respective studies can be found by following the study number links in the table, with the exception of Study BUP1005 which is a Japanese study that was not included in the complete response filing. All three of the lots represented were clinical batches.

In reviewing these data, we noted that the mean Cmax and AUC values included were determined directly from the corresponding mean concentration vs. time profiles, rather than from the individual subject values. Presented below are revised figures (Figures 7R and 8R) and a revised supporting summary table (Table 1R). The underlying individual subject metrics represent observed Cmax and calculated AUC over the 0-168h period of BTDS 10 application.

To examine quantitatively whether buprenorphine exposure varies as a function of patch age, multiple regression models were constructed using the individual subject values (N= 109) for Cmax $_{(0\text{-}168)}$ and for AUC $_{(0\text{-}168)}$, with terms for patch lot#, patch age, and their interaction. The slopes for the patch age term in the fitted Cmax and AUC models were not significantly different from zero. The fitted models for Cmax and AUC explained only 4.1 and 4.3%, respectively, of total variability. Consistent with the conclusion drawn from the earlier data, the revised data and analyses support the conclusion that differences in patch age are not associated with *in vivo* pharmacokinetic performance differences.

Table 1. Patch Age vs. BTDS Pharmacokinetic Performance Data for Figures 7 & 8

Study #	Lot#	Date of Manufacture	Study Starting Date	Patch Age, Manufacture to Study Start (days)	Patch Age (yrs)	Mean† AUC [0-168h] (pg.h/mL)	Mean† Cmax [0-168h] (pg/mL)	Study Phase
BP96-0803	7/00499/6	(b) (4)	10/28/1996	242	0.66	14056.47	112.85	1
BP96-0501*	7/00499/6		1/7/1997	313	0.86	21018.00	161.00	1
BP96-0702	7/00499/6		6/9/1997	466	1.28	17200.74	135.52	1
BP98-0201	7/00499/6		4/1/1998	762	2.09	21193.97	170.14	1
BP97-0501	7/00499/6		5/20/1998	811	2.22	21308.63	173.22	1
BP98-1204	7/01081/8B		9/21/1999	475	1.30	20816.35	81.60	1
BUP1009	7/02471/2***		10/21/2002	132	0.37	15008.53	130.48	1
BUP1005**	7/02471/2***		4/29/2003	322	0.88	15086.01	118.46	1

† Values determined from mean concentration vs. time profiles
* Upper chest application site
** Non-US study
*** The corresponding LTS customer lot# is 70142B2 for BTDS 10

Figure 7R: In Vivo Absorption as Measured by Individual Subject and Mean Peak Exposure (Cmax)

BTDS 10 Cmax (0-168h) vs. Patch Age by Lot#

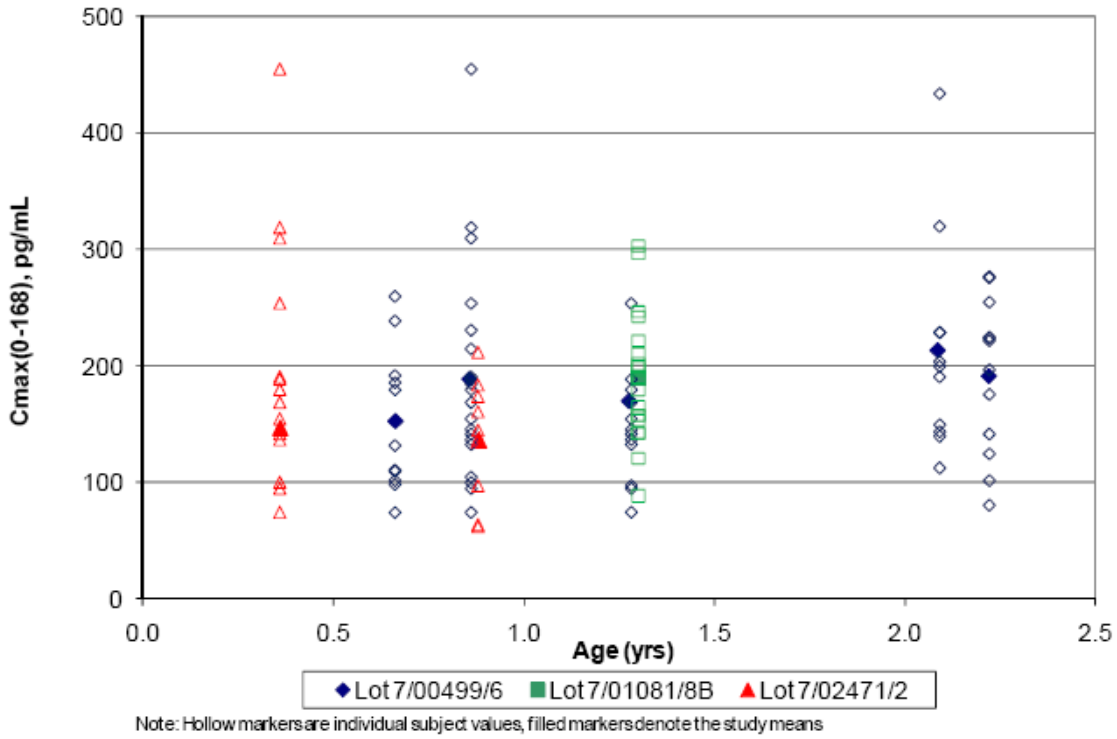


Figure 8R: Total Individual Subject and Mean Exposure During the 168 Hour Period of BTDS Application [AUC(0-168h)]

BTDS 10 AUC (0-168h) vs. Patch Age by Lot#

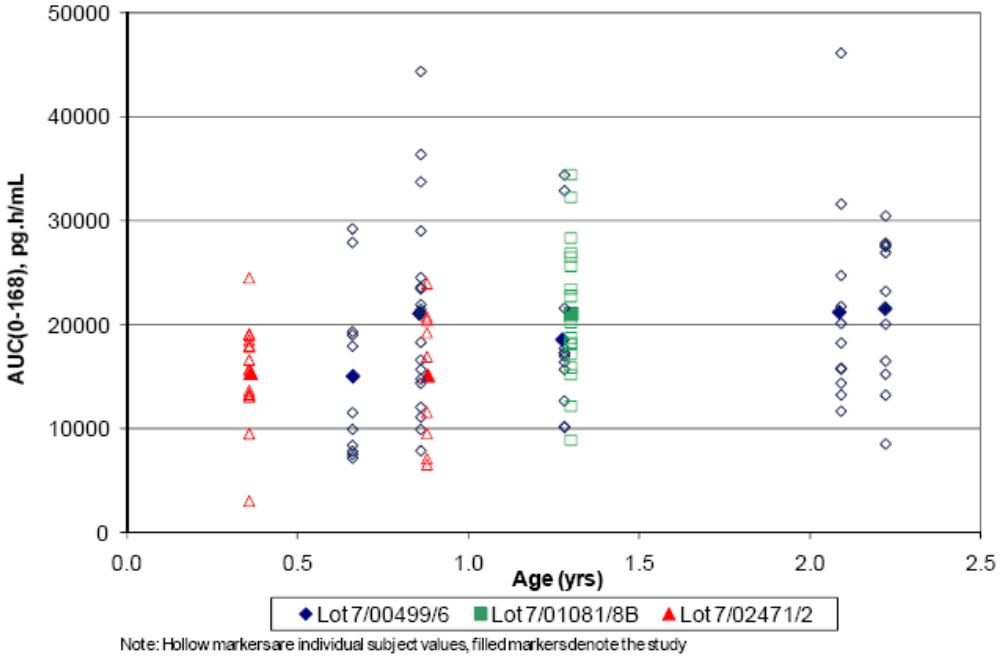


Table 1R. Patch Age vs. BTDS Pharmacokinetic Performance Data for Figures 7R & 8R

Study #	Lot#	Date of Manufacture	Study Starting Date	Patch Age, Manufacture to Study Start (days)	Patch Age (yrs)	Mean† AUC [0-168h] (pg.h/mL)	Mean† Cmax [0-168h] (pg/mL)	Study Phase
		(b) (4)						
BP96-0803	7/00499/6		10/28/1996	242	0.66	15031.17	152.21	1
BP96-0501*	7/00499/6		1/7/1997	313	0.86	21044.40	188.32	1
BP96-0702	7/00499/6		6/9/1997	466	1.28	18562.59	169.48	1
BP98-0201	7/00499/6		4/1/1998	762	2.09	21191.90	213.00	1
BP97-0501	7/00499/6		5/20/1998	811	2.22	21526.13	190.83	1
BP98-1204	7/01081/8B		9/21/1999	475	1.30	21064.45	189.92	1
BUP1009	7/02471/2***		10/21/2002	132	0.37	15350.18	146.40	1
BUP1005**	7/02471/2***		4/29/2003	322	0.88	15085.57	136.43	1

† Values are means of individual subject metrics
* Upper chest application site
** Non-US study
*** The corresponding LTS customer lot# is 70142B2 for BTDS 10

Mean Scores

The MEANS Procedure

lot=7/00499/6

Variable	Label	N	Mean	Std Dev	Minimum	Maximum
AUC168_pg_h_mL_	AUC168(pg*h/mL)	66	19703.13	8661.15	7126.80	46132.20
Cmax168_pg_mL_	Cmax168(pg/mL)	66	183.4469697	79.4204725	73.6000000	454.0000000
Patch_Age__yrs_	Patch Age (yrs)	66	1.3553030	0.6226796	0.6600000	2.2200000

lot=7/01081/8B

Variable	Label	N	Mean	Std Dev	Minimum	Maximum
AUC168_pg_h_mL_	AUC168(pg*h/mL)	19	21064.45	6709.43	8855.40	34413.15
Cmax168_pg_mL_	Cmax168(pg/mL)	19	189.9157895	55.5679890	88.4000000	303.0000000
Patch_Age__yrs_	Patch Age (yrs)	19	1.3000000	0	1.3000000	1.3000000

lot=7/02471/2

Variable	Label	N	Mean	Std Dev	Minimum	Maximum
AUC168_pg_h_mL_	AUC168(pg*h/mL)	24	15250.95	5432.22	3018.00	24494.60
Cmax168_pg_mL_	Cmax168(pg/mL)	24	142.6625000	50.3399989	40.3000000	246.0000000
Patch_Age__yrs_	Patch Age (yrs)	24	0.5550000	0.2571584	0.3600000	0.8800000

Correlations

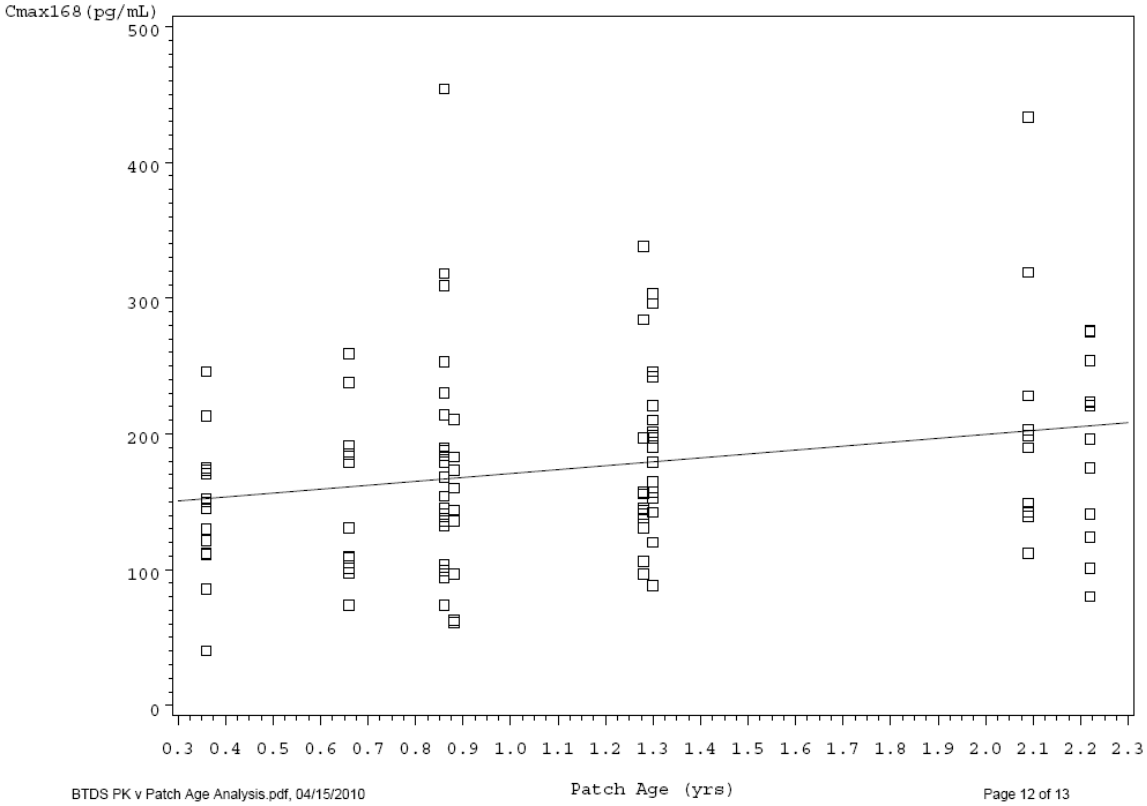
The CORR Procedure

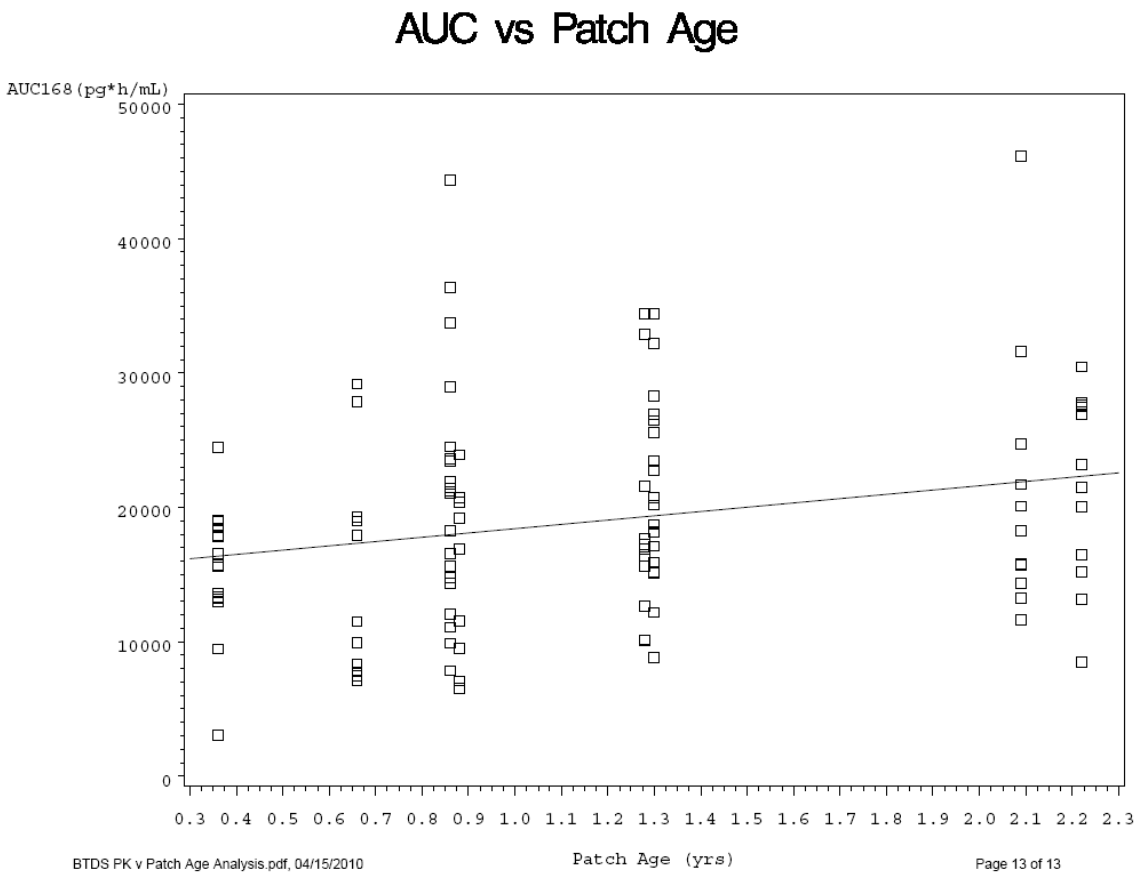
3 Variables:	AUC168_pg_h_mL_ Cmax168_pg_mL_ Patch_Age__yrs_

Simple Statistics							
Variable	N	Mean	Std Dev	Sum	Minimum	Maximum	Label
AUC168_pg_h_mL_	109	18960	7944	2066654	3018	46132	AUC168(pg*h/mL)
Cmax168_pg_mL_	109	175.59450	71.87017	19140	40.30000	454.00000	Cmax168(pg/mL)
Patch_Age__yrs_	109	1.16945	0.59619	127.47000	0.36000	2.22000	Patch Age (yrs)

Pearson Correlation Coefficients, N = 109 Prob > |r| under H0: Rho=0			
	AUC168_pg_h_mL_	**Cmax168_pg_mL_**	**Patch_Age__yrs_**
AUC168_pg_h_mL_ AUC168(pg*h/mL)	1.00000	0.96386 <.0001	0.23984 0.0120
Cmax168_pg_mL_ Cmax168(pg/mL)	0.96386 <.0001	1.00000	0.23923 0.0122
Patch_Age__yrs_ Patch Age (yrs)	0.23984 0.0120	0.23923 0.0122	1.00000

Cmax vs Patch Age





Reviewer's Comment:

From the data in Table 1R and Figures 7R and 8R, it appears that mean AUC $_{(0\text{-}168h)}$ and mean $C_{max\ (0\text{-}168h)}$ did not decrease with patch age.

To examine quantitatively whether buprenorphine exposure varies as a function of patch age, the sponsor constructed multiple regression models using the individual subject values (N= 109) for $C_{max(0\text{-}168)}$ and for $AUC_{(0\text{-}168)}$, with terms for patch lot#, patch age, and their interaction. The relevant statistical outcome of the model is reported above. The report supports the conclusion that differences in patch age are not associated with *in vivo* pharmacokinetic performance differences.

Additionally, the sponsor reported that further information on the *in vivo* performance of the BTDS during the storage period is discussed in the following two reports.

The first report, Assessment of Patch Age and Efficacy, provides information on the batches used in the Phase 3 studies including BUP.CLIN0001, a pivotal clinical study. This report also evaluated the patch performance during the long term clinical study where patients continued treatment for more than 21 months.

The second report, Analysis of Impact of the BTDS Release Rate on Clinical Efficacy, provides an analysis of the impact of age of BTDS on clinical efficacy across five studies performed in the USA. A detailed statistical analysis of data from 421 subjects by stepwise multiple regression examined the effect of the fractional 2 hour in vitro release rate on in vivo clinical efficacy. The report concludes that the change in release rate with age, up to 2 years, did not have impact on clinical efficacy of BTDS.

Both evaluations conclude that patch age accompanied by the observed decrease in in vitro dissolution along with the decrease in both adhesion strength and release strength, does not affect the clinical performance of the BTDS. However, the above mentioned reports need to be reviewed by the clinical division to accept the sponsor's conclusion.

Overall Comments:

6. *Based on the dissolution profiles of the batches kept at proposed storage condition at release and at 12 mo, 18 mo and 24 months, the reviewer recommends the following specifications:*

Proposed BTDS In Vitro Release Specifications			
Time Point (hr)	*Previous Acceptance Criteria*	*Current Sponsor's Proposed Acceptance Criteria*	***The Agency's Proposed Acceptance Criteria***
0.5			(b) (4)
2			
8			
16			

7. *The permeability study was conducted up to 72 hours (3 days). The patch's usage period can be up to 7 days. No in-vitro permeation data up to 7 days is available from patches. Therefore, assurance of the patch performance continuously for 7 days based on in-vitro permeation data at release and/or at later time points is not possible.*

8. *Based on the results and the sponsor's analysis of the in-vitro permeation, the sponsor concluded that that the permeability of the three-year old batches is equivalent to that of the freshly made batches. However, patches of the same batches at manufacture and at 3 years of age were not used. Therefore conclusion of the study is based on pooled data from various batches (Cross-study analysis).*

9. *The interaction analysis of buprenorphine with a multiple regression model using the individual subject values (N= 109) for $C_{max(0-168)}$ and for $AUC_{(0-168)}$ with terms for patch lot#, patch age supports the conclusion that differences in patch age are not associated with in vivo pharmacokinetic performance differences.*

10. *The sponsor's evaluations conclude that patch age accompanied by the observed decrease in in vitro dissolution along with the decrease in both adhesion strength and release strength does not affect the clinical performance of the BTDS. However, after usage more than* (b) (4) *of the buprenorphine remains in the patch. Therefore, it may be possible to reduce the loading dose of buprenorphine in the patch while still maintaining the required flux. The sponsor is advised to continue development work in this line following initial approval of the product. This is in line with the Agency's current thinking of promoting further development work on transdermal products with the intention to minimize the residual drug amount. The goal of this venture is to minimize the potential for abuse of the drug substance following the recommended usage period.*

Appendix: Raw data on Patch Age and Associated in-vivo parameters:

Study	Subj	AUC168	Cmax168	LOT#	PatchAge
BP960803					(b) (4)
BP960803					
BP960803					
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BP960702					

BP980201	(b) (4)	
BP980201		
BP980201		
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BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1009		

BUP1009		(b) (4)
BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1009		
BUP1005		
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BUP1005		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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/s/

TAPASH K GHOSH
05/18/2010

PATRICK J MARROUM
05/18/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-306	Submission Date(s): 09/30/09
Brand Name	Butrans™
Generic Name	Buprenorphine Transdermal System (BTDS)
Reviewer	Sheetal Agarwal, Ph.D.
Clinical Pharmacology Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Analgesia, Anesthesia, and Rheumatology Products
Sponsor	Purdue Pharma L.P. (PPLP)
Submission Type	Resubmission : Complete Response to Action Letter
Formulation; Strength(s)	Transdermal system [patch] 5, 10 and 20 mcg/h [5, 10 and 20 mg patches]
Indication	Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Dosage and Administration	In opioid-naive patients, use lowest dose BuTrans 5 mcg/h as initial dose. For patients already receiving opioids, consult conversion instructions. The BuTrans dose should not be increased before 3 days of wear. After patch removal, a minimum of 3 weeks should pass before reapplying a patch to the same skin site. When BuTrans is no longer required by the patient, doses should be tapered as part of a comprehensive treatment plan.

TABLE OF CONTENTS

List of Figures and Tables:

1. Executive Summary

1.1 RECOMMENDATIONS

From the perspective of the Office of Clinical Pharmacology, NDA 21-306 is acceptable provided that the Agency and the sponsor come to a mutually satisfactory agreement on the labeling.

1.2 PHASE IV COMMITMENTS

None.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Buprenorphine is a synthetic opioid analgesic derived from the opium alkaloid thebaine, and has partial μ-opioid agonist and κ-opioid antagonist properties. In the United States, buprenorphine is available for parenteral administration, primarily for the management of postoperative pain (NDA 18401), and as a sublingual formulation, with and without naloxone, for the treatment of opioid addiction (NDAs 20,732 and 20733). Buprenorphine is currently a Schedule III drug under the Controlled Substances Act. Purdue Pharma L.P. (PPLP) has developed the Buprenorphine Transdermal System (BTDS), under the proposed brand name Butrans™ (earlier named Norspan) in 3 dosage strengths, 5 μg/h, 10 μg/h, and 20 μg/h, to provide continuous systemic delivery of buprenorphine over a 7-day period for the management of moderate to severe pain expected to be present for an extended period of time.

NDA 21-306 was originally submitted by PPLP in November of 2000. The original NDA consisted of 17 Clinical Pharmacology studies (related to PK/PD of buprenorphine, drug-drug interactions, effects of internal and external heat, and absolute bioavailability of buprenorphine following BTDS application) which were reviewed at the time by Dr. Suliman AlFayoumi and found to be acceptable from a Clinical Pharmacology perspective (see review dated 7/15/01 for additional details).

The Agency issued a not approvable (NA) letter on 08/31/2001 to the company citing 62 deficiency items related to clinical, clinical pharmacology, preclinical, and CMC disciplines. In response to the NA letter, PPLP submitted a complete response on 09/30/2009.

The Clinical Pharmacology (CP) section of the resubmission consists of itemized responses to the CP items mentioned in the NA letter as well as data from three additional CP studies that were conducted after the original NDA submission. These are: BUP1009 (CYP3A4 drug-drug interaction study) in response to Item 54; BUP1011 (Thorough QT study) in response to Item 58; and BUP1002 (reapplication study of BTDS to the same site after different rest intervals).

Summary of the data generated by the sponsor in response to the Clinical Pharmacology items listed in the NA letter is presented below:

Item 52: Your analyses of the hepatic impairment study were based on pooled data that do not allow for a reasonable understanding of the correlation between the clinical stage of disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment.

In the resubmission, reanalyzed data from the hepatic impairment study (BP97-0112) in which the degree of hepatic impairment was separated into subgroups according to the Pugh modification of the Child Turcotte criteria was submitted.
The reanalysis shows that in patients with mild to moderate hepatic impairment, peak plasma levels (Cmax) and extent of exposure (AUCt) of buprenorphine did not increase with severity of hepatic impairment. Similar systemic exposures (AUCt) but a reduction in Cmax were observed when comparing systemic buprenorphine (administered as intravenous buprenorphine 0.3 mg) levels from patients with mild to moderate hepatic

impairment to healthy subjects. In addition, no firm conclusions can be made regarding changes in total exposure to norbuprenorphine relative to severity of hepatic impairment due to lack of sufficient data. The sponsor has recommended that mild and moderate hepatic impairment patients be started at the lowest 5 mcg/h dose of the patch as a safety feature in the D and A section of the product's label, and this reviewer concurs with that proposal.

Item 54: You have not adequately addressed concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS. Provide data to adequately address these concerns either from available literature or from in vivo drug-drug interaction studies.

Based on concerns regarding DDI potential of buprenorphine when co-administered with CYP3A4 substrates/inhibitors, the sponsor conducted an in vivo study (BUP1009) in healthy subjects using buprenorphine patch and ketoconazole. The results of this study showed that buprenorphine Cmax and AUC values are not affected when co-administered with ketoconazole. Norbuprenorphine Cmax and AUC values increased about 1.5 fold in the presence of ketoconazole.

However, when administered as sublingual tablets (buprenorphine/naloxone as Suboxone®) in a separate published study along with atazanavir, significant DDI was observed with both buprenorphine and norbuprenorphine concentrations increasing significantly. Cmax and AUC for buprenorphine increased by 1.6 and 2 fold respectively and Cmax and AUC for norbuprenorphine increased by 1.4 and 1.8 fold respectively when buprenorphine was co-administered with atazanavir. Cmax and AUC for buprenorphine increased by 1.4 and 1.7 fold respectively and Cmax and AUC for norbuprenorphine increased by 1.6 and 2 fold respectively when buprenorphine was co-administered with atazanavir/ritonavir. It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor. As such, the DDI potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition. When administered transdermally as in the case of Butrans, buprenorphine is delivered systemically directly into the blood and co-administration of oral ketoconazole may not lead to much interference in buprenorphine metabolism. Further, since buprenorphine is a high affinity substrate for CYP3A4 (Km value for buprenorphine as a substrate of CYP3A4 is 36 μM), only little amounts of uninhibited enzyme activity may be needed for its metabolism. However, when administered sublingually as Suboxone, some of the buprenorphine may enter the GIT via the oral route (that is, there is some first pass effect) and its metabolism mediated by both CYP3A4 and UGT in liver may be inhibited by enzyme inhibitors such as atazanavir.

Other Clinical Pharmacology related items:

Item 58: The electrocardiogram data do not analyze for electrocardiographic intervals. Include in the ISS analyses of electrocardiographic intervals (e.g., PR, QRS, QT, QTc, etc) in view of reports of cardiotoxicity associated with other opioids.

In addition to analysis of ECG intervals from previous studies, the sponsor has performed a thorough QT/QTc study (BUP 1011) to evaluate the effect of BTDS on the QT and QTc intervals. An extract from Dr. Christine Garnett's review is presented here (see QT-IRT review dated 12/23/09 for additional details). The study failed to exclude a 10 ms increase in QT for both therapeutic (10 mg) and supratherapeutic (40 mg) dose levels. The upper 90% CI only was 10.9 ms at 13 h postdose for BTDS 10 mg; however, the mean ΔΔQTc was less than 6 ms at all other timepoints. It is unlikely to be related to buprenorphine concentrations or its metabolites because the exposure is constant across the sampling times. The therapeutic dose of BTDS 20 mg is therefore considered to have no clinically meaningful effect on QT. For the 40-mg dose, the maximum mean ΔΔQTcF was 11 ms (upper 90%CI: 15 ms) at 2 h postdose and exceeded the 10-ms threshold at 6 additional timepoints. No significant relationship between buprenorphine concentrations and QTcI prolongation was identified. This

finding is most likely because of the limited number of PK samples collected at 1, 13, and 23.5 h postdose and the limited range of concentrations within each subject.

Reapplication site study: In addition to the above responses/studies, the sponsor conducted an *in vivo* study (BUP1002) to evaluate a safe interval between reapplication of BTDS patches such that buprenorphine exposure in terms of Cmax and AUC does not increase. The results of this reapplication study showed that mean plasma concentration profiles of buprenorphine were similar for 21 and 28 rest days groups indicating that a rest period of 21-28 days i.e., 3-4 weeks is required to reduce variability in buprenorphine absorption due to reapplication.

Summary of findings from original Clinical Pharmacology (CP) review:

A summary of CP findings from original review of NDA 21-306 by Dr. Suliman AlFayoumi related to aspects not covered above is presented below.

1. ER relationship: There is no exposure-response relationship for buprenorphine patches. A pooled data analysis of the relationships between PD markers for pain relief and buprenorphine concentration did not reveal any correlation. The buprenorphine concentrations assessed in the analysis ranged from 0 to 500 pg/ml.
2. Absolute BA: The absolute bioavailability of buprenorphine from the three dose strengths of BTDS ranged within 15-16% after a 7-day application period (Study BP97-0501).
3. Dose proportionality: Exposure metrics suggest that dose proportionality exists for all three dose strengths over a 7-day application period. However, the same trend is not evident over a 3-day application period.
4. Flux rates: Studies suggest that the mean flux rates over a 7-day application period are 5, 10 and 20 µg/hr for BTDS 5, 10 and 20, respectively. However, for a 3-day application period, the mean flux rates are (6-7.5), (5.8-17) and (34-39) µg/hr for BTDS 5, 10 and 20, respectively. Hence, the flux rates for the 3-day application period appear to clearly differ from those of the 7-day application period.
5. Interchangeability to different body sites for patch application: Application of BTDS 10 to the midaxillary line, the upper outer arm, the upper chest or the upper back resulted in comparable systemic buprenorphine levels. BTDS applications may be applied interchangeably to all 4 sites for an application period of 7 days.
6. Effect of external heat: Fever (internal heat) did not alter the PK of buprenorphine with BTDS applications. However, application of external heat resulted in 26-55% higher Cmax relative to application without heat.
7. Special populations:
    a. Renal impairment: An analysis of pooled data from Phase III studies showed no clear trends in the relationship of creatinine clearance and buprenorphine plasma levels. There is no need for dose adjustment with renal function.
    b. Age: The effect of age on buprenorphine PK was investigated in study BP96-0702 and using analysis of pooled clinical pharmacology studies. Overall, no significant age effect was observed on buprenorphine PK. There is no need for dose adjustment in the elderly.
    c. Gender: The effect of gender on buprenorphine PK was investigated using analysis of pooled clinical pharmacology studies. Overall, no significant gender effect was observed on buprenorphine PK.
    d. Race: The effect of ethnicity on buprenorphine PK was investigated using analysis of pooled clinical pharmacology studies. Overall, no significant ethnicity effect was observed on buprenorphine PK.
    e. Body weight: The effect of body on buprenorphine PK was investigated using analysis of pooled clinical pharmacology studies. Overall, a small decrease in buprenorphine Cmax and

AUC were observed with an increase in body weight (R^2 for the correlation of body weight with AUC was 0.024 and for the correlation of body weight with Cmax was 0.025). No dose adjustment is needed based on body weight.

8. Drug-drug interactions (DDI):
    a. Pharmacodynamic (PD) DDI studies suggested that midazolam, prochlorperazine and thiazide diuretics did not exacerebate opioid adverse events, particularly respiratory depression, when co-administered with a BTDS application.

Overall, adequate information is available characterizing the CP attributes of the product.

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

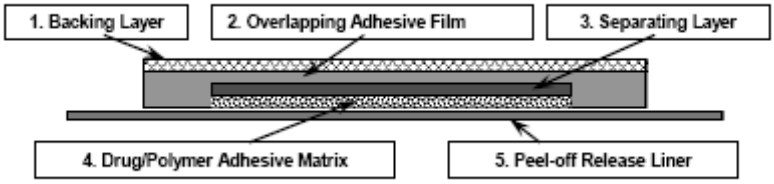
Purdue Pharma L.P. (PPLP) has developed the Buprenorphine Transdermal System (BTDS) in 3 dosage strengths, 5 µg/h, 10 µg/h, and 20 µg/h, to provide continuous systemic delivery of buprenorphine over a 7-day period for the management of moderate to severe pain expected to be present for an extended period of time. The 3 strengths differ only in size and active surface area, as the composition of the drug-containing adhesive matrix is identical for each strength. NDA 21-306 was originally submitted by PPLP in November 2000. The application contained a total of 23 clinical studies. The original NDA had 17 CP studies. and the overall CP section of the NDA was found to be acceptable. However, the NDA was not approved and FDA issued a not approvable (NA) action letter on August 31, 2001. The NA letter contained 62 deficiency items related to clinical, CP, preclinical, and CMC disciplines. Following receipt of the NA letter, PPLP participated in several end-of-review discussions with FDA in an effort to further understand FDA's perspective on one or more deficiency items. In these meetings, related to CP issues, sponsor and the Agency came to an agreement regarding the manner in which the deficiencies would be addressed. Prior to the resubmission of this NDA, a type C pre-resubmission meeting was held on 09/15/2008 to discuss the sponsor's final plan in in addressing the items in the NA letter. No CP related issues were raised in this meeting. The sponsor's plan seemed adequate to address CP related items in the letter.

The resubmission (complete response to NA letter) was submitted to the Agency on 09/30/2009. The CP section consists of 3 new studies: BUP1009 (CYP3A4 related drug-drug interaction study) in response to Item 54; BUP1011 (Thorough QT study) in response to Item 58; and BUP1002 (reapplication of BTDS to the same site after different rest intervals study) and a reanalysis of the previously conducted hepatic impairment study (BUP97-0112). Studies BUP1009, BUP1002 and reanalyzed results from Study BUP97-0112 are reviewed in this submission; the QT study will be reviewed by the QT/IRT review team.

2.1.2 What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?

Drug Product: Butrans is a rectangular or square, beige-colored system consisting of a protective liner and functional layers (Figure 1). Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a beige-colored web backing layer; (2) an adhesive rim without buprenorphine; (3) a separating foil over the buprenorphine-containing adhesive matrix; (4) the buprenorphine-containing adhesive matrix; and (5) a peel-off release liner. Before use, the release liner covering the adhesive layer is removed and discarded. The active ingredient in Butrans is buprenorphine. The inactive ingredients in each system are: levulinic acid, oleyl oleate, povidone, and polyacrylate cross-linked with aluminum.

Figure 1: Cross section diagram of Butrans



Three different strengths of Butrans are available: 5, 10, and 20 mcg/h (Table 1). The composition of all 3 strengths is identical except for the size of the patch (Table 2). The active component of the system is buprenorphine. The remaining components are pharmacologically inactive. The proportion of buprenorphine

base mixed in the adhesive matrix is the same in each of the 3 strengths. The amount of buprenorphine released from each system per hour is proportional to the active surface area of the system. The skin is the limiting barrier to diffusion from the system into the bloodstream.

Table 1: Butrans product specifications

				Amount Delivered After Recommended Usage (7 days)	
Strength (Total amount)	*Active Surface Area*	*Delivery rate*	*Duration*	*Amount Delivered*	*% Used*
5 mg	6.25 mm^2	5 µg/h	7 days	(b) (4)	
10 mg	12.5 mm^2	10 µg/h	7 days		
20 mg	25 mm^2	20 µg/h	7 days		

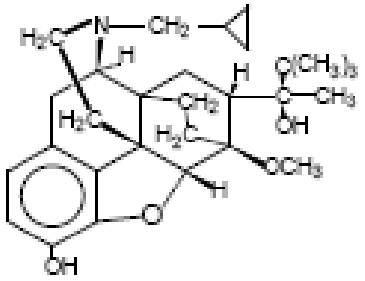
Table 2: Butrans Composition

Component	*Function*	*5 mg*	*10 mg*	*20 mg*
Buprenorphine	Drug substance	5	10	20
Levulinic acid Oleyl oleate Povidone (PVP), USP Polyacrylate (b) (4) (b) (4)	(b) (4)			
Aluminum acetylacetonate (b) (4)	Cross-linking agent (b) (4) (b) (4)	(b) (4)		

(b) (4)

Drug: Buprenorphine is a weak base with a pKa of 8.4. The chemical name of buprenorphine is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α, 7α, (S)]. The structural formula is depicted in (Figure 2:

Figure 2: Structure of Buprenorphine



The molecular weight of buprenorphine base is 467.6; the empirical formula is C29H41NO4. Buprenorphine base occurs as a white, or almost white powder and is very slightly soluble in water, freely soluble in acetone, soluble in methanol and ether, and slightly soluble in cyclohexane. The pKa is 8.5 and the melting point is about 217ºC.

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

Mechanism of Action: Buprenorphine is an opioid analgesic with sub-nanomolar affinity for human recombinant μ opioid receptors. Buprenorphine also has sub-nanomolar affinity for human recombinant κ opioid receptors and low nanomolar affinity for δ opioid receptors. In addition, buprenorphine has nanomolar affinity for ORL-1 (nociceptin) receptors, where it acts as a moderate agonist. Its clinical actions result from binding to the opioid receptors. Buprenorphine is a partial μ-agonist and a κ antagonist. Buprenorphine may also have pharmacological actions mediated by δ and ORL-1 opioid receptors.

Central Nervous System: The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Therapeutic Indication: Management of moderate to severe pain expected to be present for an extended period of time.

2.1.4 What are the proposed dosage and route of administration?

Dosage:: 5 mcg/h (5 mg patch); 10 mcg/h (10 mg patch) and 20 mcg/h (20 mg patch)

Route Of Administration: Transdermal

2.2 GENERAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical studies:

Thirty five clinical studies in total have been submitted in the resubmission (2 new pivotal studies: BUP3024 and BUP3015, were conducted post the NA letter in 2001). The design of pivotal study BUP3024 was submitted for special protocol assessment (SPA) and an agreement with the FDA was reached prior to its initiation. Study BUP3015 used a similar enriched design, primary efficacy variable, and 12-week, fixed-dosing duration that had been agreed to by the FDA for BUP3024. Demonstration of efficacy in this resubmission relies on the results of pivotal studies BUP3024 and BUP3015 (Table 3); substantial additional support for the efficacy of Butrans is provided by data from 9 other studies. All studies used to support the Butrans efficacy claims in this submission were randomized, parallel group, double-blind, and multicenter and

all, except Phase 3B conversion study BUP3018, were controlled. Control treatments varied from study to study but included a placebo control group in all controlled studies except BUP3015 and BP98-1201. BUP3015 was a superiority study using Butrans 5 mcg/h as a low-dose reference treatment, and BP98-1201 was an equivalence study using a combination hydrocodone/acetaminophen (HCD/APAP) active control. Several placebo-controlled studies also included an active control.

In addition, the sponsor mentions that 4 four studies that were originally planned as part of this program were terminated prematurely for administrative reasons, not because of efficacy or safety issues. Three of these studies, BUP3019, BUP3011, and BUP3014, have been excluded from the integrated efficacy analyses. Pivotal study BUP3015 was terminated early but not excluded, as it was nearly complete at the time of termination and all enrolled subjects completed the study. All decisions regarding the termination of studies were made prior to unblinding. For final assessment of the safety and efficacy findings, see the clinical review by Dr. Robert Levin.

Below is a list of all the clinical studies that were submitted. Studies designated with the 'BUP' prefix were not included in the original NDA (2000 submission).

• 13 controlled, double-blind, multiple-dose Phase 3 studies in subjects with chronic pain; (BP96-0101, BP96-0102, BP96-0604, BP98-1201, BP99-0203, BUP3002*, BUP3011*, BUP3012*, BUP3014*, BUP3015*, BUP3019*, BUP3024, and BUP3201*); the 7 studies marked with an asterisk had individual open-label extension periods.
• 1 uncontrolled, open-label extension Phase 3 study (BP96-0103) which enrolled subjects with chronic pain from 3 of the 13 controlled studies (BP96-0101, BP-96-0102, BP96-0604)
• 1 uncontrolled, multiple-dose, double-blind Phase 3 study (BUP3018) in which subjects with chronic pain were converted from Vicodin to Butrans
• 2 placebo-controlled, double-blind, single- and multiple-dose Phase 2 studies (BP96-0104, BUP2003) in subjects with nonchronic pain
• 18 controlled and uncontrolled, single- and multiple-dose clinical pharmacology studies (BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96 0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1202, BP98-1204, BP99-0204, BUP1002, BUP1009, and BUP1011).

Table 3: Study designs of the two pivotal studies in support of efficacy for the product

Study number/ no. centers – location	Study features [a]	Number of subjects in Full Analysis Set by treatment arm	Primary efficacy outcome/ FDA requested outcome	Treatment effect [b]	Conclusion
BUP3024 86 centers – US	12 week, placebo-controlled	257 BTDS 10 or 20 mcg/h 284 Placebo	Average pain over the last 24 hours (NRS) at week 12	-0.58 ± 0.23	BTDS is superior to placebo, *P* = .010
BUP3015 75 centers – US	12 week, active-controlled [c]	221 BTDS 5 mcg/h 219 BTDS 20 mcg/h 220 OxyIR 40 mg/d	Average pain over the last 24 hours (NRS) at weeks 4, 8, and 12	-0.67 ± 0.16	BTDS 20 is superior to BTDS 5, *P* <.001

Clinical Pharmacology (CP) studies:

In addition to the 17 CP studies reviewed in the original NDA submission in 2000, data from 3 additional studies (CP studies: drug-drug interaction study with CYP3A4 inhibitor; reapplication site study and a thorough QT study) were reviewed in this resubmission. Hepatic impairment study results were reanalyzed to reflect differences in the mild and moderate hepatic impairment subgroups (based on Child-Pugh criteria) as compared to healthy subjects. These results were also reviewed in this resubmission. All but one of the clinical pharmacology and clinical efficacy studies used the proposed marketing formulation of Butrans patches: CP study BP97-0112 (hepatic impairment study) used only IV buprenorphine.

An extract of important CP study results from the original NDA is presented below:

Buprenorphine is highly bound to plasma proteins (96%). Buprenorphine is cleared by CYP3A4-mediated metabolism and by glucuronide conjugation. Norbuprenorphine is the only known active metabolite of buprenorphine. The systemic exposure of norbuprenorphine was shown to be 1-5% of that of buprenorphine after administration of buprenorphine via short I.V. infusion. The bioavailability of a 7-day application of a single Butrans dose is 15%. In vitro metabolism studies did not suggest metabolic DDIs at clinically relevant systemic buprenorphine concentrations. Pharmacodynamic DDI studies suggested that midazolam, prochlorperazine and thiazide diuretics did not exacerebate opioid adverse events, particularly respiratory depression, when co-administered with a Butrans application. Dose proportionality for the Butrans 5, 10 and 20 mg strengths was established for the 7-day application period. Application of external heat (i.e.-heat pad) resulted in a 26-55% increase in buprenorphine plasma concentrations. A population PK analysis conducted by the sponsor indicated that age, gender and ethnicity had no significant relationships to Cmax or AUC of buprenorphine.

2.2.2 Does this drug prolong the QT or QTc interval?

The Interdisciplinary Review Team for QT studies (IRT-QT team) made the following observations and conclusions:

In this Phase 1, randomized, placebo- and positive-controlled, parallel group, dose escalating study, 132 healthy subjects were evenly and randomly divided into three groups stratified by gender: placebo, moxifloxacin (positive control), and Buprenorphine Transdermal System (BTDS) [included therapeutic (Butrans 10 mg) and supratherapeutic (2 x Butrans 20 mg) doses]. Subjects were evaluated on 2 baseline days (Days -2 and -1) and 2 treatment days (Day 6 and Day 13), with 13 time points on each day and 4 ECGs around each time point. The overall summary of findings is presented in Table 1.

The study failed to exclude a 10 ms increase in QT for both therapeutic and supratherapeutic dose levels. The upper 90% CI only was 10.9 ms at 13 h postdose for Butrans 10 mg; however, the mean ΔΔQTc was less than 6 ms at all other timepoints. It is unlikely to be related to buprenorphine concentrations or its metabolites because the exposure is constant across the sampling times. The therapeutic dose of BUTRANS 10 mg is therefore considered to have no clinically meaningful effect on QT. For the 40-mg dose, the maximum mean ΔΔQTcF was 11 ms (upper 90%CI: 15 ms) at 2 h postdose and exceeded the 10-ms threshold at 6 additional timepoints.

No significant relationship between buprenorphine concentrations and QTcI prolongation was identified. This finding is most likely because of the limited number of PK samples collected at 1, 13, and 23.5 h postdose and the limited range of concentrations within each subject.

Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Butrans (10 mg and 40 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Day	Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
6	BTDS 10 mg	13	7.2	(3.4, 10.9)
	Moxifloxacin 400 mg*	3	14.5	(10.4, 18.7)
13	BTDS 40 mg	2	10.6	(6.0, 15.3)
	Moxifloxacin 400 mg*	3	14.5	(10.4, 18.7)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment exceeded 5 ms.

2.2.3 What is the Sponsor's pediatric plan for Butrans?

No studies were performed in children. Waiver for the age group **Birth to 6 years 11 months** will be granted f**or** the following reasons:

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed).
- The number of pediatric patients less than 7 years of age with chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time is small. Therefore studies with Butrans in this patient group for the proposed indication would be difficult or highly impracticable to undertake.

For the age group **7 to 16 years old**, pediatric data requirments are deferred as adult studies are complete and ready for approval. Sponsor will be required to conduct studies to assess PK and safety as post marketing requirement. Efficacy will be extrapolated from adults and thus is not needed for this age group.

2.3 INTRINSIC FACTORS

2.3.1 What is the influence of mild/moderate hepatic impairment on the pharmacokinetics of the buprenorphine?

In study BP97-0112 involving patients with mild to moderate hepatic impairment, peak plasma levels (Cmax) and extent of exposure (AUCt) of buprenorphine did not increase with severity of hepatic impairment. Similar systemic exposures (AUCt) but a reduction in Cmax were observed when comparing systemic buprenorphine (administered as intravenous buprenorphine 0.3 mg) levels from healthy subjects to that of patients with mild to moderate hepatic impairment. In addition, no firm conclusions can be made regarding changes in total exposure to norbuprenorphine relative to severity of hepatic impairment due to lack of sufficient data. The sponsor has recommended that mild and moderate hepatic impairment patients be started at the lowest 5 mcg/h dose of the patch as a safety feature in the D and A section of the product's label, and this reviewer concurs with that proposal.

In addition, it should be noted that severe hepatic impairment and end-stage dialysis patients were not enrolled in this study and the product label should still contain cautionary language about using the product in these two groups.

In Study BP97-0112,mild and moderate hepatic impairment did not lead to increases in buprenorphine and norbuprenorphine exposures. There was a decrease in the Cmax values for both buprenorphine and norbuprenorphine in the mild and moderate hepatic impairment groups as compared to healthy volunteers. In mild hepatic impairment patients, the mean Cmax values for buprenorphine and norbuprenorphine were 54% and 73% of that of the healthy subjects and in moderate hepatic impairment patients, the Cmax values for buprenorphine and norbuprenorphine were 39% and 59% of that of the healthy subjects (Table 5 and 6 and Figure 3 and 4). The scatter plot in Figure 4 for AUCt of norbuprenorphine shows that few data points were available for norbuprenorphine analysis in all the groups. There do not appear to be significant differences in AUCt values of the healthy and the mild hepatic impairment groups with respect to norbuprenorphine. AUCt values for norbuprenorphine moderate hepatic impairment group could not be calculated accurately since only 2 data points were available. AUCinf could not be calculated for this group because of large % of extrapolation required from time t to infinity.

Table 5: Summary of Buprenorphine Pharmacokinetic Metrics by Study Group

PK parameter	Healthy (N=12) Mean (SD)	Mild (N=8) Mean (SD)	Moderate (N=4) Mean (SD)
Cmax (pg/mL)	11770.00 (6983.16)	6377.50 (3840.38)	4640.00 (1753.34)
AUC_T (pg·min/mL)	342298.83 (80042.09)	328553.63 (70875.15)	293262.00 (116285.18)
AUCinf* (pg·min/mL)	--	--	--
Tmax (min)	10.83 (1.95)	11.13 (1.73)	12.50 (5.00)
$T_{1/2}$ (min)	759.00 (455.81)	904.63 (508.43)	897.00 (246.38)
Vd(SS) (L)	430.00 (287.91)	621.63 (460.67)	672.75 (258.72)
Cl tot (mL/min)	778.42 (246.61)	733.38 (159.20)	757.50 (225.28)

Figure 3: Buprenorphine Cmax and AUCt distribution around the median

(The whiskers in the box plots depict the maximum and the minimum values. The scatter plots depict how many data points were actually available for evaluation of the respective PK parameter.)

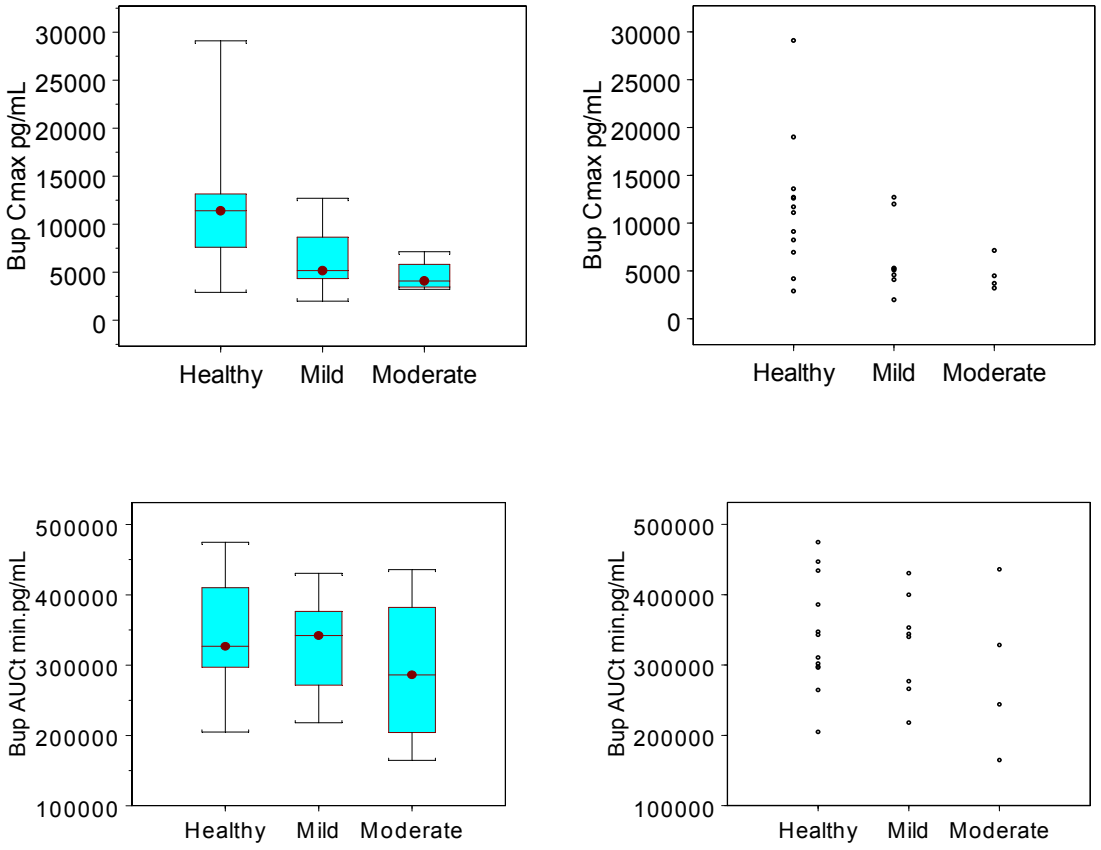
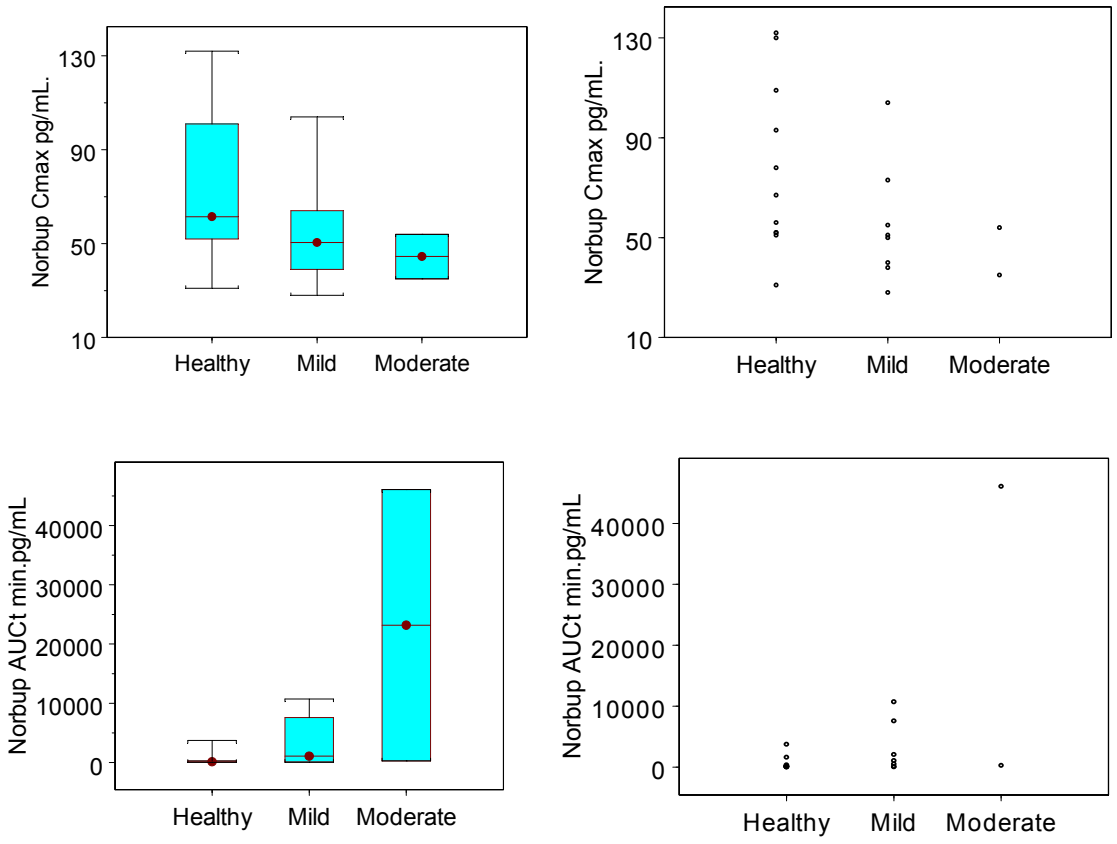


Table 6: Summary of Nor-Buprenorphine Pharmacokinetic Metrics by Study Group

PK parameter	Healthy (N=12) Mean (SD)	Mild (N=8) Mean (SD)	Moderate (N=2) Mean (SD)
Cmax (pg/mL)	75.25 (33.42)	54.88 (23.93)	44.50 (13.44)
AUC_T (pg·min/mL)	12723.33 (21479.18)	16572.75 (19933.55)	23175.00
AUCinf* (pg·min/mL)	--	--	--
Tmax (min)	14.17 (6.34)	30.38 (36.83)	42.50 (45.96)
$T_{1/2}$ (min)	549.58 (1092.60)	3160.29** (4248.03**)	--
Vd(SS) (L)	--	--	--
Cl tot (mL/min)	--	--	--

Figure 4: Norbuprenorphine Cmax and AUCt distribution Around the Median



2.4 EXTRINSIC FACTORS

2.4.1 What is the minimum time interval between reapplication of patch to the same skin site?

Mean plasma concentration profiles of buprenorphine were similar for no rest and 21 and 28 rest days groups indicating that a rest period of 21-28 days i.e., 3-4 weeks is required to reduce variability in buprenorphine absorption due to reapplication.

Since repeat application of the patch to the same site may affect the PK (due to changes in skin characteristics from the first the previous patch application) it is important to evaluate a safe interval between reapplication of Butrans patches such that buprenorphine exposure in terms of Cmax and AUC does not increase. The sponsor conducted an open label PK study (BUP1002) with varying periods of rest days (0 through 28) in a parallel group design. The study protocol limits the study volunteers to re-use the same skin site [on the deltoid region of the dominant arm (right if right-handed)] for reapplication of BUTRANS. Since the 5, 10 and 20 mg patches are compositionally proportional, and the bup kinetics are linear and dose proportional between doses of 5-20 mg, it can be expected that 20 mg Butrans will lead to doubling of the exposure values observed in this study for 10 mg Butrans.

Mean plasma concentration profiles of buprenorphine were similar for no rest and 21 and 28 rest days groups indicating that a rest period of 21-28 days i.e., 3-4 weeks is required to reduce variability in buprenorphine absorption due to reapplication (Figure 5 and Table 7). Although statistically significant differences were observed with Cmax (Figure 6) and AUC values (Figure 7) at 21 and 28 rest days groups as compared with no rest group, these differences are not clinically significant. Moreover, the adverse events profile was similar between these three groups.

Figure 5: Mean (+ SE) Plasma Buprenorphine Concentration-Time Curve by # of Rest Days

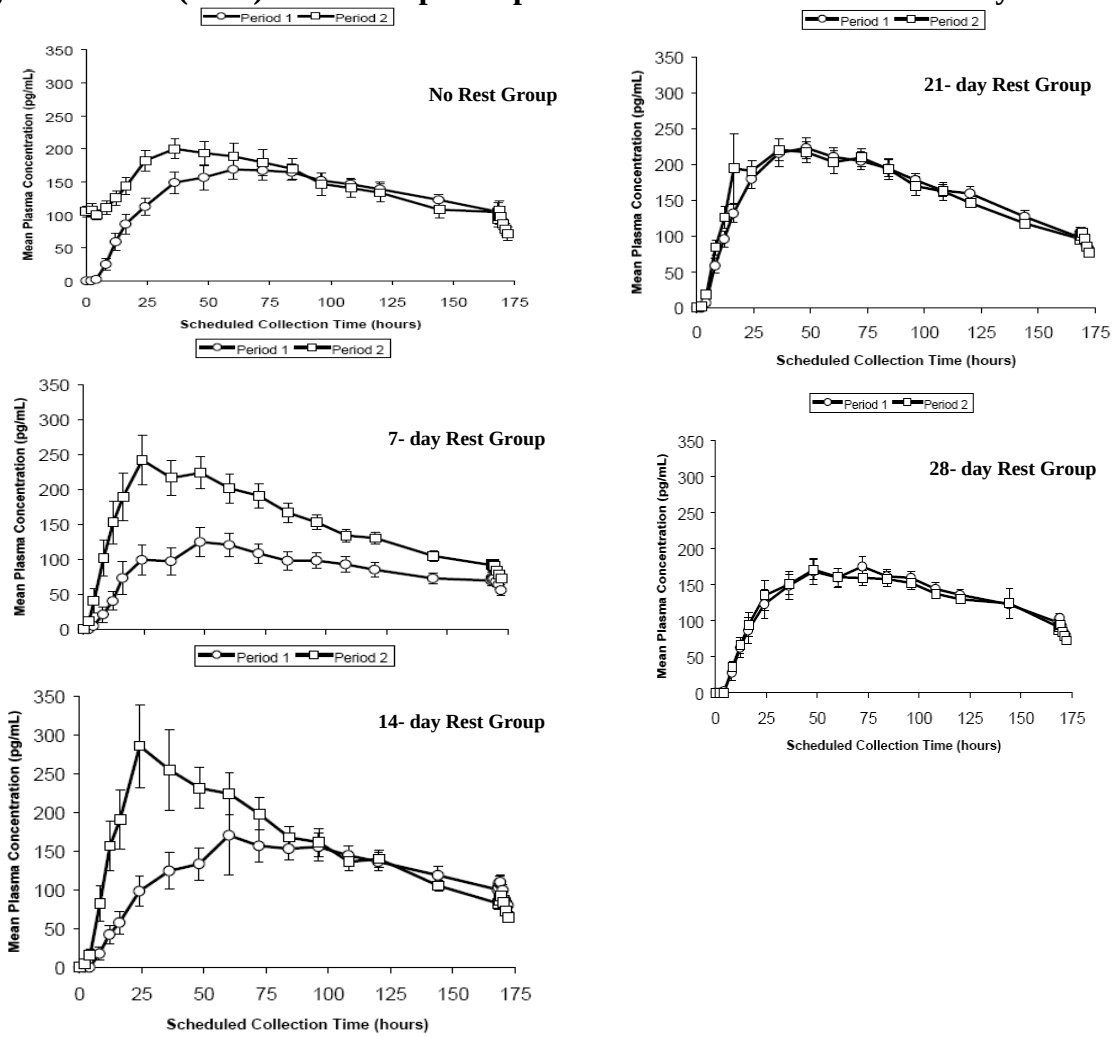


Figure 6: Distribution of Cmax values for different reapplication periods

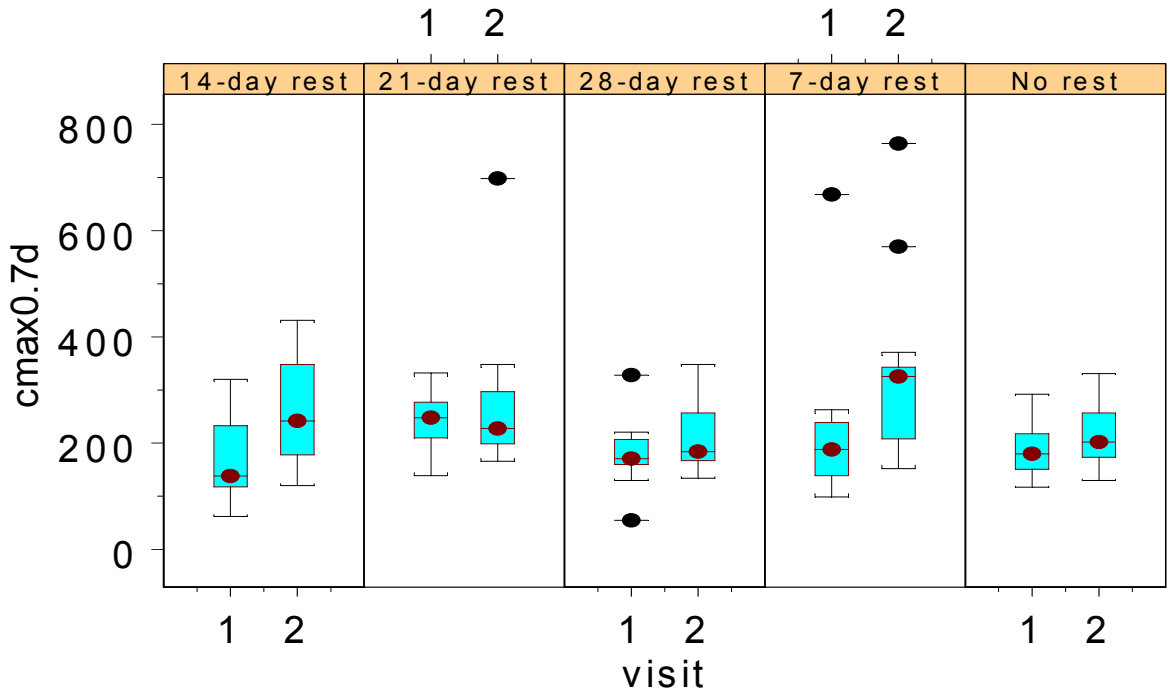


Figure 7: Figure 6: Distribution of AUC values for different reapplication periods

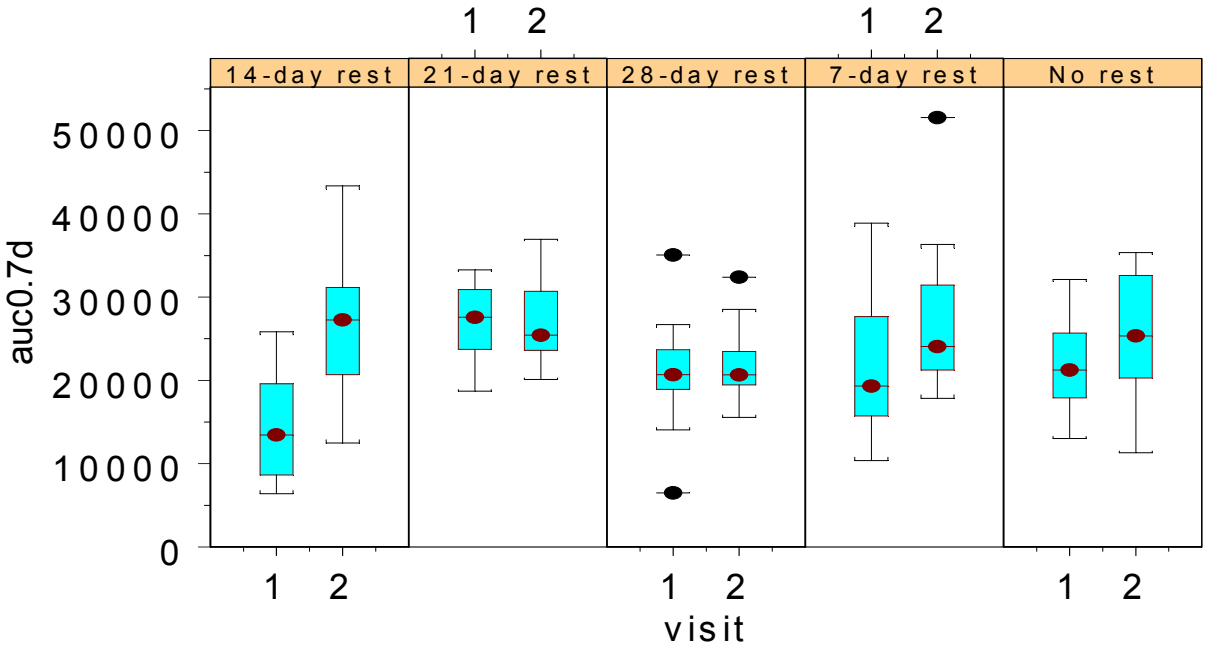


Table 7: PK Parameters for Reapplication Time Study

Pharmacokinetic Metric	BTDS 10 Group				
	No Rest (N = 12)	7-Day Rest (N = 11)	14-Day Rest (N = 13)	21-Day Rest (N = 12)	28-Day Rest (N = 12)
	Arithmetic Mean (± SE)				
First application					
AUC_{0-3d} (pg/mL·h)	8680 (± 920)	7651 (± 1514)	6465 (± 1091)	12258 (± 836)	8890 (± 1054)
$Cmax_{0-3d}$ (pg/mL)	183 (± 17)	193 (± 50)	151 (± 24)	241 (± 15)	185 (± 16)
AUC_{0-7d} (pg/mL·h)	21946 (± 1686)	20541 (± 2645)	14707 (± 1851)	27040 (± 1298)	22086 (± 1591)
$Cmax_{0-7d}$ (pg/mL)	188 (± 16)	206 (± 48)	160 (± 22)	245 (± 14)	192 (± 15)
$Tmax_{0-7d}$ (h)	74 (± 7)	86 (± 6)	78 (± 15)	55 (± 6)	76 (± 11)
Second application					
AUC_{0-3d} (pg/mL·h)	12316* (± 1062)	14733 (± 2255)	13571 (± 1671)	12931 (± 908)	9056 (± 888)
$Cmax_{0-3d}$ (pg/mL)	216 (± 17)	300 (± 52)	262 (± 31)	278 (± 41)	182 (± 14)
AUC_{0-7d} (pg/mL·h)	25126* (± 2285)	27543 (± 3093)	26174 (± 2414)	27123 (± 1475)	21790 (± 1365)
$Cmax_{0-7d}$ (pg/mL)	216* (± 17)	300 (± 52)	262 (± 31)	278 (± 41)	202 (± 18)
$Tmax_{0-7d}$ (h)	42 (± 3)	38 (± 6)	36 (± 5)	46 (± 4)	63 (± 10)

2.4.2 What is the drug-drug interaction potential of buprenorphine?

2.4.2.1 Co-administration with ketoconazole, a strong CYP3A4 inhibitor:

Plasma buprenorphine concentrations, when delivered by Butrans 10 mg, did not accumulate during co-medication with ketoconazole 200 mg BID. Butrans dose adjustment is not needed for subjects taking concomitant ketoconazole.

Since buprenorphine is thought to be mainly metabolized by CYP3A4, sponsor conducted study BUP1009 to assess the effect on buprenorphine PK when co-administered with a CYP3A4 inhibitor such as ketoconazole. Mean plasma concentration profiles of buprenorphine were similar between the two treatments i.e. Butrans +placebo vs. Butrans+ ketoconazole (Table 5 and Figure 4) indicating that a selective CYP3A4 inhibitor did not affect CYP3A4 mediated buprenorphine to norbuprenorphine metabolism. From Table 2, the estimated ratio of population geometric means (Butrans with ketoconazole / Butrans with ketoconazole placebo) for AUCt and Cmax, and their associated 90% confidence intervals (CI's) were within the range of 80% to 125% (Table 6) indicating no difference in buprenorphine exposure for the two treatments. Mean Cmax and AUCt values of norbup and norbup-gluc (Table 1 and Figure 1) were higher when keto was present. Norbuprenorphine glucuronide AUCinf could not be accurately estimated in most of the subjects from both treatments due to unreliable terminal half-lives and/or AUCt/AUCinf ratio of less than 0.80.

Table 8: Summary of Bup, Nor-Bup, Bup-gluc and Norbup-gluc PK parameters (BLQ = below limit of quantitation; -- = not detected; NE = not evaluable)

	Bup		Stats for Bup	Norbup		Bup-gluc		Norbup-gluc	
	+ keto	- keto	Ratio (Lower and Upper 90% CIs)	+ keto	- keto	+ keto	- keto	+ keto	- keto
Cmax (pg/mL)	142.2 ± 53.7	145.5 ± 48.7	0.978 (0.877-1.091)	63.4 ± 25.9	44.6 ± 11.1	88.5 ± 85.6	--	218.2 ± 99.4	141.875 ± 47.6
AUC last (pg•h/mL)	16354.8 ± 6197.3	16627.9 ± 5559.7	0.994 (0.872-1.133)	5091.0 ± 3208.3	3207.8 ± 1746.4	342.4 ± 488.2	--	21376.9 ± 9808.2	15840.5 ± 5034.5
AUC inf (pg•h/mL)	18238.5 ± 6624.5	19012.5 ± 6599.2	0.867 (0.707-1.062)	NE	BLQ	BLQ	--	BLQ	17318.9 ± 657.2
T1/2 (h)	22.04 ± 7.52	25.38 ± 7.99		35.2 ± 6.6	66.2 ± 15.9	BLQ	--	54.1 ± 9.5	40.0 ± 3.0
Tmax (h)	100.7 ± 41.8	100.5 ± 30.6		167.4 ± 35.3	152.7 ± 30.2	174.4 ± 1.7	--	164.4 ± 31.5	153 ± 26.6

Table 9: Summary of Buprenorphine Pharmacokinetic Metrics by Treatment

Metrics	BTDS 10 mg With Ketoconazole 200 mg (N=18)	BTDS 10 mg With Ketoconazole Placebo (N=16)	Ratio	Difference	90% CI Lower	90% CI Upper
AUC_t (pg•h/mL)						
N	18	16				
Mean ± SD	16354.8 ± 6197.3	16627.9 ± 5559.7				
(min - max)	(6098.5 - 30656.6)	(3672.5 - 27686.2)				
Exponentiated LSM	15272.0	15359.2	0.994		0.872	1.133
AUCinf (pg•h/mL)						
N	13	9				
Mean ± SD	18238.5 ± 6624.5	19012.5 ± 6599.2				
(min - max)	(7852.1 - 31513.5)	(4573.4 - 28415.3)				
Exponentiated LSM	15569.9	17962.6	0.867		0.707	1.062
C_{max} (pg/mL)						
N	18	16				
Mean ± SD	142.2 ± 53.7	145.5 ± 48.7				
(min - max)	(48.6 - 232.0)	(40.3 - 246.0)				
Exponentiated LSM	131.28	134.2	0.978		0.877	1.091
$t_{1/2}$ (h)						
N	13	9				
Mean ± SD	22.04 ± 7.52	25.38 ± 7.99				
(min - max)	(9.78 - 36.52)	(17.38 - 37.83)				
LSM	22.38	24.75		-2.367	-9.943	5.209
T_{max} (h)						
N	18	16				
Mean ± SD	100.7 ± 41.8	100.5 ± 30.6				
(min - max)	(24.0 - 176.0)	(48.0 - 168.0)				
Exponentiated LSM	100.27	106.19		-5.913	-18.773	6.947
CL/f (mL/h)						
N	13	9				
Mean ± SD	626923 ± 259000	683657 ± 570236				
(min - max)	(317325 - 1273551)	(351923 - 2186543)				
Lamdaz (1/h)						
N	13	9				
Mean ± SD	0.036 ± 0.016	0.03 ± 0.008				
(min - max)	(0.019 - 0.071)	(0.018 - 0.04)				

2.4.2.2 Co-administration with antiviral agents, CYP3A4 substrates/inhibitors:

Literature survey indicates that three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected (Bruce et al., 2006). Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. PK interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these PK interactions did not result in any significant PD effects, and no dose changes were needed for buprenorphine or the NNRTIs in the trial (Clin Infect Dis. 2006 Dec 15;43 Suppl 4:S224-34). Studies have shown some antiretroviral protease inhibitors with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine PK and no significant PD effects were seen (Clin Infect Dis. 2006 Dec 15;43 Suppl 4:S235-46). However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine when buprenorphine was administered via the sublingual route as Suboxone®. Cmax and AUC for buprenorphine increased by 1.6 and 2 fold respectively and Cmax and AUC for norbuprenorphine increased by 1.4 and 1.8 fold respectively when buprenorphine was co-administered with atazanavir. Cmax and AUC for buprenorphine increased by 1.4 and 1.7 fold respectively and Cmax and AUC for norbuprenorphine increased by 1.6 and 2 fold respectively when buprenorphine was co-administered with atazanavir/ritonavir. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly (Drug Alcohol Depend. 2007 Dec 1;91(2-3):269-78).

It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor. As such, the DDI potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition. When administered transdermally as in the case of Butrans, buprenorphine is delivered systemically directly into the blood and co-administration of oral ketoconazole may not lead to much interference in buprenorphine metabolism. Further, since buprenorphine is a high affinity substrate for CYP3A4 (Km value for buprenorphine as a substrate of CYP3A4 is 36 μM), only little amounts of uninhibited enzyme activity may be needed for its metabolism. However, when administered sublingually as Suboxone, some of the buprenorphine may enter the GIT via the oral route (that is there is some first pass effect) and its metabolism mediated by both CYP3A4 and UGT in liver may be inhibited by enzyme inhibitors such as atazanavir.

2.4.2.3 Co-administration with other CYP3A4 and CYP2D6 substrates (effect of buprenorphine on other drugs):

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes (Biol. Pharm. Bull. 25(5) 682—685 (2002) and DMD 31:768–772, 2003). However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

2.5 ANALYTICAL SECTION

2.5.1 What bioanalytical methods are used to assess concentrations?

BUP1002: [redacted] (b) (4) Validation of an LC/MS/MS Method for the Quantitation of Buprenorphine and Norbuprenorphine in Human EDTA Plasma Method and [redacted] (b) (4) LC-MS/MS Assay Validation of Buprenorphine3-D-glucuronide and Norbuprenorphine-3-D-glucuronide in Human Plasma

BUP1009: [redacted] (b) (4): LC/MS/MS Assay Validation of Buprenorphine and Norbuprenorphine in K2EDTA Human Plasma and [redacted] (b) (4) LC/MS/MS Assay Validation of Ketoconazole in Human Plasma)

2.5.2 What are the accuracy, precision and sensitivity and selectivity limits?

Please see individual study reports for this information.

2.5.4 *What was the QC sample plan?*

For a run to be acceptable, a minimum of 66.67% of the total number of QC samples must not have deviated by more than ±15% from their nominal values.

2.5.5 *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Please see individual study reports for this information.

3. Preliminary Labeling Recommendations

Following are the highlights of the labeling comments at the time of the writing this review.
(Reviewer suggested changes: ~~Strikeout text~~ is suggested for deletion and underlined text is suggested for addition)

(b) (4)

(b) (4)

5 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.1. INDIVIDUAL STUDY REVIEWS

4.1.1. DDI Study with Ketoconazole (keto)

A Single Center, Randomized, Double-Blind, Crossover Study to Assess Buprenorphine Accumulation and Description of Its Metabolites During Co-Medication of BTDS and Ketoconazole, Used As a CYP3A4 Inhibitor, in Healthy Subjects

Study Design:	A single center, randomized, double-blind, crossover study examining BTDS patch (10 mg) with ketoconazole tablet (200 mg) administration in one period and BTDS patch (10 mg) with ketoconazole placebo tablet administration in the other period.
Objectives:	**Primary:** 1. To assess the pharmacokinetics of buprenorphine and its metabolites (nor-buprenorphine, buprenorphine 3 glucuronide and nor-buprenorphine glucuronide) in the presence and absence of ketoconazole. 2. Safety evaluation of BTDS and ketoconazole in healthy subjects. **Secondary:** Confirmation of CYP3A4 inhibition by observation of nor-buprenorphine production.
Protocol Number:	**BUP1009**
Total Duration:	56 days
Number of Subjects Randomized/Completed:	Randomized 20; completed 15
Diagnosis and Main Criteria for Inclusion:	Healthy male and female subjects aged 18 to 54 years, demonstrating successful inhibition of CYP3A4 using the EBT (erythromycin breath test) probe.
Demographics of Study Population:	6 black (4 men; 2 women); 14 white (12 men; 2 women) Mean age = 31.8 years Mean weight = 74.4 kg
Test Formulations:	BTDS 10 mg transdermal patch (batch/lot number: 70142B2), Ketoconazole 200 mg oral tablet (batch/lot number: 92P0204E)
Reference Formulations:	BTDS 10 mg transdermal patch (batch/lot number: 70142B2) and Ketoconazole placebo oral tablet (batch/lot number: CB27-26).
Treatment Schedule:	During Period 1, subjects wore BTDS 10 mg patch between days 3 and 10 and were administered ketoconazole (200 mg orally bid) or ketoconazole placebo (orally bid) between days 1 and 11. A washout period of 18 days then followed. During Period 2, subjects wore BTDS 10 mg patch between days 19 and 26 and were administered ketoconazole (200 mg orally bid) or ketoconazole placebo (orally bid) between days 17 and 27.
Study Phase:	Phase 1
Study Initiation Date:	21-Oct-2002
Study Completion Date:	20-Jun-2003
Principal Investigator and Study Site:	Robert Noveck, MD Clinical Research Center 2237 Poydras Street, New Orleans, LA 70119 USA (504) 826-5000
Bioanalytical Site:	(b) (4)

Bioanalytical validation:

Plasma concentrations of buprenorphine (bup), nor-buprenorphine (norbup), their glucuronide metabolites and ketoconazole (keto) were quantified by high performance liquid chromatography with tandem mass spectrometry. The bioanalytical analyses were conducted using method number 42-0217 for bup and norbup; 32-0222 for buprenorphine 3 glucuronide (bup-gluc) and nor-buprenorphine glucuronide (norbup-gluc) and 32-0223 for ketoconazole (keto).

The limit of quantitation for buprenorphine, nor-buprenorphine, buprenorphine 3 glucuronide, and nor-buprenorphine glucuronide was 20 pg/mL, 20 pg/mL, 25 pg/mL, and 25 pg/mL, respectively.

Assay precision, accuracy, sensitivity and selectivity and stability:

Method 42-0217:

Inter and Intra-day precision and accuracy of Buprenorphine and Norbuprenorphine:

Analyte	Assay Range	Intraday Precision (%CV)	Intraday Accuracy (%Diff)	Interday Precision (%CV)	Interday Accuracy (%Diff)
Buprenorphine	20 to 5000 pg/mL	3.3 to 10.4%	-5.0 to 8.6%	3.8 to 7.2%	-3.3 to 3.5 %
Norbuprenorphine	20 to 5000 pg/mL	2.9 to 14.2%	-8.7 to 5.8%	5.2 to 9.0%	-3.7 to 10.5%

Selectivity and specificity: of the method was evaluated by extracting and analyzing six individual lots of blank human plasma with and without either buprenorphine and norbuprenorphine or their corresponding IS. Interference ≤20% of the peak area of the lowest standard was observed at the retention time of the peak for buprenorphine and norbuprenorphine at 20 pg/mL and ≤5% at the retention time of the peak for the IS. The precision and accuracy data for 60 pg/mL of buprenorphine and norbuprenorphine spiked in six different lots of human plasma were within the acceptable range. Pooled human plasma was used as the blank matrix throughout the validation.

Method 32-0223:

Intra-day precision and accuracy of Ketoconazole:

Analysis	Concentrations (ng/mL)[a]			
Date	20	60	750	9000
12/20/02	20.378	63.213	729.618	9681.460
	20.269	68.328	793.347	9790.367
	21.199	57.958	773.834	10102.587
	22.806	60.789	819.941	9296.053
	23.577	68.459	889.686	9778.305
	21.878	59.595	800.021	9864.311
N	6	6	6	6
Mean	21.685	63.057	801.075	9752.181
Std. Dev.	1.328	4.475	53.135	264.784
%CV	6.1	7.1	6.6	2.7
% Diff	8.4	5.1	6.8	8.4

Inter-day precision and accuracy of Ketoconazole:

Run ID	Analysis Date	Concentrations (ng/mL) 20	60	750	9000
021220-320223-HU-PL-Intra-RR	12/20/02	20.378	63.213	729.618	9681.460
		20.269	68.328	793.347	9790.367
		21.199	57.958	773.834	10102.587
		22.806	60.789	819.941	9296.053
		23.577	68.459	889.686	9778.305
		21.878	59.595	800.021	9864.311
021228-320223-HU-PL-Inter1-RR	12/28/02	21.281	73.900	796.187	9739.059
		21.884	62.315	806.926	9064.743
		20.171	59.568	789.560	9471.971
		21.555	69.022	794.825	10174.938
		16.692	65.313	832.983	9368.684
		21.731	60.775	848.777	10981.757
021230-320223-HU-PL-Inter2-RR	12/30/02	21.565	59.367	761.118	8536.933
		20.521	59.431	754.693	8609.652
		22.832	68.729	785.637	8428.607
		18.837	62.737	823.220	9173.511
		20.317	60.033	771.524	8326.745
		17.969	58.858	809.083	8633.446
	N	18	18	18	18
	Mean	20.859	63.244	798.943	9390.174
	Std. Dev.	1.723	4.611	36.760	708.475
	%CV	8.3	7.3	4.6	7.5
	% Diff	4.3	5.4	6.5	4.3

Selectivity and specificity: of the method was evaluated by extracting and analyzing six individual lots of blank human plasma with and without either keto or IS. Interference, if any, at the retention time of the peak for keto was ≤ 20% of the mean peak area of the lowest standard at 20 ng/mL and ≤ 5% at the retention time of the peak for the IS. The precision and accuracy data for 50 ng/mL of keto spiked in six different lots of human plasma was within the acceptable range. Pooled human plasma was used as the blank matrix throughout the validation.

Method 32-0223:

Room Temperature Stability: keto was found to be stable in human plasma at room temperature for 17.5 h.
Freeze/Thaw Stability: QC samples at two concentrations (100 and 5000 ng/mL, n=5) were frozen at -70°C (for a minimum of 24 h for Cycle 1 and a minimum of 12 h for Cycles 2 & 3) and thawed at room temperature. This freeze/thaw cycle was repeated three times. Keto samples were stable after three freeze/thaw cycles.
Autosampler Stability at Room Temperature: keto was stable in reconstitution solvent at room temperature for 257 h.
Whole Blood Stability: keto was found to be stable in whole blood for up to 120 minutes.
Analyte Solution Stability: keto was found to be stable in methanol at -20°C for 154 days and at room temperature for approximately 6 h.
Long-Term Frozen Storage Stability: keto was found to be stable in human plasma at -70 °C for 80 days.

Drug Concentration Measurements:

Blood samples for determining bup, nor-bup and their glucuronide metabolite concentrations were obtained for each subject on Days 3 and 19 immediately before BTDS patch application (0 h); and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 h. Blood samples were also obtained at 2, 4, 6, 8, 12, 24, 36, and 48 h

following removal of the BTDS patch (Days 10 and 26). Blood samples for determining the levels of ketoconazole were also obtained at 8 AM on days 9 and 25.

PK results:

Mean observed plasma concentration – time curves for bup, norbup, bup-gluc and norbup-gluc with BTDS 10 mg patch following both treatments are presented in Table 1 and Figure 1 respectively.

Figure A: Mean (+SD) Plasma Concentrations of Bup, Norbup, Bup-gluc and Norbup-gluc Over Time by Treatment: PK Population (N = 18 for BTDS plus Ketoconazole, N = 16 for BTDS plus Placebo)

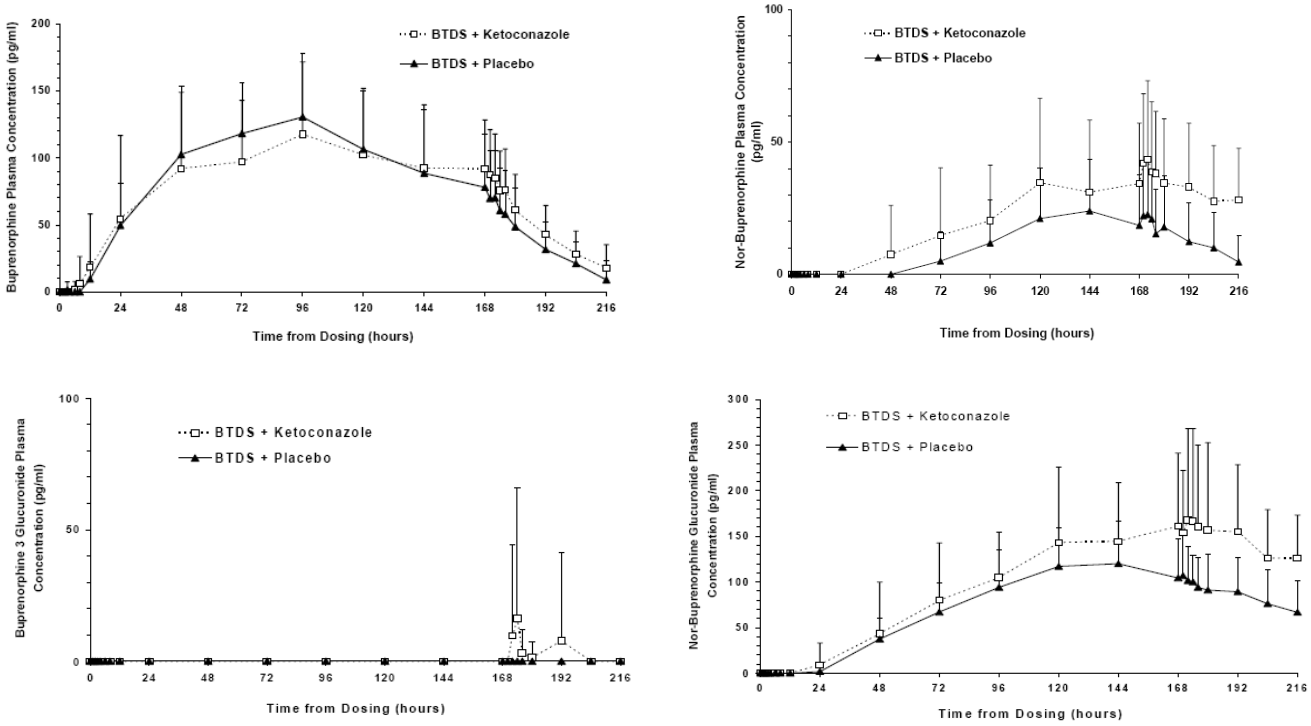


Table A: Summary of Bup, Nor-Bup, Bup-gluc and Norbup-gluc PK parameters (BLQ = below limit of quantitation; -- = not detected; NE = not evaluable):

	Bup		Stats for Bup	Norbup		Bup-gluc		Norbup-gluc	
	+ keto	- keto	Ratio (Lower and Upper 90% CIs)	+ keto	- keto	+ keto	- keto	+ keto	- keto
Cmax (pg/mL)	142.2 ± 53.7	145.5 ± 48.7	0.978 (0.877-1.091)	63.4 ± 25.9	44.6 ± 11.1	88.5 ± 85.6	--	218.2 ± 99.4	141.875 ± 47.6
AUC last (pg•h/mL)	16354.8 ± 6197.3	16627.9 ± 5559.7	0.994 (0.872-1.133)	5091.0 ± 3208.3	3207.8 ± 1746.4	342.4 ± 488.2	--	21376.9 ± 9808.2	15840.5 ± 5034.5
AUC inf (pg•h/mL)	18238.5 ± 6624.5	19012.5 ± 6599.2	0.867 (0.707-1.062)	NE	BLQ	BLQ	--	BLQ	17318.9 ± 657.2
T1/2 (h)	22.04 ± 7.52	25.38 ± 7.99		35.2 ± 6.6	66.2 ± 15.9	BLQ	--	54.1 ± 9.5	40.0 ± 3.0
Tmax (h)	100.7 ± 41.8	100.5 ± 30.6		167.4 ± 35.3	152.7 ± 30.2	174.4 ± 1.7	--	164.4 ± 31.5	153 ± 26.6

Table B: Summary of Buprenorphine PK Metrics by Treatment: PKPopulation

Metrics	BTDS 10 mg With Ketoconazole 200 mg (N=18)	BTDS 10 mg With Ketoconazole Placebo (N=16)	Ratio	Difference	90% CI Lower	90% CI Upper
AUC_t (pg•h/mL)						
N	18	16				
Mean ± SD	16354.8 ± 6197.3	16627.9 ± 5559.7				
(min - max)	(6098.5 - 30656.6)	(3672.5 - 27686.2)				
Exponentiated LSM	15272.0	15359.2	0.994		0.872	1.133
AUCinf (pg•h/mL)						
N	13	9				
Mean ± SD	18238.5 ± 6624.5	19012.5 ± 6599.2				
(min - max)	(7852.1 - 31513.5)	(4573.4 - 28415.3)				
Exponentiated LSM	15569.9	17962.6	0.867		0.707	1.062
C_{max} (pg/mL)						
N	18	16				
Mean ± SD	142.2 ± 53.7	145.5 ± 48.7				
(min - max)	(48.6 - 232.0)	(40.3 - 246.0)				
Exponentiated LSM	131.28	134.2	0.978		0.877	1.091
$t_{1/2}$ (h)						
N	13	9				
Mean ± SD	22.04 ± 7.52	25.38 ± 7.99				
(min - max)	(9.78 - 36.52)	(17.38 - 37.83)				
LSM	22.38	24.75		-2.367	-9.943	5.209
T_{max} (h)						
N	18	16				
Mean ± SD	100.7 ± 41.8	100.5 ± 30.6				
(min - max)	(24.0 - 176.0)	(48.0 - 168.0)				
Exponentiated LSM	100.27	106.19		-5.913	-18.773	6.947
CL/f (mL/h)						
N	13	9				
Mean ± SD	626923 ± 259000	683657 ± 570236				
(min - max)	(317325 - 1273551)	(351923 - 2186543)				
Lamdaz (1/h)						
N	13	9				
Mean ± SD	0.036 ± 0.016	0.03 ± 0.008				
(min - max)	(0.019 - 0.071)	(0.018 - 0.04)				

Reviewer's summary:

1. As part of subject screening, Erythromycin Breath Tests (EBT) were done on all potential subjects. CYP 3A4 inhibition was calculated by taking the difference of the baseline 14C Erythromycin metabolism, subtracting the 14C Erythromycin metabolism during ketoconazole treatment, dividing this difference by the baseline 14C Erythromycin metabolism, and multiplying by 100 to express results in the form of percent inhibition. Following single dose of 200mg ketoconazole, the randomized population (N=20) showed a wide range of CYP 3A4 inhibition from 33% to 82% with a mean of 64.5%. Four subjects had less the 50% inhibition, eight subjects had inhibitions between 50% to 70%, and eight subjects had greater than 70% inhibition.
2. Mean plasma concentration profiles of bup were similar between the two treatments i.e. BTDS+placebo vs. BTDS+keto (Table A and Figure A) indicating that a selective CYP3A4 inhibitor did not affect CYP3A4 mediated bup to norbup metabolism. From Table B, the estimated ratio of population geometric means (BTDS with ketoconazole / BTDS with ketoconazole placebo) for AUCt and Cmax, and their associated 90% confidence intervals (CI's) were within the range of 80% to 125% indicating no difference in buprenorphine exposure for the two treatments.
3. Mean Cmax and AUCt values of norbup and norbup-gluc (Table A and Figure A) were higher when keto was present. Norbuprenorphine glucuronide AUCinf could not be accurately estimated in most of the subjects from both treatments due to unreliable terminal half-lives and/or AUCt/AUCinf ratio of less than 0.80.
4. The sponsor points to the possibility of bup being a high affinity substrate of CYP3A4 such that residual activity of CYP3A4 left over after inhibition may be adequate enough. Following BTDS10 application the maximum bup plasma concentrations (mean Cmax of 142 pg/ml for BTDS10 plus keto, and Cmax of 146 pg/ml for BTDS10 plus placebo) were more than 100,000-fold lower than the previously reported Km value of 36 μM for buprenorphine as a substrate of CYP3A4. In addition to this observation, the results from hepatic impairment study are also in line with the results from this study. Mild and moderate hepatic impairment did not lead to any significant differences in exposures of bup indicating that despite significant inhibition by keto or significant hepatic impairment, only small fractions of the CYP3A4 enzymes are needed for norbup metabolism following BTDS10.
5. From this study, it can be concluded that Butrans doses need not be adjusted in presence of specific CYP3A4 inhibitors.

4.1.2. Reapplication Site Study

A Parallel Open-Label Study to Examine Plasma Concentrations of Buprenorphine Following Reapplication of 10-mg Buprenorphine Transdermal System (BTDS) After Variable Application Site Rest Periods in Naltrexone Blocked Healthy Subjects

Study Design:	A parallel, open-label, single-center, repeated-dose study with variable application site rest periods, using 10-mg BTDS on 2 occasions for 7 days each. The primary comparisons were the AUC0-3d and Cmax0-3d. The secondary comparisons were AUC0-7d, Cmax0-7d, and Tmax0-7d. Cmin was also compared.
Objectives:	The objective of this study was to determine the minimum application site rest period that ensured that reapplication of 10-mg BTDS to the same site in the deltoid region would not result in increased absorption of drug in normal healthy subjects.
Protocol Number:	**BUP1002**
Total Duration:	14 days each group
Number of Subjects Randomized/Completed:	Enrolled 83; completed 64
Diagnosis and Main Criteria for Inclusion:	Healthy male and female subjects aged 18 to 45 years
Demographics of Study Population:	66 males, 4 females 6 black 49 white, 11 black, 1 hispanic, 7 asian and 2 others Mean age = 25.9 yr Mean weight = 77 kg
Test Formulations:	BTDS 10 mg for 2 applications of 7 days each Transdermal 10 mg 7/01081/8B
Reference Formulations:	Naltrexone 25 mg bid beginning prior to application and lasting until 3 days after the BTDS is removed Oral tablet 50 mg PF446A
Treatment Schedule:	One BTDS 10 was applied for 7 days, on days 1 to 8, followed by a second 7-day application for 1 of the following groups of days: 8 to 15, 15 to 22, 22 to 29, 29 to 36, or 36 to 43. Dosing with 25 mg of naltrexone began the evening prior to each BTDS and continued bid until 3 days after removal of BTDS
Study Phase:	Phase 1
Study Initiation and Completion Dates:	19-Nov-2000 to 18-Mar-2001
Principal Investigator and Study Site:	Glen Apseloff, MD, FCP Ohio State University Department of Pharmacology 5084 Graves Hall 333 West 10th Avenue Columbus, OH 43210-1239 Phone: (614) 292-8600 Fax: (614) 292-4253
Bioanalytical Site:	(b) (4)

Bioanalytical validation:

(b) (4) Validation of an LC/MS/MS Method for the Quantitation of Buprenorphine and Norbuprenorphine in Human EDTA Plasma Method and (b) (4): LC-MS/MS Assay Validation of Buprenorphine-3-D-glucuronide and Norbuprenorphine-3-D-glucuronide in Human Plasma

Assay Accuracy Precision, Sensitivity, Selectivity and Stability:

Method 25720-2:

Buprenorphine:
Inter and Intra-day precision: Between 1.1-7.9 CV%
Inter and Intra-day accuracy: Between -3.3 to +2.5 RE%

Norbuprenorphine:
Inter and Intra-day precision: Between 1.2-13.7 CV%
Inter and Intra-day accuracy: Between -3.3 to + 8.3 RE%

Sensitivity and selectivity: 8 lots of control human EDTA plasma were assayed, and 8 out of 8 did not show interfering peaks at the retention time of the compounds of interest. Buprenorphine and norbuprenorphine were spiked into each lot at a concentration equal to the LOQ for buprenorphine and twice the LOQ for norbuprenorphine. For the plasma lots, 8 out of 8 for buprenorphine quantitated within 20% of the theoretical LOQ (20 pg/mL) and 7 out of 8 for norbuprenorphine quantitated within 15% of the theoretical 100 pg/mL spike value when regressed against calibrating standards. Specificity for buprenorphine and norbuprenorphine was tested against naltrexone and 6-beta-naltrexol. No interference with buprenorphine or norbuprenorphine was observed.

Stability:

	Period		As percent of Control	
	Buprenorphine	Norbuprenorphine	Buprenorphine	Norbuprenorphine
Benchtop	74.5 h at RT under yellow light	74.5 h at RT under yellow light	99-102	97-102
Freeze/Thaw	6 cycles	6 cycles	100-101	93-99
Long term Storage	15 wk at -70ºC	4 wk at -70ºC	99-100	98-105
In the Extracted Sample				
Reinjection	4 days 14 h	4 days 14 h	100-103	100-103
Refrigeration	4 days 13 h	4 days 13 h	100-103	100-103

Method 32-0222:

Inter and Intra-day precision and accuracy of Buprenorphine-3-glucuronide and Norbuprenorphine-3-glucuronide:

Analyte	Assay Range (pg/mL)	Intraday Precision (%CV)	Intraday Accuracy (%Diff)	Interday Precision (%CV)	Interday Accuracy (%Diff)
Buprenorphine-3β-D-glucuronide	25 to 10,000	0.9 to 5.4%	-5.9 to 10.3%	4.7 to 9.2%	-7.1 to 11.3%
Norbuprenorphine-3β-D-glucuronide	25 to 10,000	0.7 to 6.4%	-4.8 to 9.6%	2.2 to 9.0%	0.8 to 8.7%

Selectivity and specificity: of the method were evaluated by extracting and analyzing six individual lots of blank human plasma with and without buprenorphine-3-D-glucuronide and norbuprenorphine-3-D-glucuronide. No significant interference was observed at the retention time of the peak for any of the analytes. The precision and accuracy data for 25 pg/mL of buprenorphine-3[3-D-glucuronide and norbuprenorphine-3-D-glucuronide spiked in six different lots of human plasma were within the acceptable range. Pooled human plasma made from six different lots was used as the blank matrix, and Type I water was used as reagent blank throughout the validation.

Stability:
Room Temperature Stability: buprenorphine-3-D-glucuronide and norbuprenorphine-3-D-glucuronide were found to be stable in human plasma at room temperature for 6 h.
Freeze/Thaw Stability: QC samples at two concentrations (50 and 9000 pg/mL, n=5) for buprenorphine-3-D-glucuronide and norbuprenorphine-3-D-glucuronide, were frozen at -20°C (for a minimum of 24 h for the first cycle and a minimum of 12 h for the following cycles) and thawed at room temperature. This freeze/thaw Cycle was repeated three times. Buprenorphine-3-D-glucuronide and norbuprenorphine-3-D-glucuronide samples were stable after three freeze/thaw cycles.
Autosampler Stability at RT: buprenorphine-3-D-glucuronideand norbuprenorphine-3-Dglucuronide were stable in reconstitution solvent at room temperature for 196.5 h.
Whole Blood Stability: buprenorphine-3-D-glucuronide and norbuprenorphine-3-D-glucuronide to be stable in whole blood up to two h.
Analyte Solution Stability: stable in methanol at room temperature for 6 h.
Long-Term Frozen Storage Stability: stable in human plasma at -70 °C for atleast 80 days.

Drug Concentration Measurements:

Blood samples for determining buprenorphine concentrations were obtained during each of the 2 study periods within 30 minutes prior to each application of the BTDS and at the following times after its placement: 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 168.25, 168.5, 168.75, 169, 170, 171, and 172 h. Immediately after the h 168 blood draw, the system was removed.

PK results:

Mean observed plasma concentration – time curves for bup with BTDS 10 mg patch following rest days of 0 to 28 days are presented in Figure B and Table C. Cmax, Tmax and AUC comparisons at 3 and 7 days are represented in Figure C. Statistical comparisons are presented in Table D.

Figure B: Mean (± SE) Plasma Buprenorphine Concentration-Time Curve by # of Rest Days

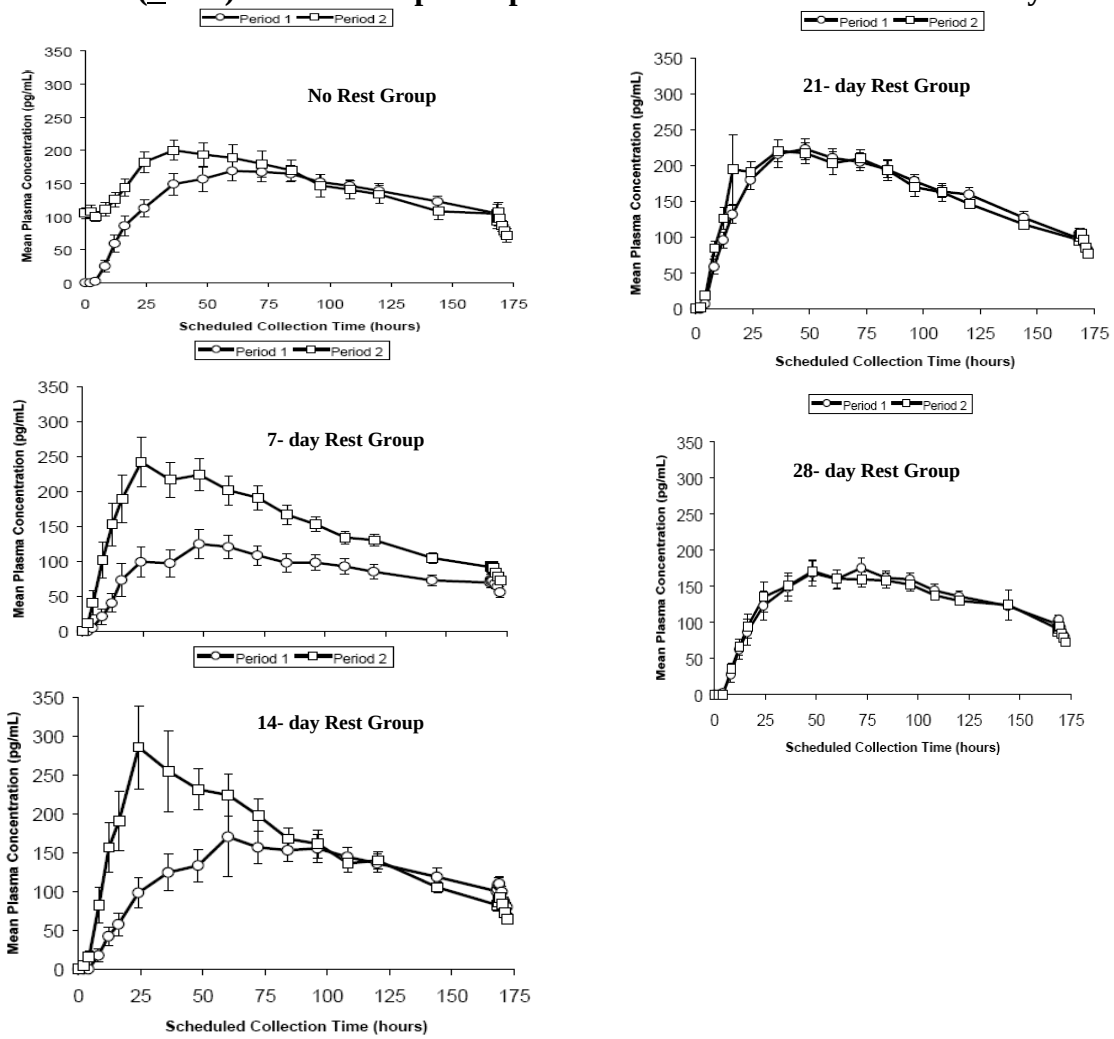
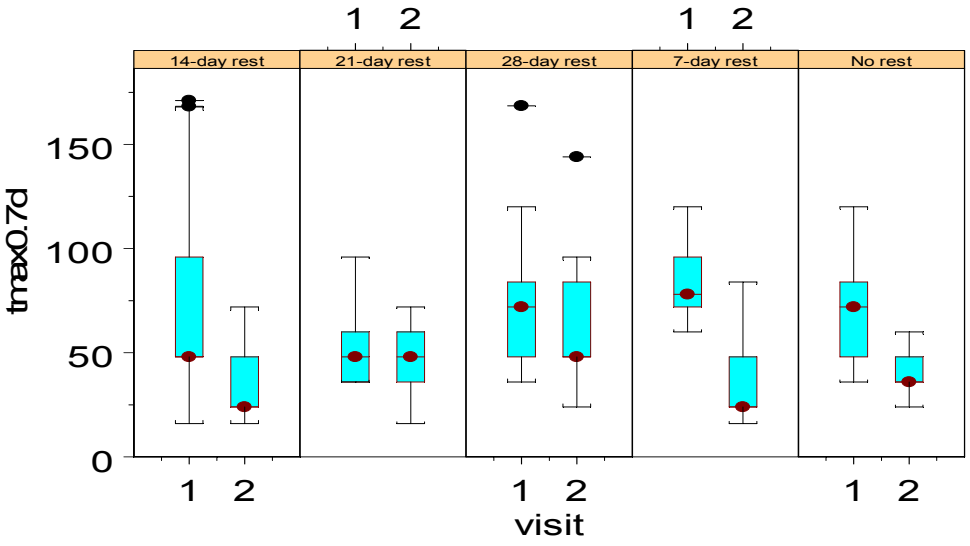
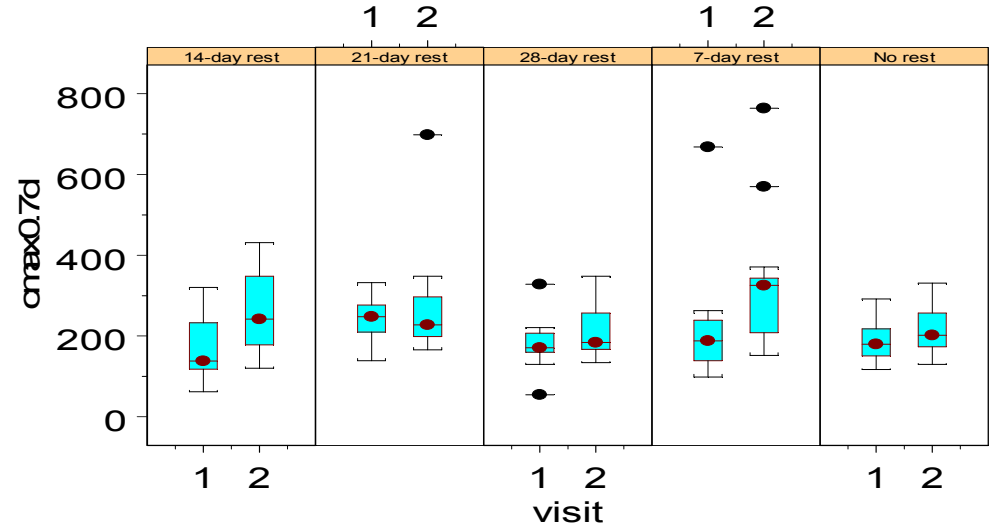


Figure C: Tmax, Cmax and AUC comparisons (at 7 days)





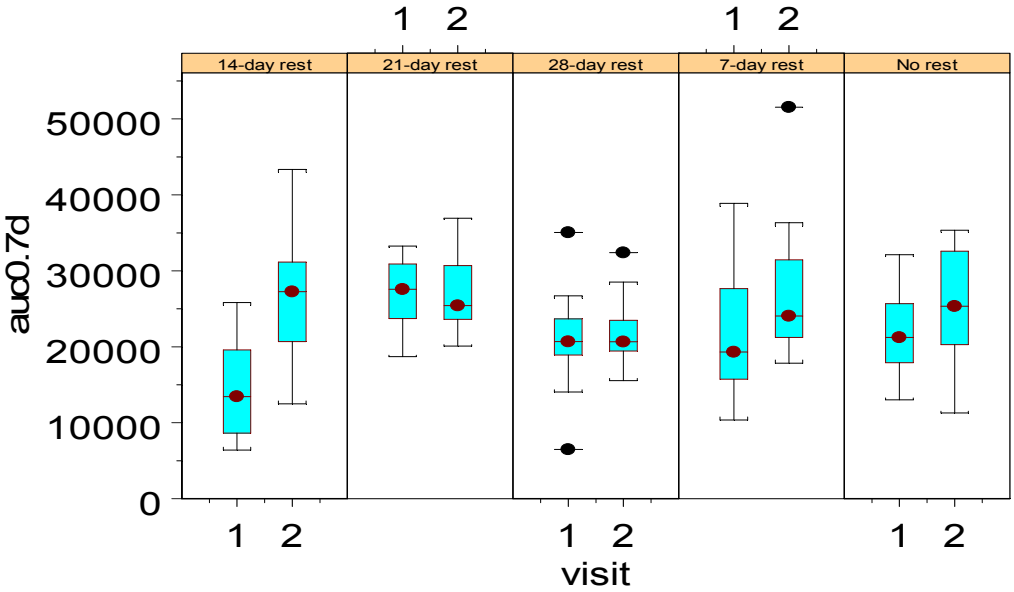


Table C: PK Parameter Comparisons for Treatments (No Rest, 7/14/21/28 days of Rest)

Pharmacokinetic Metric	BTDS 10 Group				
	No Rest (N = 12)	7-Day Rest (N = 11)	14-Day Rest (N = 13)	21-Day Rest (N = 12)	28-Day Rest (N = 12)
	Arithmetic Mean (± SE)				
First application					
AUC_{0-3d} (pg/mL·h)	8680 (± 920)	7651 (± 1514)	6465 (± 1091)	12258 (± 836)	8890 (± 1054)
$Cmax_{0-3d}$ (pg/mL)	183 (± 17)	193 (± 50)	151 (± 24)	241 (± 15)	185 (± 16)
AUC_{0-7d} (pg/mL·h)	21946 (± 1686)	20541 (± 2645)	14707 (± 1851)	27040 (± 1298)	22086 (± 1591)
$Cmax_{0-7d}$ (pg/mL)	188 (± 16)	206 (± 48)	160 (± 22)	245 (± 14)	192 (± 15)
$Tmax_{0-7d}$ (h)	74 (± 7)	86 (± 6)	78 (± 15)	55 (± 6)	76 (± 11)
Second application					
AUC_{0-3d} (pg/mL·h)	12316* (± 1062)	14733 (± 2255)	13571 (± 1671)	12931 (± 908)	9056 (± 888)
$Cmax_{0-3d}$ (pg/mL)	216 (± 17)	300 (± 52)	262 (± 31)	278 (± 41)	182 (± 14)
AUC_{0-7d} (pg/mL·h)	25126* (± 2285)	27543 (± 3093)	26174 (± 2414)	27123 (± 1475)	21790 (± 1365)
$Cmax_{0-7d}$ (pg/mL)	216* (± 17)	300 (± 52)	262 (± 31)	278 (± 41)	202 (± 18)
$Tmax_{0-7d}$ (h)	42 (± 3)	38 (± 6)	36 (± 5)	46 (± 4)	63 (± 10)

Table D: Statistical Comparisons for AUC and Cmax values (not corrected from left over from first dose)

Pharmacokinetic Metric (Geometric Means)	BTDS 10 Group			
	First Application	Second Application	Ratio (%)[a] (Second Application/ First Application	90% CI[b] (Lower, Upper)
AUC_{0-3d} (pg/mL·h)				
No rest	8137	11767*	145*	124*, 168*
7-day rest	6332	13403	212	165, 272
14-day rest	5331	12221	229	197, 267
21-day rest	11932	12601	106	93, **120**[c]
28-day rest	8310	8646	104	89, **121**[c]
$Cmax_{0-3d}$(pg/mL)				
No rest	173	208*	120*	105*, 137*
7-day rest	156	269	173	140, 213
14-day rest	127	239	188	163, 215
21-day rest	236	256	108	91, **129**[c]
28-day rest	178	177	99	89, **111**[c]
AUC_{0-7d} (pg/mL·h)				
No rest	21215	23785*	112*	100*, 125*
7-day rest	18974	26100	138	118, 161
14-day rest	13303	24764	186	164, 211
21-day rest	26675	26704	100	91, 110
28-day rest	21497	21361	99	91, 109
$Cmax_{0-7d}$ (pg/mL)				
No rest	181	208*	115*	103*, 128*
7-day rest	175	270	154	132, 180
14-day rest	143	239	167	147, 190
21-day rest	240	256	107	90, 127
28-day rest	187	194	104	88, 122

*Not corrected for the contribution of the first BTDS application.
[a]Ratio is the value from the second BTDS application divided by the first BTDS application based on least squares means from ANOVA for period and subject.
[b]Ratios and 90% CI were calculated from the ANOVA for the logarithmic-transformed values of AUC and Cmax.

Reviewer's summary:

1. Since repeat application of the patch to the same site may affect the PK (due to changes in skin characteristics from the first the previous patch application) it is important to evaluate a safe interval between reapplication of BTDS patches such that bup exposure in terms of Cmax and AUC does not increase. The sponsor conducted an open label PK study with varying periods of rest days (0 through 28) in a parallel group design. The study protocol limits the study volunteers to re-use the same skin site [on the deltoid region of the dominant arm (right if right-handed)] for reapplication of BTDS. Since the 5, 10 and 20 mg patches are compositionally proportional, and the bup kinetics are linear and dose proportional between doses of 5-20 mg, it can be expected that 20 mg BTDS will lead to doubling of the exposure values observed in this study for 10 mg BTDS.
2. Mean plasma concentration profiles of bup were similar for 21 and 28 rest days groups indicating that a rest period of 21-28 days i.e., 3-4 weeks is required to reduce variability in bup absorption due to reapplication (Figure B and Tables C and D).
3. Higher values of mean AUC0-7d were observed after the second BTDS application compared with the first application for the no rest, 7-day rest, and 14-day rest treatment groups indicating that a rest period of 0-14 days is not sufficient before reapplication of BTDS to the same site (Figure C).
4. In all the treatment groups mean Tmax values were shorter with the second application (rest or no rest) in all the treatment groups indicating that bup absorption is faster with repeated applications (Table C).

5. It was noted that control values in the 21-day rest group are greater than control values in any other group. Since covariate dependent analysis was not performed, it is difficult to assess the reason for higher values in that group. The sponsor however, reviewed PK data from their other studies and observed that the PK values noted in the 21-day rest group are similar to those observed in some other studies conducted with the same product in healthy volunteers. Thus, at this point there is no particular concern with the higher control values observed in the 21-day rest group.
6. The information obtained from this study is carried over to the label of BTDS in the dosage and administration section as "After patch removal, a minimum of 3 weeks should pass before reapplying a patch to the same skin site."

4.1.3 Reanalysis of Hepatic Impairment Study Results

A Single-Dose Pharmacokinetic Study of Buprenorphine in Healthy Adults and Adult Subjects With Hepatic Impairment

Study Design:	A single-dose, open-label, analytically blinded, parallel pharmacokinetic study in healthy and hepatically impaired male and female subjects
Objectives:	To assess the effect of hepatic impairment on the pharmacokinetics of intravenously administered buprenorphine.
Protocol Number:	**BUP97-0112**
Total Duration:	15 days
Number of Subjects Randomized/Completed:	Twenty-four subjects (8 with mild hepatic impairment, 4 with moderate hepatic impairment, 12 healthy).
Diagnosis and Main Criteria for Inclusion:	Twenty-four male and female subjects (8 with mild hepatic impairment [Pugh Child Turcotte A], 4 with moderate hepatic impairment [Pugh Child Turcotte B] and 12 healthy subjects) were enrolled and all 24 completed the study and were included in the pharmacokinetic analysis. Healthy subjects were matched as closely as possible with regard to body weight, age, and gender of the hepatically impaired subjects. The study allowed for severe hepatic impaired subjects to be enrolled, however, none were enrolled.
Demographics of Study Population:	Twenty-four adults between the ages of 36 and 70 years, with a mean age of 55, including 16 males and 8 females; 9 whites, 3 blacks, and 12 Hispanics.
Test Formulations:	Buprenex® Injectable 0.3 mg/mL Intravenous (IV) Lot # 3822
Treatment Schedule:	Each subject received 0.3 mg/mL buprenorphine (Buprenex® Injection) given as an intravenous infusion over a 10-minute time period
Study Phase:	Phase 1
Study Initiation Date:	March 25, 1998
Study Completion Date:	May 14, 1998
Principal Investigator and Study Site:	Kenneth C. Lasseter, MD Clinical Pharmacology Associates 2060 NW 22nd Avenue Miami, FL 33142 (305)634-0777
Bioanalytical Site:	Purdue Research Center 444 Saw Mill River Road Ardsley, NY 10502 (914)709-2000

Bioanalytical measurements:

The assay involved solid phase extraction of the plasma followed by separation and detection using a validated LC/MS/MS method numbered PDMBA-MR-0599. . The lower limit of quantitation for both analytes was determined to be 25 pg/mL. The assay was linear and validated over a range of 25 to 600 pg/mL.

Drug concentration measurements:

Blood samples for the determination of plasma buprenorphine and norbuprenorphine concentrations were obtained on Day 1 (dosing) at the following times: 0 h (predose) and at 10 minutes (end of infusion), 15, 20, 30, and 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 h postdose (Day 2).

PK results: Mean PK parameters for bup and norbup are listed in tables 1 and 2 respectively. Figures 1 and 2 depict box and scatter plots for Cmax and AUC values for bup and norbup respectively. The box plots help in looking at the distribution of the data around the median. The whiskers in the box plots depict the maximum

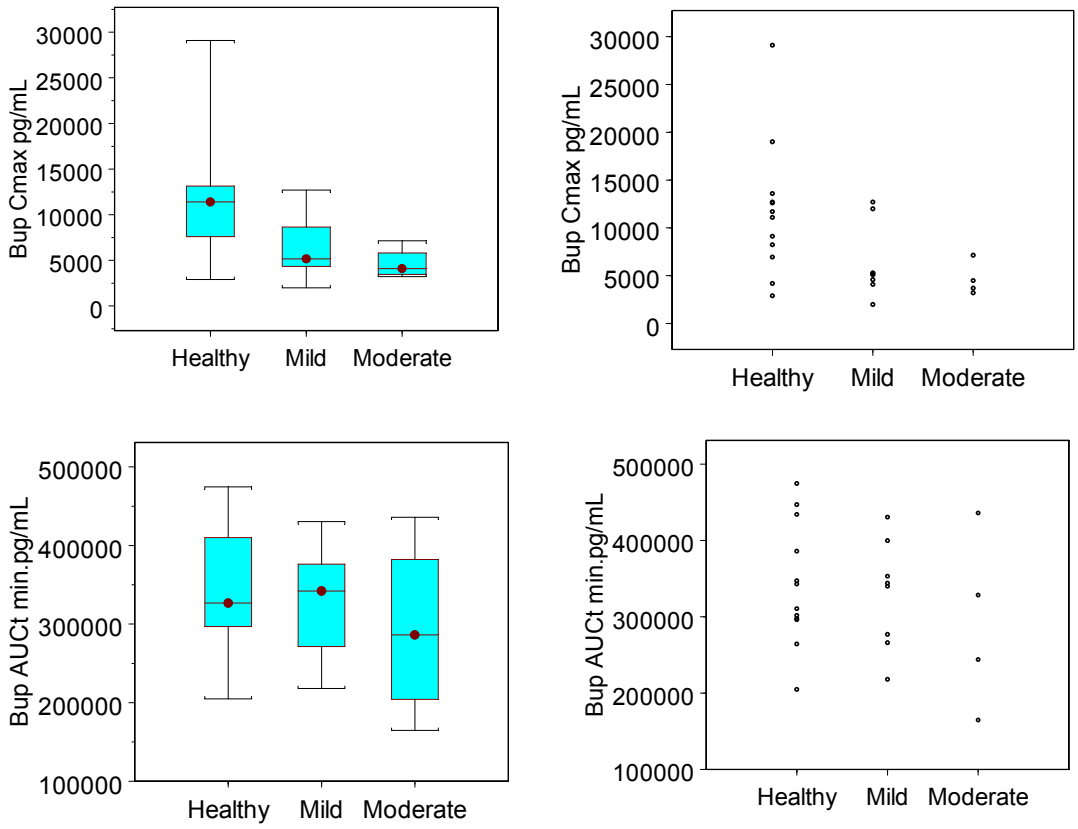
and the minimum values. The scatter plots depict how many data points were actually available for evaluation of the respective PK paramater.

Table E: Summary of Buprenorphine Pharmacokinetic Metrics by Study Group

PK parameter	Healthy (N=12) Mean (SD)	Mild (N=8) Mean (SD)	Moderate (N=4) Mean (SD)
Cmax (pg/mL)	11770.00 (6983.16)	6377.50 (3840.38)	4640.00 (1753.34)
AUC_T (pg·min/mL)	342298.83 (80042.09)	328553.63 (70875.15)	293262.00 (116285.18)
AUCinf* (pg·min/mL)	--	--	--
Tmax (min)	10.83 (1.95)	11.13 (1.73)	12.50 (5.00)
$T_{1/2}$ (min)	759.00 (455.81)	904.63 (508.43)	897.00 (246.38)
Vd(SS) (L)	430.00 (287.91)	621.63 (460.67)	672.75 (258.72)
Cl tot (mL/min)	778.42 (246.61)	733.38 (159.20)	757.50 (225.28)

Fig.D: Buprenorphine Cmax, AUCt and AUCinf distribution

(The whiskers in the box plots depict the maximum and the minimum values. The scatter plots depict how many data points were actually available for evaluation of the respective PK parameter).



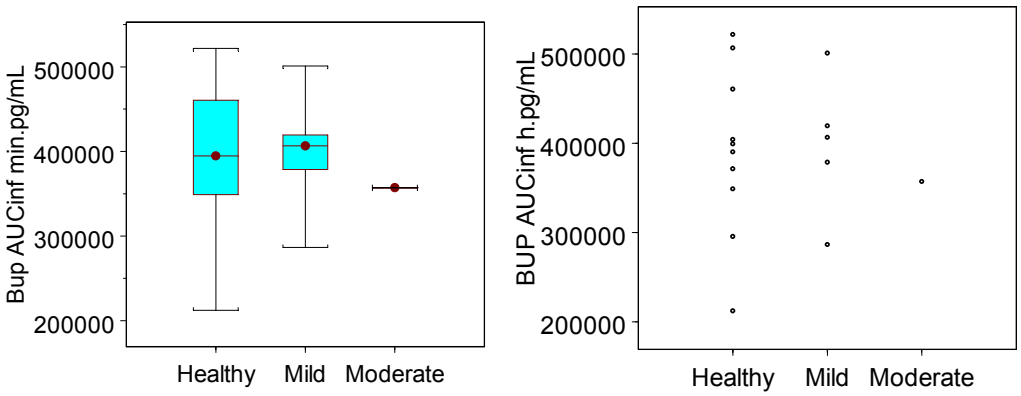
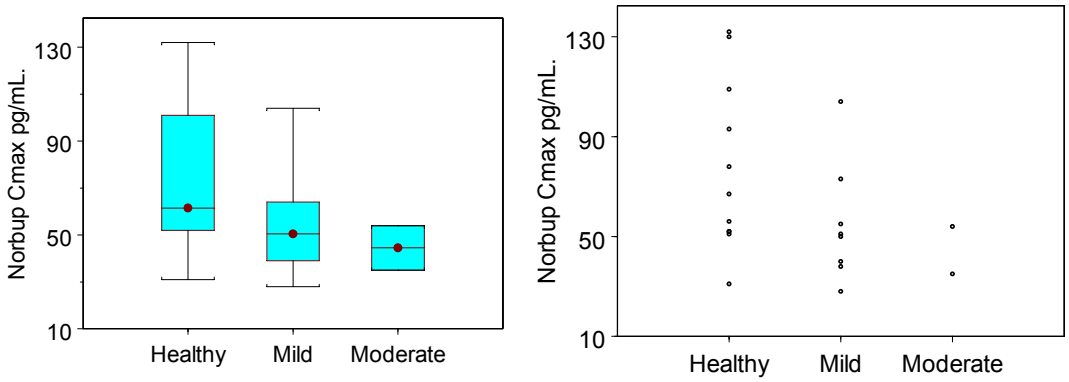
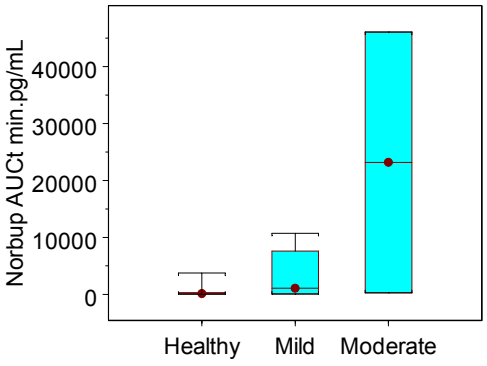


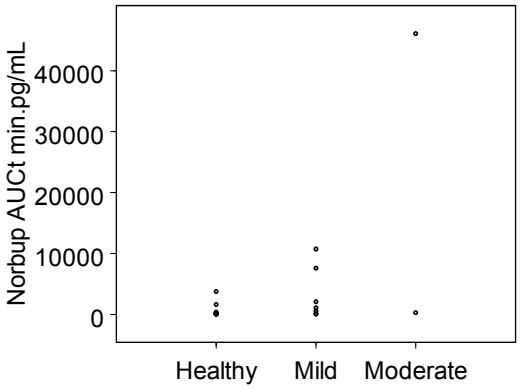
Table F: Summary of Nor-Buprenorphine PK Metrics by Study Group

PK parameter	Healthy (N=12) Mean (SD)	Mild (N=8) Mean (SD)	Moderate (N=2) Mean (SD)
Cmax (pg/mL)	75.25 (33.42)	54.88 (23.93)	44.50 (13.44)
AUC_T (pg·min/mL)	12723.33 (21479.18)	16572.75 (19933.55)	23175.00
AUCinf* (pg·min/mL)	--	--	--
Tmax (min)	14.17 (6.34)	30.38 (36.83)	42.50 (45.96)
$T_{1/2}$ (min)	549.58 (1092.60)	3160.29** (4248.03**)	--
Vd(SS) (L)	--	--	--
Cl tot (mL/min)	--	--	--

Fig.E: Norbuprenorphine Cmax, AUCt and AUCinf distribution







Reviewer's summary:

1. Although the data in this study is highly variable, from Table E and Figure D, it appears that peak plasma levels (Cmax) and extent of exposure over time AUCt (in this case upto 24 h) do not increase significantly with severity in hepatic impairment.
2. Cmax of bup was lower in hepatic impairment patients. For mild hepatic impairment patients, the mean Cmax value was only 54% of that for the healthy and for moderate hepatic impairment patients, the Cmax value was only 39% of that for the healthy. In addition, since only 4 and 1 data points are available for the calculation of extent of exposure parameter, AUCinf, for the moderate and mild hepatic impairment groups respectively, it is not possible to make any conclusions for AUCinf, relative to severity of hepatic impairment.
3. From Table F and Figure E, it appears that Cmax and AUCt of norbup do not increase with severity in hepatic impairment.
4. Cmax of norbup was lower in hepatic impairment patients. For mild hepatic impairment patients, the mean Cmax value was only 73% of that for the healthy and for moderate hepatic impairment patients, the Cmax value was only 59% of that for the healthy. The box plot in Figure E for AUCt shows that few data points were available for norbup analysis in all the groups. There do not appear to be significant differences in AUCt of the healthy and the mild hepatic impairment groups with respect to norbup. AUCinf could not be calculated for this group because of large % of extrapolation required.
5. It is interesting to note that the norbup concentrations in this study appear to be much lower as compared to parent; i.e., 1-5% of bup. With the other PK study reviewed in this submission i.e., BUP1002, the norbup plasma concentrations are 15-20% of bup in healthy subjects where Butrans is administered.
6. From this study, it can be concluded that hepatic impairment may not result in higher concentrations of bup or norbup when bup is administered IV.
7. The sponsor has recommended that mild and moderate hepatic impairment patients be started at the lowest 5 mcg/h dose of the patch as a safety feature in the D and A section of the product's label, and we concur with that comment.
8. It should be noted that severe hepatic impairment patients were not enrolled in this study and the product label should still contain cautionary language about using the product in this group.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEETAL S AGARWAL
03/10/2010

SURESH DODDAPANENI
03/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Sheetal Agarwal, 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: **09/18/08**	IND No.: Serial No.:	NDA No. 21306	Submission Date: 08/31/08	
NAME OF DRUG BuTrans (Norspan) Buprenorphine transdermal system 5 µg/h, 10 µg/h, and 20 µg/h	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Purdue Pharma L.P. (PPLP)

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- ☐ PHASE III PROTOCOL
- ☐ DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☐ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☒ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)

Pre-re-submission meeting

- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☐ OTHER *(SPECIFY BELOW):*

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 COMMENT(S)

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

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor appears to have an adequate plan to address the Clinical Pharmacology-related items (52, 53 and 54) cited in the NA letter. The adequacy of the data will be reviewed after a Complete Response is submitted.

In addition, the sponsor appears to have an adequate plan to address some other items (46 and 58) that may require Clinical Pharmacology input.

The plan to address the outliers issue raised in item 59 is unclear from the meeting package. This will be dealt with during the filing review of the Complete Response.

In their meeting package, the sponsor did not raise any questions related to Clinical Pharmacology NA items. The Clinical Pharmacology review team does not have any comments for the sponsor at this time.

No further action is indicated at this time.

MEETING PACKAGE BACKGROUND AND REVIEW:

Buprenorphine is a synthetic opioid analgesic derived from the opium alkaloid thebaine, and has partial μ-opioid agonist and κ-opioid antagonist properties. In the United States, buprenorphine is available for parenteral administration, primarily for the management of postoperative pain, and as a sublingual formulation, with and without naloxone, for the treatment of opioid addiction at buprenorphine doses up to 16 mg per day. Buprenorphine is currently a Schedule III drug under the Controlled Substances Act. Purdue Pharma L.P. (PPLP) has developed the Buprenorphine Transdermal System (BTDS), which they now want to call BuTrans (earlier called Norspan) in 3 dosage strengths, 5 μg/h, 10 μg/h, and 20 μg/h, to provide continuous systemic delivery of buprenorphine over a 7-day period for the management of moderate to severe pain expected to be present for an extended period of time.

NDA 21-306 was originally submitted by PPLP in November 2000. The Agency issued a not approvable (NA) letter (available in DFS) containing 62 deficiency items addressing issues related to clinical, preclinical, and CMC disciplines.

This submission consists of the sponsor's plan of action in coming up with a Complete Response to address the items in the NA letter. The Type C industry meeting was held on September 15, 2008. The purpose of this meeting was to seek agreement regarding the technical and scientific discipline issues related to the preparation for the Complete Response. As mentioned earlier, no Clinical Pharmacology related issues were raised in the meeting by either the sponsor or by us (the Clinical Pharmacology review team).

Clinical Pharmacology-related specific items (52, 53 and 54) and items (46, 58 and 59) that may require Clinical Pharmacology input (in the NA letter) along with the sponsor's proposed plan to address the issues are listed below.

Item 52: Your analyses of the hepatic impairment study were based on pooled data that do not allow for a reasonable understanding of the correlation between the clinical stage of disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment.

SPONSOR'S COMMENTS:

A reanalysis of the hepatic impairment study (BP97-0112) in which the degree of hepatic impairment was separated into subgroups according to the Pugh modification of the Child Turcotte criteria was conducted. The reanalysis shows that similar results were obtained in mild and moderate hepatic impairment subgroups to that of the overall hepatic impaired subject group. This information will be addressed in the label. The reanalysis results and regulatory communication are contained in a separate document entitled "PPLP Response Plans to NA Letter Items Additional Information." (Appendix 1)

Item 53: The assay used in study BP95-0901 was not validated and therefore, the pharmacokinetic data from that study were not reported. As a trend toward an exposure-response relationship was noted, samples from this study should be reassayed and the data specifically analyzed to assess pharmacokinetic/ pharmacodynamic relationships.

SPONSOR'S COMMENTS:

A briefing package was submitted to FDA on October 8, 2001 prior to the November 6, 2001 end of review teleconference. At this meeting PPLP stated that there were no remaining blood samples from this study, thus reanalysis of samples was not feasible. In FDA's minutes of this discussion dated November 28, 2001, the Division agreed with this assessment.

Item 54: You have not adequately addressed concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS. Provide data to adequately address these concerns either from available literature or from in vivo drug-drug interaction studies.

SPONSOR'S COMMENTS:

An *in vivo* drug-drug interaction (DDI) study (Clinical Study BUP1009) in healthy subjects using buprenorphine and ketoconazole was conducted and a final study report was submitted to IND 50,273 on September 17, 2004 (Serial No. 370). The final study report will be included in the Complete Response, and this information will be addressed in the label. The final study report conclusions and regulatory communication are contained in a separate document entitled "PPLP Response Plans to NA Letter Items Additional Information." (Appendix 1)

REVIEWER'S COMMENTS:

The sponsor appears to have an adequate plan to address the Clinical Pharmacology related items (52, 53 and 54) cited in the NA letter. The adequacy of the data will be reviewed after a complete response is submitted.

Item 46: The stability data indicate that the adhesion strength and the release strength decrease with time. Provide data/justification to demonstrate the drug product at the end of shelf life performs acceptably for these attributes during patient use.

SPONSOR'S COMMENTS:

PPLP has performed an analysis of PK performance vs. patch age. The results of this analysis will be provided as justification for product shelf life.

Item 58: The electrocardiogram data do not analyze for electrocardiographic intervals. Include in the ISS analyses of electrocardiographic intervals (e.g., PR, QRS, QT, QTc, etc) in view of reports of cardiotoxicity associated with other opioids.

SPONSOR'S COMMENTS:

Item 58 of the NA letter stated that the submitted ECG data did not analyze ECG intervals. The sponsor was directed to include analyses of the electrocardiographic intervals "in view of reports of cardiotoxicity associated with other opioids". We have analyzed the ECG intervals from the previously submitted studies. These data are from normal volunteers. We will also submit ECG safety data from studies BUP3012, BUP3011, BUP3014, BUP3015, BUP3019 and BUP3024 (integrated where appropriate). The interval data will be analyzed as directed by the ICH E14 guidance including both assessments of central tendencies and categorical analyses. In addition, in view of the effects of Orlaam and methadone on repolarization (QT/QTc prolongation and torsade de pointes) we have performed a thorough QT/QTc study (BUP 1011) to evaluate the effect of BTDS on the QT and QTc intervals. The final study report for BUP1011 will be included in the Complete Response as well.

Item 59: A potential problem with the design of studies BP96-0604 and BP99-0203 was the fact that during the titration period, patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reached at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both. Address this issue, both in regard to the completed studies, and in the design of future studies.

SPONSOR'S COMMENTS:

A detailed response has already been provided to the FDA and FDA's response is contained in the regulatory communication contained in a separate document entitled "PPLP Response Plans to NA Letter Items Additional Information." (Appendix 1)

REVIEWER'S COMMENTS:

The sponsor appears to have an adequate plan to address some other items (46 and 58) that may require Clinical Pharmacology input. The plan to address the outliers issue raised in Item 59 is unclear from the meeting package. This will be dealt with during the filing review of the complete response.

Item 52: Your analyses of the hepatic impairment study were based on pooled data that do not allow for a reasonable understanding of the correlation between the clinical stage of disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment.

PPLP Response Summary

Table 1. PK Summary Table for Buprenorphine

	Healthy (N=12)		Mild (N=8)		Moderate (N=4)	
PK parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Cmax (pg/mL)	11770.00	6983.16	6377.50	3840.38	4640.00	1753.34
AUC_T (pg·min/mL)	342298.83	80042.09	328553.63	70875.15	293262.00	116285.18
AUCinf* (pg·min/mL)	--	--	--	--	--	--
Tmax (min)	10.83	1.95	11.13	1.73	12.50	5.00
$T_{1/2}$ (min)	759.00	455.81	904.63	508.43	897.00	246.38
Vd(SS) (L)	430.00	287.61	621.63	460.67	672.75	258.72
Cltot (mL/min)	778.42	246.61	733.38	159.20	757.50	225.28

*AUCinf was not estimable in a majority of the subjects; therefore, summary statistics were not reported.

Table 2. PK Summary Table for Norbuprenorphine

	Healthy (N=12)		Mild (N=8)		Moderate (N=2)	
PK parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Cmax (pg/mL)	75.25	33.42	54.88	23.93	44.50	13.44
AUC_T (pg·min/mL)	12723.33	21479.18	16572.75	19933.55	23175.00	32401.05
AUCinf * (pg·min/mL)	--	--	--	--	--	--
Tmax (min)	14.17	6.34	30.38	36.83	42.50	45.96
$T_{1/2}$ (min)	549.58	1092.60	3160.29*	4248.03**	--	--
Vd(SS) (L)	--	--	--	--	--	--
Cltot (mL/min)	--	--	--	--	--	--

*AUCinf was not estimable in a majority of the subjects; therefore, summary statistics were not reported.
**N=7

Table 3. Ninety-Percent Confidence Intervals of Ratios for Cmax and AUCt

Mild (n=8) versus Healthy (n=12) Subjects			
Ratio Metrics	**Ratio (LS Mean)**	**Low CI Ratio**	**High CI Ratio**
Buprenorphine–AUCt	0.96	0.80	1.16
Buprenorphine–Cmax	0.55	0.34	0.89
Norbuprenorphine–AUCt	1.20	0.33	4.33
Norbuprenorphine–Cmax	0.74	0.53	1.04

Moderate (n=4) versus Healthy (n=12) Subjects			
Ratio Metrics	**Ratio (LS Mean)**	**Low CI Ratio**	**High CI Ratio**
Buprenorphine - AUCt	0.83	0.62	1.11
Buprenorphine - Cmax	0.44	0.25	0.79
Norbuprenorphine - AUCt	0.73	0.07	7.72
Norbuprenorphine - Cmax	0.63	0.35	1.14

The reanalysis shows that the degree of hepatic impairment (mild vs. moderate) does not appear to affect overall systemic exposure to buprenorphine.

Item 52 Regulatory Correspondence Summary

A briefing package was submitted to FDA on October 8, 2001 prior to the November 6, 2001 end of review teleconference. At this meeting PPLP replied that the reanalysis would be submitted. In FDA's minutes of this meeting dated November 28, 2001, the Division replied this was acceptable.

Item 54: You have not adequately addressed concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS. Provide data to adequately address these concerns either from available literature or from in vivo drug-drug interaction studies.

PPLP Response Summary

Final Clinical Study Report BUP1009 Conclusions (21-Apr-2004):

- Plasma buprenorphine concentrations, when delivered by BTDS 10 mg, did not accumulate during co-medication with ketoconazole 200 mg BID.
- BTDS 10 mg plus ketoconazole 200 mg BID was well tolerated. No apparent safety concerns following treatment with BTDS 10 mg plus ketoconazole were identified.
- With significant inhibition of CYP3A4 achieved, the plasma concentrations of norbuprenorphine and norbuprenorphine glucuronide metabolites were not lower following ketoconazole administration due to the low concentrations of the buprenorphine present in the plasma following BTDS10 application
- BTDS dose adjustment is not needed for subjects taking concomitant CYP3A4 inhibitors.

Item 54 Regulatory Correspondence Summary

A briefing package was submitted to FDA on October 8, 2001 prior to the November 6, 2001 end of review teleconference.

PPLP response regarding Item 54:

> The metabolism of buprenorphine has been established to occur via both CYP3A4 and glucuronidation (NDA 21-306, Item 6, Section 6.3.10.2.1, Attachment 5 of this submission). Due to the non-CYP450 route of metabolism, significant drug interactions with CYP450 inhibitors are not anticipated, even with inhibitors of CYP3A4. To definitively address any possibility of interactions with inhibitors of CYP3A4, PPLP proposes to conduct a drug interaction study in volunteers receiving buprenorphine and ketoconazole.
>
> Is this approach acceptable to the Division?

In FDA's minutes dated 11/28/01, the Division replied:

> Purdue proposed to conduct an *in vivo* drug-drug interaction (DDI) study. The Division stated this was an acceptable approach. Due to time constraints, it was decided that details of the study could be discussed later in a teleconference, if needed.

PPLP's correspondence, dated 1/8/02, to FDA's minutes noted differences:

Official Meeting Minutes:

Purdue proposed to conduct an *in vivo* drug-drug interaction (DDI) study. The Division stated this was an acceptable approach. Due to time constraints, it was decided that details of the study could be discussed later in a teleconference, if needed.

PPLP Significant Differences (revised text follows):

PPLP proposed to conduct an *in vivo* drug-drug interaction (DDI) study in volunteers **using buprenorphine and ketoconazole**. The Division stated that this was an acceptable approach. Due to time constraints, it was decided that the details of the study could be discussed later in a teleconference, if needed.

FDA's response, dated 4/2/02, to PPLP's comments concerning FDA's 11/28/01 meeting minutes:

Purdue proposed to conduct an *in vivo* drug interaction (DDI) study. The Division stated that this was an acceptable approach. Due to time constraints, it was decided that the details of the study could be discussed later in a teleconference, if needed.

Purdue proposed the following revisions:

PPLP proposed to conduct an *in vivo* drug-drug interaction (DDI) study in volunteers <u>using buprenorphine and ketoconazole</u>. The Division stated that this was an acceptable approach. Due to time constraints, it was decided that the details of the study could be discussed later in a teleconference, if needed.

- The Division acknowledges the revision.

Action items/Outcomes from the meeting (11/6/01 EOR teleconference) were as follows and PPLP agreed:

3. If needed, Purdue will request a teleconference to discuss the *in vivo* drug-drug interaction study (issue #54).

Study protocol BUP1009 was sent to the FDA on October 18, 2002. The FDA replied on March 18, 2003:

We have completed the clinical review of your submission and have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However, responses to them is requested.

1. Although the risk of respiratory depression is low, include measurement of oxygen saturation in the vital signs. In addition, include a SOP for management of adverse events (AEs) due to buprenorphine and/or ketoconazole.

2. Provide pre-specific stopping criteria and clarify the stopping criterion "inability to tolerate study medications".

On March 24, 2003 PPLP replied:

> Please refer to Purdue Pharma L.P.'s (PPLP) IND 50,273 for the Buprenorphine Transdermal System (BTDS) submitted to the Agency on 4 April 1996 (Serial No. 000). We also refer to your 18 March 2003 letter regarding our 16 October 2002 correspondence (Serial No. 208) for the BUP1009 clinical protocol.
>
> This correspondence concerns the Agency's completed review of the BUP1009 protocol and subsequent comments. Please note that last patient for this study was completed on 20 December 2002. No respiratory depression was reported in this single dose study. We will take the Agency's recommendations (e.g., "pre-specified stopping criteria") into account when developing future phase 1 studies.

A final BUP1009 clinical study report was submitted to the agency on September 17, 2004 (Serial no. 370):

> Please refer to Purdue Pharma L.P's (PPLP) investigational New Drug Application (IND) #50,273 for the Buprenorphine Transdermal System (BTDS) submitted to the agency on April 4, 1996. Reference is also made to our October 16, 2002 submission of a protocol Amendment: New Protocol and Investigator Documentation (serial No. 208) with **Protocol BUP1009**, to the Agency's March 18, 2003 letter with comments on this protocol, and to our response dated March 25, 2003 (Serial No. 226).
>
> We herein are submitting a Final Study Report for study **Protocol BUP1009**, entitled "A Single Center, Randomized, Double-Blind, Crossover Study to Assess Buprenorphine Accumulation and Description of its Metabolites During Co-Medication of BTDS and Ketoconazole, Used As a CYP3A4 Inhibitor, in Healthy Subjects".

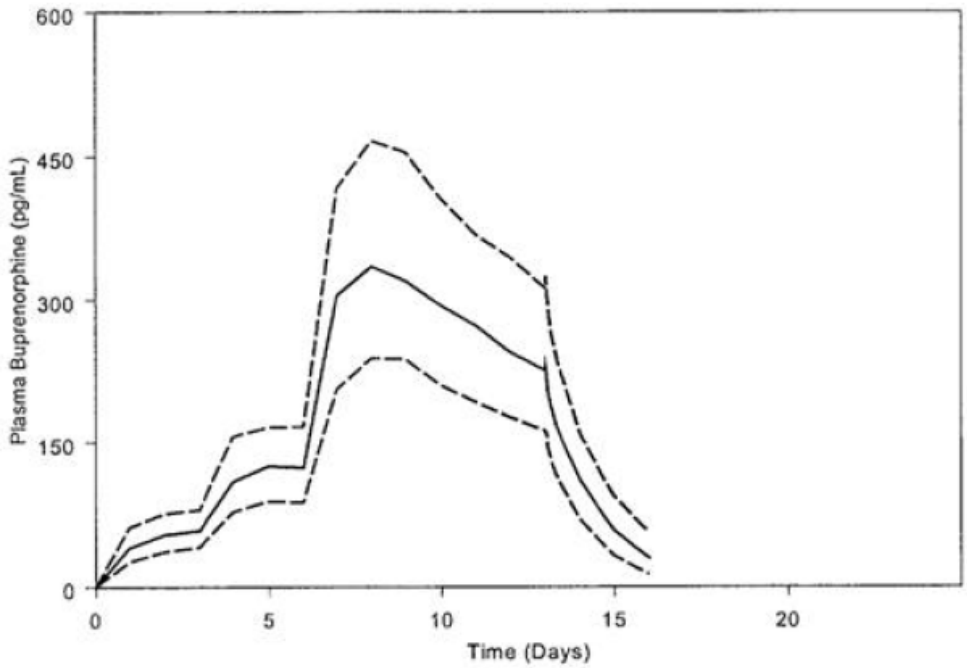
Item 59: A potential problem with the design of studies BP96-0604 and BP99-0203 was the fact that during the titration period, patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reached at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both. Address this issue, both in regard to the completed studies, and in the design of future studies.

Item 59 Regulatory Correspondence Summary

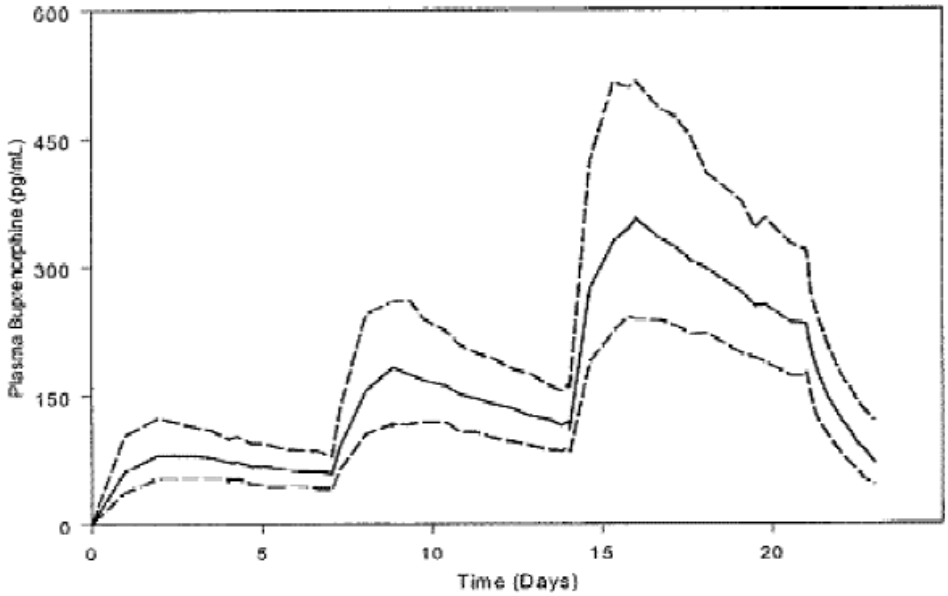
A briefing package was submitted to FDA on October 8, 2001 prior to the November 6, 2001 end of review teleconference.

PPLP response regarding Item 59:

> The Cmax at about 107 hours was observed in only one study (BP97-0501) and in only one strength, BTDS 5. This observation was driven by 3 high outlier values at that time point (see figure below). At later time points, buprenorphine returned to



Dose escalation (5 x 3d, 10 x 3d, 20 x 7d)
Solid line = median of 500 simulated subjects with typical demographics.
Dashed lines = 25th and 75th quantiles of 500 simulated subjects with typical demographics



Dose escalation (5 x 7d, 10 x 7d, 20 x 7d)
Solid line = median of 500 simulated subjects with typical demographics.
Dashed lines = 25th and 75th quantiles of 500 simulated subjects with typical demographics

Therefore, this information supports the position that dose escalation as early as day 3 does not result in overtitration of treatment relative to dose escalation on day 7.

Does FDA agree?

In FDA's minutes, dated November 28, 2001, the Division replied:

Purdue provided a detailed response to this issue in the meeting package. It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.

PPLP's correspondence, dated January 8, 2002, to FDA's minutes noted differences:

Official Meeting Minutes

Purdue provided a detailed response to this issue in the meeting package. It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.

PPLP Significant Differences: Minutes should read as follows:

Purdue provided a detailed response to this issue in the pre-meeting package. A statement that the FDA agreed with Purdue's position that three days was adequate time for dosing escalation initiated discussion of this item. The data, which were discussed in some detail, showed that plateau buprenorphine concentration is reached mostly on Day 2 using both raw data and Clinical Trial Simulations. In addition, using the validated population pharmacokinetic model, PPLP provided the population prediction that confirmed dose escalation every 3 days is not premature because buprenorphine concentrations on Day 3 of BTDS wear are similar to buprenorphine concentrations on Day 7 of BTDS wear. Dr. Rappaport stated that he found the outlier data interesting and suggested it might be addressed is a separate teleconference.

FDA's response, dated April 2, 2002, to PPLP's disagreements concerning FDA's November 28, 2001 meeting minutes:

Purdue provided a detailed response to this issue in the meeting package. It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.

Purdue proposed the following revisions

Purdue provided a detailed response to this issue in the pre-meeting package. A statement that FDA agreed with Purdue's position that three days was adequate time for dosing escalation initiated discussion of this item. The data, which was discussed in some detail, showed that plateau buprenorphine concentration is reached mostly on Day 2 using both raw data and Clinical Trial Simulations. In addition, using the validated population pharmacokinetic model, PPLP provided the population prediction that confirmed dose escalation every 3 days is not premature because buprenorphine concentrations on Day 3 of BTDS wear are similar to buprenorphine concentration on Day 7 of BTDS

wear. Dr. Rappaprt stated that he found the outlier data interesting and suggested it might be addressed in a separate teleconference. ~~It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.~~

- The Division acknowledges these revisions but also reminds Purdue that there are outliers that are unaccounted for by their population PK model.

Action items/Outcomes from the meeting (11/6/01 EOR teleconference) were as follows:

8. If needed, Purdue will request a teleconference to discuss the titration period for studies BP96-0604 and BP99-0203 (issue #59).

FDA agreed with PPLP's proposed revision of the 11/6/01 EOR action item #8:

10. If requested by FDA, Purdue <*will*> provide additional information on the outlier analysis, however a teleconference in the issue of adequacy of the dosing interval is not required (issue#59).

- The Division acknowledges these revisions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sheetal Agarwal
9/22/2008 09:28:31 AM
BIOPHARMACEUTICS

Lei K Zhang
9/27/2008 08:56:26 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/30/2008 08:44:12 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-306**	**Brand Name**	**Norspan**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Buprenorphine**
Medical Division	**ACCDDP (HFD-170)**	**Drug Class**	**Opioid**
OCPB Reviewer	**Suliman AlFayoumi**	**Indication(s)**	**Continuous Analgesia**
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Transdermal Application**
		Dosing Regimen	**5, 10 & 20 mg**
Date of Submission	**11/3/00**	**Route of Administration**	**Transdermal**
Estimated Due Date of OCPB Review	**7/30/01**	**Sponsor**	**Purdue Pharma, L.P.**
PDUFA Due Date	**9/3/01**	**Priority Classification**	**3 S**
Division Due Date	**7/31/01**		

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:	X			
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			3 Pharmacodynamic DDI studies
In-vivo effects of primary drug:				
In-vitro:	X			
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:	X			
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		**17**	**16**	

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	**1. Is there an exposure/response relationship for BTDS with respect to safety and efficacy?** **2. What is the effect of heat on the PK/PD of BTDS?** **3. Is the PK of BTDS linear?** **4. Can BTDS be applied interchangeably to different body sites?**
Other comments or information not included above	**Please let me know if there are any problems with printouts (827-0234).**
Primary reviewer Signature and Date	**Suliman Al-Fayoumi, 7/5/01**
Secondary reviewer Signature and Date	

CC: NDA 21-306, HFD-850(PLee), HFD-170(SShepherd), HFD-870(SDoddapaneni, HMalinowski, JHunt), CDR (B. Murphy)

Clinical Pharmacology and Biopharmaceutics Review

NDA: **21-306**

Trade Name: Norspan

Active Ingredient: Buprenorphine

Sponsor: Purdue Pharma L.P.

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

Type of Submission: Original NDA

Code: 3 S

Stamp Date: 11/3/2000

Related INDs: (b) (4)

Synopsis

Buprenorphine is a synthetic opioid analgesic that possesses μ-opioid agonist activity combined with κ-opioid antagonist properties.

Buprenorphine has been marketed in the US since 1982 as an injectable dosage form. In the current submission, the sponsor has developed buprenorphine transdermal delivery system (BTDS) in 5, 10 and 20 mg strengths for 7 day application (168 hrs) for use in the management of pain in patients requiring continuous opioid analgesia.

The Clinical Pharmacology and Biopharmaceutics section of the NDA consists of 17 studies on the pharmacokinetics/pharmacodynamics of buprenorphine, drug-drug interactions, effects of heat, and absolute bioavailability of buprenorphine following BTDS application. A complete listing of the clinical pharmacology and biopharmaceutics-related studies submitted to this NDA is included in Appendix 1.

The sponsor has adequately characterized the relevant clinical pharmacology and biopharmaceutics-related aspects of Norspan.

Buprenorphine is highly bound to plasma proteins (96%). Buprenorphine is cleared by CYP3A4-mediated metabolism and by glucuronide conjugation. Norbuprenorphine is the only known active metabolite of buprenorphine. The systemic exposure of norbuprenorphine was shown to be 1-5% of that of buprenorphine after administration of buprenorphine via short I.V. infusion. The bioavailability of a 7-day application of a single BTDS dose is 15%. *In vitro* metabolism studies did not suggest metabolic drug-drug interactions at clinically relevant systemic buprenorphine concentrations. Pharmacodynamic drug-drug interaction studies suggested that midazolam, prochlorperazine and thiazide diuretics did not exacerebate opioid adverse events, particularly respiratory depression, when co-administered with a BTDS application. Dose proportionality for the BTDS 5, 10 and 20 mg strengths was established for the 7-day application period. Application of external heat (i.e.-heat pad) resulted in a 26-55% increase in buprenorphine plasma concentrations. A population PK analysis conducted by the sponsor indicated that age, gender and ethnicity had no significant relationships to C_{max} or AUC of buprenorphine.

Recommendations:

The Human Pharmacokinetics and Bioavailability section of NDA 21-306 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. OCPB-related labeling language will be addressed at the appropriate time.

The following comments should forwarded to the sponsor:

1. Data from the hepatic impairment study were pooled. The sponsor is requested to re-analyze data by hepatic impairment subgroup (i.e.-mild and moderate hepatic impairment subgroups).
2. Despite the sponsor's assertion that there was no definite exposure-response relationship observed for buprenorphine, study BP95-0901 pointed to a clear trend for the measured pharmacodynamic markers (both effect and adverse events). Unfortunately, the analytical assay utilized at the time for determination of buprenorphine plasma concentrations was not validated. Hence, the pharmacokinetics of BTDS in the study was not reported. It might be of value for the sponsor to re-analyze any samples still available from that study using a validated assay and evaluate the data for PK/PD relationships.
3. The sponsor is requested to adequately address concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS.
4. The sponsor should consider retaining the 0.5 hr sampling time point as well as including at least one additional time point (possibly around 12 hrs) to the proposed dissolution test to better characterize the dissolution profile of BTDS. In addition, the sponsor should consider setting tighter specifications for passing the dissolution test as the current proposed criteria seem to be too broad. The proposed specifications are as follows:

Test Point (hr)	% Buprenorphine dissolved
0.5	(b) (4)
2	
24	

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1. What is the pharmacological class, scientific rationale and intended use of Norspan (buprenorphine transdermal system)?

Norspan, a transdermal system intended for systemic delivery of buprenorphine over a 7 day period, is being sought for marketing in the US for the management of patients with pain requiring continuous opioid analgesia .

Buprenorphine is a synthetic opioid analgesic that possesses μ-opioid agonist activity combined with κ-opioid antagonist properties. The analgesic activity of buprenorphine at low to moderate doses is 20-50 times that of morphine with a longer duration of action.

Buprenorphine has been marketed in the US since 1982 as an injectable dosage form (Buprenex® Injection, NDA 18-401). Injectable buprenorphine has been primarily used for the management of postoperative pain. It has also been used in the following settings: preoperative sedation and analgesia, adjunct to surgical anesthesia, and relief of moderate to severe pain associated with cancer, trigeminal neuralgia, ureteral calculi, myocardial infarction and accidental injury.

Buprenorphine is characterized by a poor oral bioavailability, hence, oral and sublingual buprenorphine are 1/15 and 2/3 as potent, respectively, relative to parenteral buprenorphine. However, parenteral buprenorphine has a relatively short duration of action (6-8) hrs. The sponsor has developed buprenorphine transdermal delivery system (BTDS) in 5, 10 and 20 mg strengths for 7 day wear (168 hrs).

The sponsor is seeking approval for marketing Norspan (5, 10 and 20 mg strengths) for the management of patients with pain requiring continuous opioid analgesia.

The sponsor claims that continuous delivery of buprenorphine will provide a baseline pain relief for patients with mild to moderate chronic pain.

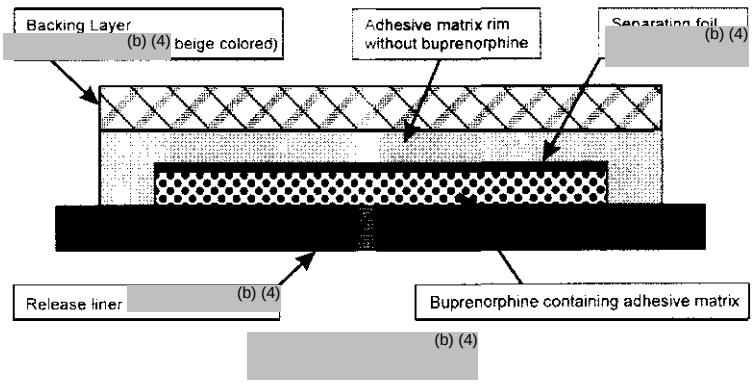


Fig. 1. Illustration of the composition of BTDS.

2. Is there an exposure-response relationship for buprenorphine with respect to safety or efficacy?

A pooled data analysis of the relationships between pharmacodynamic markers and buprenorphine concentration either showed the lack of any correlation or failed to reveal any consistent trends.

Data pooled from several clinical pharmacology studies were analyzed by the sponsor using NonMem software so as to explore the relationships between pharmacodynamic variables and buprenorphine plasma concentration. Due to the highly variable and subjective nature of the primary efficacy endpoint (analgesia), the pharmacodynamic variables evaluated in the analysis were exclusively safety-related. The pharmacodynamic variables included in the analysis included vital signs variables such as systolic and diastolic blood pressure, pulse and respiratory rate, as well as adverse event variables such as nausea, dizziness and sleepiness. The buprenorphine concentrations assessed in the analysis ranged from 0 to 500 pg/ml.

Overall, none of the analyzed pharmacodynamic variables showed any clear trends in relation to buprenorphine plasma concentration.

3. What are the basic pharmacokinetic characteristics of BTDS?

Bioavailable buprenorphine is highly bound to plasma proteins (96%) and distributes extensively throughout the body (V_d = 430 L). Buprenorphine is cleared by CYP3A4-mediated metabolism and by glucuronide conjugation. Norbuprenorphine is thought to be the only active metabolite of buprenorphine. The systemic exposure of norbuprenorphine is generally 1-5% of that of buprenorphine.

Following a single BTDS 10 application, it generally takes 17 hrs for delivery of detectable systemic levels of buprenorphine (25 pg/ml).

Buprenorphine is highly bound to plasma proteins (96%). It also distributes extensively throughout the body as evidenced by a V_d of 430 L. Published studies have shown that buprenorphine CSF concentrations were 15-25% of concurrent plasma concentrations.

Based on *in vitro* studies, little metabolism of buprenorphine appears to take place in the skin. Bioavailable buprenorphine is eliminated by hepatic metabolism, with subsequent biliary and renal excretion. Hepatic metabolism of buprenorphine results in two major metabolites, Norbuprenorphine (by CYP3A4) and buprenorphine-3-O-glucuronide (by UGT1A1/1A3). Total clearance of buprenorphine was estimated at 55 L/hr in postoperative patients. A complete summary of the pharmacokinetic results is provided in appendix 2.

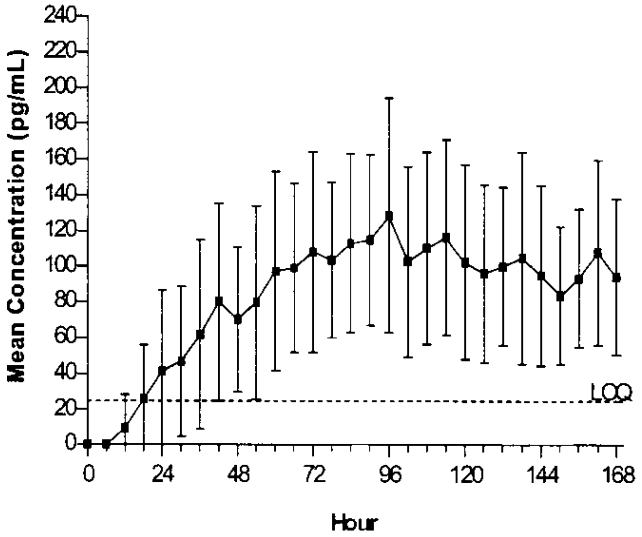


Fig. 2. Mean plasma conc-time profile for buprenorphine following BTDS 10 administration (study BP96-0803).

4. What is the fraction of buprenorphine that is bioavailable after application of BTDS?

The absolute bioavailability of buprenorphine from the three dose strengths of BTDS ranged within 15-16% after a 7-day application period.

The results of study BP97-0501 indicate that the absolute bioavailabilities of BTDS 5, 10 and 20 are 16%, 15% and 16%, respectively after a 7-day application period.

5. Is the pharmacokinetics of BTDS linear?

Exposure metrics suggest that dose proportionality exists for all three dose strengths over a 7-day application period. However, the same trend is not evident over a 3-day application period.

One early study, BP96-0304, evaluated the single-dose pharmacokinetics of the 3 Norspan dose strengths over a 3-day application period. The results indicate that the 5 and 10 mg dose strengths were similar, while the 20 mg dose strength was clearly different from the 10 mg strength. A similar study conducted in patients with moderate to severe pain following orthopedic surgery (BP96-0104) indicated there were major deviations from dose proportionality on AUC and C_{max} for all three dose strengths.

Another study, BP97-0501, which evaluated the single-dose pharmacokinetics of the 5, 10 and 20 mg strengths of Norspan suggested dose proportionality between all three dose strengths on AUC. However, major deviations were observed for the C_{max} data.

Two studies, BP96-0101 (6-day duration) and BP-0102 (7-day duration), point to dose proportionality on AUC and C_{max} for all three dose strengths over a 6-7 day application period.

Overall the data suggest that dose proportionality exists with the 7-day application period, but not with the 3-day application period.

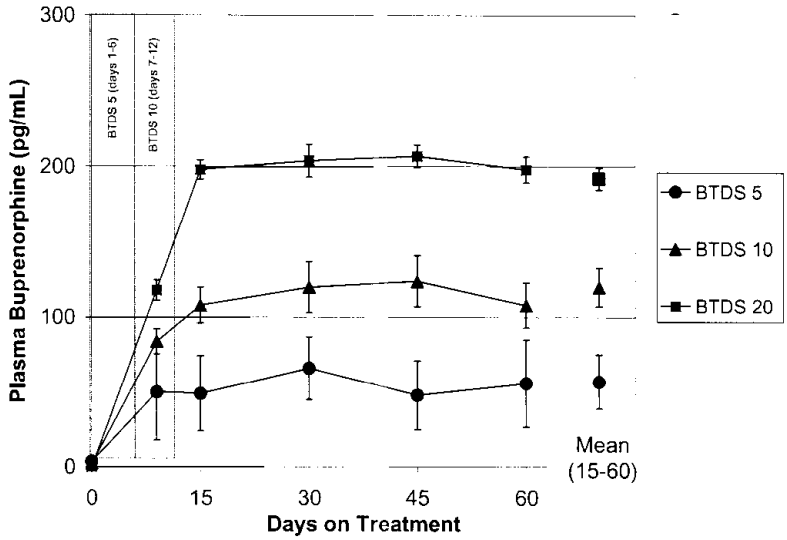


Fig. 3. Mean plasma buprenorphine conc-time profiles by day (study BP96-0102)

6. What are the flux rates of BTDS applications?

Combined data from studies with 7-day application periods indicate that the flux rates for BTDS 5, 10 and 20 are 5 µg/hr, (7.3-10) µg/hr and 20 µg/hr, respectively.

Early study reports in the NDA submission used 12.5, 25 and 50 µg/hr as the nominal flux rates for BTDS 5, 10 and 20, respectively. Subsequently, ensuing study reports used values of 5, 10 and 20 µg/hr as the nominal flux rates for BTDS 5, 10 and 20, respectively. The sponsor contended that the initial flux rate values were determined in a pilot study in 1992 using residual analysis. Subsequent studies relied on multiple approaches to determine flux rates and pointed to the latter values of flux rates as being a more appropriate designation for flux rates.

Studies suggest that the mean flux rates over a 7-day application period are 5, 10 and 20 µg/hr for BTDS 5, 10 and 20, respectively. However, for a 3-day application period, the mean flux rates are (6-7.5), (5.8-17) and (34-39) µg/hr for BTDS 5, 10 and 20, respectively. Hence, the flux rates for the 3-day application period appear to clearly differ from those of the 7-day application period.

Table 1. Summary of the pooled flux rate data for studies with BTDS applications

	BP96-0304 (3-day)	BP96-0104 (3-day)	BP96-1102 (3-day)	BP96-0501 (7-day)	BP96-0702 (7-day)	BP96-0803 (7-day)	BP97-0501 (7-day)
BTDS 5	**6**	**7.5**	**---**	**---**	**---**	**---**	**5**
BTDS 10	**17**	**15.8**	**14.3**	**9.5-10**	**8.5**	**7.3**	**10**
BTDS 20	**34**	**39.1**	**---**	**---**	**---**	**---**	**20**

7. Can BTDS be applied interchangeably to different body sites?

Application of BTDS 10 to the midaxillary line, the upper outer arm, the upper chest or the upper back resulted in comparable systemic buprenorphine levels. BTDS applications may be applied interchangeably to all 4 sites for an application period of 7 days.

In study BP96-0501, a single BTDS 10 applied to the midaxillary line, the upper outer arm, the upper chest or the upper back resulted in similar exposure metrics with all four application sites. Using the midaxillary line as the reference, the largest difference was observed with the application to the upper back, where the AUC test/reference ratio was 1.26.

Overall, BTDS application to the midaxillary line and the upper chest sites may be considered interchangeable over an application period of 7 days. However, applications to the midaxillary line may not be considered interchangeable with those to the upper outer arm and the upper back, since those two sites resulted in increases in exposure of up to 37% and 46%, respectively, relative to the midaxillary line. It should be noted that in another study (BP96-0501), a 26-55% increase in buprenorphine plasma levels with local heat pad application was associated with a significant increase in opioid-related adverse events.

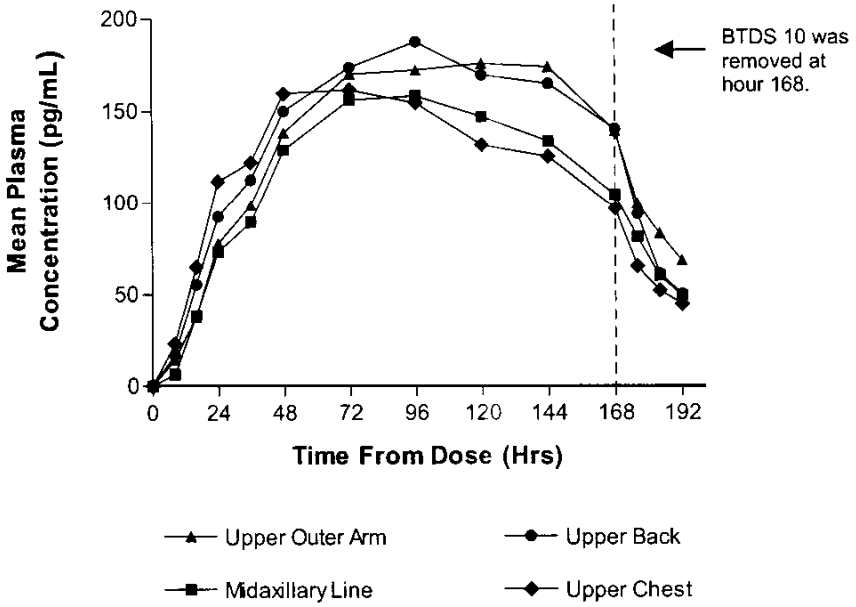


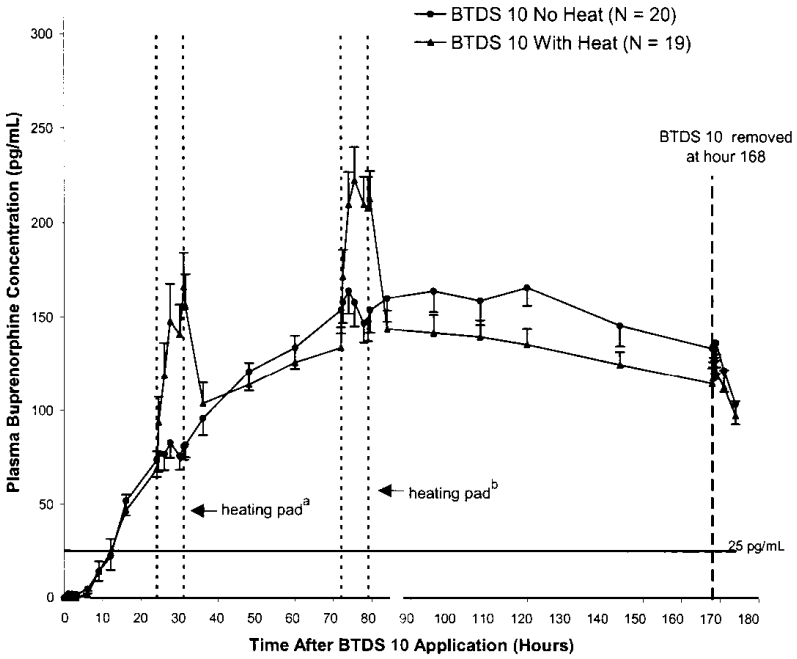
Fig 4. Mean plasma buprenorphine conc-time profiles following administration of BTDS 10 to four different application sites on the body

8. What is the effect of heat on buprenorphine pharmacokinetics?

Fever (internal heat) did not alter the pharmacokinetics of buprenorphine with BTDS applications. However, application of external heat resulted in 26-55% higher C_{max} relative to application without heat.

Induction of fever in subjects on BTDS (BP96-1102) did not show a difference in buprenorphine pharmacokinetics relative to subjects without fever. Application of a heating pad to BTDS for three 2-hr intervals over a 7 hr period on days 2 and 4 resulted in a 26-55% increase in systemic buprenorphine concentrations relative to BTDS treatment without heat. Albeit not deemed clinically relevant, there was a clear increase in opioid-related adverse events with the heating pad application.

0As a result of the aforementioned studies, the sponsor incorporated the following language in the labeling; (b) (4)



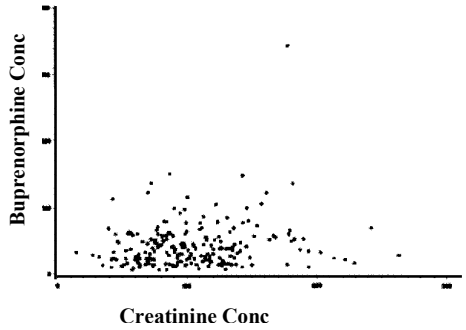
[a]Day 2: heating pad applied hours 24 to 26, 26.5 to 28.5, and 29 to 31
[b]Day 4: heating pad applied hours 72 to 74, 74.5 to 76.5, and 77 to 79
Limit of quantitation = 25 pg/mL

Fig. 5. Mean plasma conc-time profiles following administration of BTDS 10 applications with and without a heat pad.

9. Is there a need for dosage adjustment?

9.1. Special populations

Renal Impairment: No studies have been carried out by the sponsor to evaluate the impact of renal impairment on the pharmacokinetics of buprenorphine. Buprenorphine is primarily cleared by metabolism. Thus, impaired renal function is unlikely to have a major effect on buprenorphine pharmacokinetics. An analysis of pooled data from Phase III studies showed no clear trends in the relationship of creatinine clearance and buprenorphine plasma levels (see figure below). There is no need for dose adjustment with renal function.



Hepatic Impairment: In a study involving patients with mild to moderate hepatic impairment, similar systemic exposures (AUC) but a 50% reduction in C_{max} were observed when comparing systemic buprenorphine levels from healthy subjects to that of patients with mild to moderate hepatic impairment.

The systemic exposure to norbuprenorphine did not seem to be affected by mild to moderate hepatic impairment. The sponsor did not evaluate patients with severe hepatic impairment in the study. The interpretation of the results of the study is obscured by the fact that the sponsor used pooled data from patients with mild to moderate hepatic impairment. Thus, the sponsor should re-analyze the study data by hepatic impairment subgroup.

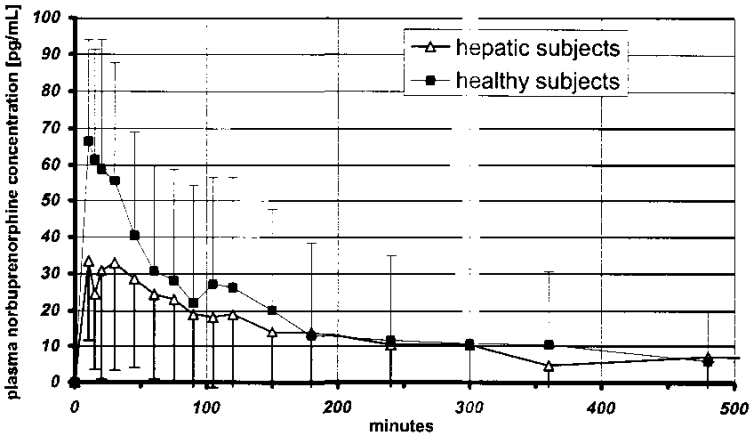
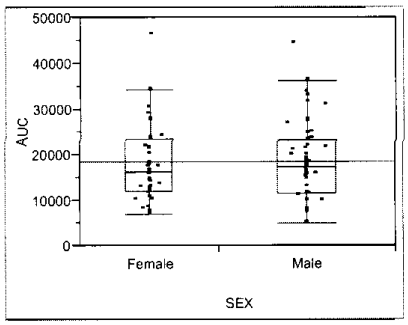
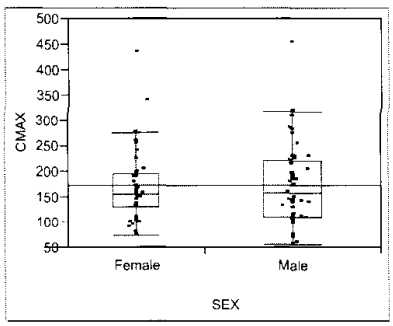


Fig. 6. Mean plasma buprenorphine conc-time profiles after adminisration of buprenorphine I.V. infusion (0.3 mg) in healthy subjects and patients with mild to moderate hepatic-impairment

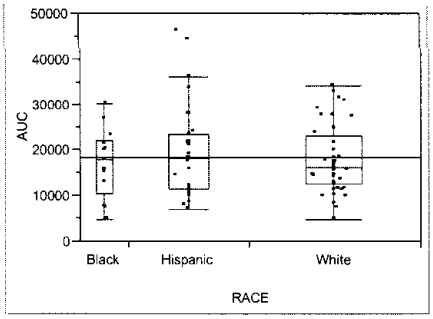
Age: The effect of age on buprenorphine pharmacokinetics was investigated in study BP96-0702 and using analysis of pooled clinical pharmacology studies. Overall, no significant age effect was observed on buprenorphine pharmacokinetics (see figure below). There is no need for dose adjustment in the elderly.

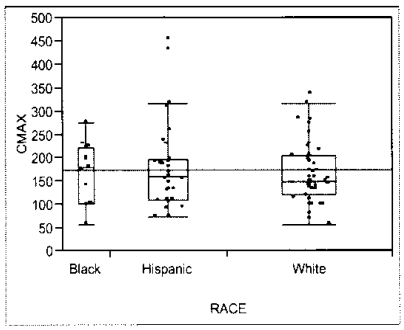
Gender: The effect of gender on buprenorphine pharmacokinetics was investigated using analysis of pooled clinical pharmacology studies. Overall, no significant gender effect was observed on buprenorphine pharmacokinetics (see figures below). There is no need for dose adjustment in women.



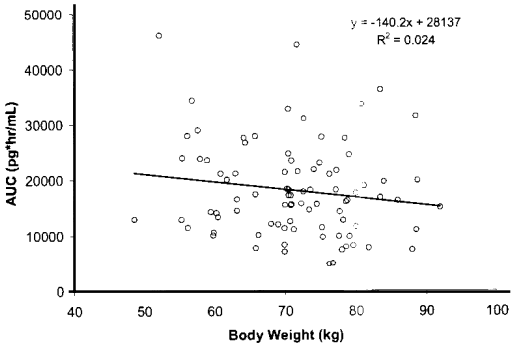


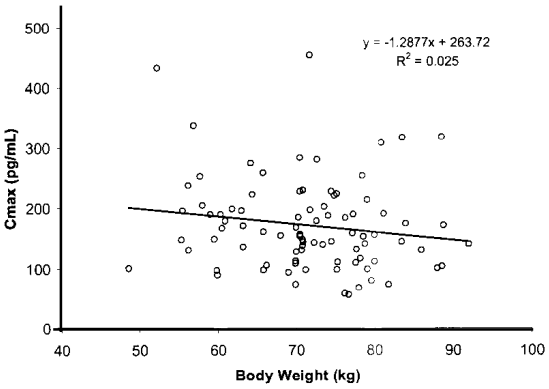
Ethnicity: The Clinical Pharmacology studies undertaken by the sponsor included subjects from a wide range of ethnic backgrounds (mainly Black, Hispanic and White). The effect of ethnicity on buprenorphine pharmacokinetics was investigated using analysis of pooled clinical pharmacology studies. Overall, no significant ethnicity effect was observed on buprenorphine pharmacokinetics (see figures below). Preliminary data suggest that there is no need for dose adjustment based on ethnicity.





Body Weight: The effect of body on buprenorphine pharmacokinetics was investigated using analysis of pooled clinical pharmacology studies. Overall, a small decrease in buprenorphine C_{max} and AUC were observed with an increase in body weight (see figures below).





9.2. Drug-Drug Interactions

Based on *in vitro* studies in human microsomes and hepatocytes, buprenorphine does not seem to inhibit the metabolism of CYP450 enzymes at clinically relevant concentrations (PKDM-BUP-DM002). The sponsor has not conducted any *in vivo* metabolic drug-drug interaction studies. The sponsor indicates that metabolism of buprenorphine is not expected to be affected by CYP3A4 inhibition as multiple pathways are involved in the clearance of buprenorphine. However, published data suggest that potent CYP3A4 inhibitors such as some HIV inhibitors (ritonavir, indinavir and sequinavir) and

ketoconazole might result in clinically relevant drug-drug interactions when co-adminsitered with buprenorphine (Iribarne *et al.*, 1998).

The sponsor also investigated the potential pharmacodynamic interactions between BTDS on one hand and midazolam (BP97-1001), prochlorperazine (BP98-0202) and thiazide diuretics (BP97-0303) on the other. Overall, similar pharmacokinetic and safety profiles were observed.

No clinically relevant pharmacodynamic drug-drug interactions were noted when buprenorphine was co-adminsitered with midazolam, prochlorperazine or thiazide diuretics. Appropriate statements warning of potential drug-drug interactions should be incorporated into the labeling.

In Vitro Inhibition of Norbuprenorphine Formation From Buprenorphine by CYP3A4 Inhibitors in Human Liver Microsomes

Inhibitor	Ki (μM)
Ketoconazole	0.6
Ritonavir	0.02
Indinavir	0.8
Saquinavir	7
Nifedipine	129
Fluoxetine	N
Norfluoxetine	100
Fluvoxamine	260

N = No inhibition
Iribarne, et al, 1998

10. Were the bioanalytical methods utilized in the Clinical pharmacology studies adequately validated?

The bioanalytical method was specific, precise, sensitive, linear and reproducible.

The analytical assay utilized throughout the Clinical Pharmacology and Biopharmaceutics-related studies relied on liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS). The analytical assay was adequately validated with respect to sensitivity, specificity, precision and reproducibility (see Appendix 3).

11. Were the dissolution test conditions and specifications appropriately selected?

The selected dissolution method appears to be a reasonable surrogate for stability testing of BTDS 5, 10 and 20 mg. However, the sponsor needs to include at least one additional sampling time point between 2 and 24 hrs to better characterize the dissolution profile of BTDS. Also, the sponsor should consider tighter specifications for passing the dissolution test as the current proposed criteria seem to be too broad.

The proposed dissolution rate test relied on USP method 6 (rotating cylinder, 50 rpm), whereby 600 ml of 0.9% sodium chloride solution is heated to 32° C. (b) (4) The dissolution medium is sampled at 0.5, 2 and 24 hrs. An HPLC/UV analytical method is used for subsequent analysis of samples.

Batch analyses were conducted for several batches of BTDS 5, 10 and 20, which were primarily used for evaluation of stability. All the tested batches met the specifications set by the sponsor (see appendix 2). Based on the observed dissolution data, the sponsor should consider setting tighter dissolution specifications. In addition, the sponsor made no attempts at establishing an *in vitro*/*in vivo* correlation for BTDS.

Proposed Dissolution Specifications

Test Point	Percent Buprenorphine Dissolved
0.5	(b) (4)
2	
24	

12. Does the proposed labeling language for BTDS conform with CPB study findings?

See Appendix 4 for the proposed Clinical Pharmacology and Biopaharmaceutics-related labeling language for BTDS.

Appendix 1

3.6.14.1. Table of Analytical Methodology Studies

TABLE 3.6.14.1.

Buprenorphine Method Reports – Clinical Studies

Study	Title	Analyte Method	Method/Number Issue Date	Method Validation Report	Matrix	Sample Size (mL)	Calibration Range	Analytical Site
Clinical Pharmacology								
BP95-0901	IV vs Single vs Multi Dose	Buprenorphine LC/MS/MS	NO PK DATA REPORTED Bioanalytical Error (Ref Report No. PDM#96-1030M)					(b) (4)
BP96-0304	Dose Prop	Buprenorphine LC/MS/MS	TM-332	TM-332	Plasma	0.5	25-600 pg/mL	
BP96-0501	Sites	Buprenorphine LC/MS/MS	PDM #97-0812M:0	PDM #97-0812V:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP96-0702	Elderly	Buprenorphine LC/MS/MS	PDM #97-0812M:0	PDM #97-0812V:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP96-0803	7-day Duration of Application	Buprenorphine LC/MS/MS	PDM #97-0812M:0	PDM #97-0812V:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP96-1102	Two temp (endo)	Buprenorphine LC/MS/MS	TM-332	TM-332	Plasma	0.5	25-600 pg/mL	(b) (4)
BP97-0112	Hepatic (PRA)	Buprenorphine/ Norbuprenorphine LC/MS/MS	PDMBA-BUP-MR-0599:2	PDMBA-BP1298VP-VR-0599:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP97-0303	Hypotension	Buprenorphine/ Norbuprenorphine LC/MS/MS	PDMBA-BUP-MR-0599:2	PDMBA-BP1298VP-VR-0599:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP97-0501	IV Absol BA (PRA)	Buprenorphine/ Norbuprenorphine LC/MS/MS	PDMBA-BUP-MR-0599:2	PDMBA-BP1298VP-VR-0599:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP97-1001	Resp Depress w/ Midazol	Buprenorphine/Midazolam Fentanyl LC/MS/MS	TM-332 TM-360 TM-343	TM-332 TM-360 TM-343	Plasma	0.5 (bup) 0.05 (midzim) 0.5 (fent)	25-600 pg/mL (bup) 5-150 ng/mL (midzim) 0.05-15 ng/mL (fent)	(b) (4)
BP98-0201	Flux Rate	Buprenorphine LC/MS/MS	PKDM BP0897M:1	PKDM BP0897V:1	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.

TABLE 3.6.14.1. (continued)

Buprenorphine Method Reports – Clinical Studies

Study	Title	Analyte Method	Method/Number Issue Date	Method Validation Report	Matrix	Sample Size (mL)	Calibration Range	Analytical Site
Clinical Pharmacology (continued)								
BP98-0202	Resp Depress w/ Prochlor	Buprenorphine, Prochlorperazine, Fentanyl LC/MS/MS	TM-332 TM-351 TM-343	TM-332 TM-351 TM-343	Plasma	0.5 (bup) 0.2 (proc) 0.5 (fent)	25-600 pg/mL (bup) 5.47-1090 ng/mL (proc) 0.05-15 ng/mL (fent)	(b) (4)
BP98-1204	Ext Heat	Buprenorphine LC/MS/MS	PDMBA-BUP-MR-0599:2	PDMBA-BP1298VP-VR-0599:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center, Ardsley, N.Y.
BP99-0204	Steady State	Buprenorphine LC/MS/MS	PDMBA-BUP-MR-0599:2	PDMBA-BP1298VP-VR-0599:0	Plasma	0.5	25-600 pg/mL	Purdue Research Center Ardsley, N.Y.
Phase 2 Trials								
BP96-0104	Post OP	Buprenorphine LC/MS/MS	TM-332	TM-332	Plasma	0.5	25-600 pg/mL	(b) (4)
Phase 3 Trials								
BP96-0101	Osteo, Percocet	Buprenorphine LC/MS/MS	20442 1 20442 2	20442 1 20442 2	Plasma	1.0	25-600 pg/mL	(b) (4)
BP96-0102	Low Back, Percocet	Buprenorphine LC/MS/MS	V1330P1	V1330P1	Plasma	1.0	25-600 pg/mL	

Appendix 2

Clinical Pharmacology – Single Application Studies
Summary of Mean (SD) Pharmacokinetic Metrics

Study No.	Dose (mg)	Day	Analyte	N	Cmax (pg/mL)	Tmax (h)	AUC (pg·h/mL)	AUC∞ (pg·h/mL)	T½ (h)
BP96-0304	2 x BTDS 5	3	Buprenorphine	16	190 ± 66	70 ± 13	12070 ± 5065	ND	25 ± 10
	BTDS 10	3	Buprenorphine	15	222 ± 91	68 ± 13	14028 ± 5182	ND	26 ± 9
	BTDS 20	3	Buprenorphine	17	307 ± 99	71 ± 9	20467 ± 7178	ND	24 ± 7
BP96-0501	BTDS 10	7	Buprenorphine	20	178 ± 78	95 ± 32	21731 ± 10191	ND	ND
	BTDS 10	7	Buprenorphine	20	199 ± 88	115 ± 34	25250 ± 10726	ND	ND
	BTDS 10	7	Buprenorphine	20	188 ± 91	84 ± 35	22647 ± 9668	ND	ND
	BTDS 10	7	Buprenorphine	20	207 ± 63	100 ± 32	25706 ± 8357	ND	ND
BP96-0702	BTDS 10	7	Buprenorphine	12	152 ± 56	122 ± 45	18543 ± 6992	ND	ND
	BTDS 10	7	Buprenorphine	12	170 ± 72	98 ± 36	20011 ± 7915	ND	ND
BP96-0803	BTDS 10	7	Buprenorphine	12	142 ± 57	107 ± 26	14140 ± 7279	ND	ND
BP96-1102	BTDS 10	7	Buprenorphine	20	138 ± 99	68 ± 11	6144 ± 4029	8731 ± 4576	39 ± 40
	BTDS 10	7	Buprenorphine	20	131 ± 84	71 ± 6	6209 ± 4957	8523 ± 5268	39 ± 50
BP98-1204	BTDS 10	7	Buprenorphine	19	190 ± 55	111 ± 37	21798 ± 6960	ND	ND
	BTDS 10	7	Buprenorphine	19	238 ± 80	73 ± 11	20624 ± 6199	ND	ND

(Cross-references: Tables 14.4.2, 14.4.3, 14.4.4, and 14.4.5 in CSR BP96-0304; Tables 14.4.2, 14.4.3, and 14.4.4.1 in CSR BP96-0501; Table 14.4.3 in CSR BP96-0702; Table 14.4.2 in CSR BP96-0803; Table14.4.5 in CSR BP96-1102; Table 14.4.5 in CSR BP99-1204.)

Clinical Pharmacology – Single Application Studies
Summary of Mean ± SE (N) Pharmacokinetic Metrics

Study No.	Dose (mg)	Days	Analyte	Cmax (pg/mL)	T max (h)	AUC (pg/mL·h)	AUC∞ (pg/mL·h)	T½ (h)
BP97-0501	BTDS 5	7	Buprenorphine	179 ± 34 (12)	107 ± 10 (12)	12647 ± 2015 (12)	12087 ± 1839 (6)	17 ± 4 (6)
	BIV		Buprenorphine	438 ± 29 (12)	24 ± 0.01 (12)	9543 ± 486 (12)	10753 ± 772 (8)	8 ± 1 (8)
	BTDS 10	7	Buprenorphine	191 ± 19 (12)	99 ± 12 (12)	24311 ± 2355 (12)	27035 ± 2444 (10)	26 ± 4 (10)
	BIV		Buprenorphine	443 ± 27 (11)	24 ± 1.4 (11)	9887 ± 575 (11)	10669 ± 554 (9)	6 ± 1 (9)
	BTDS 20	7	Buprenorphine	471 ± 77 (9)	90 ± 13 (9)	51106 ± 6156 (9)	54294 ± 6919 (8)	35 ± 4 (8)
	BIV		Buprenorphine	461 ± 49 (8)	24 ± 0.04 (8)	9043 ± 487 (8)	9929 ± 540 (8)	9 ± 1 (8)
	BTDS 5	7	Norbuprenorphine	52 ± 10 (12)	116 ± 19 (12)	4248 ± 1507 (11)	ND	ND
	BIV		Norbuprenorphine	50 ± 3 (12)	30 ± 2 (12)	882 ± 113 (12)	ND	ND
	BTDS 10	7	Norbuprenorphine	64 ± 11 (12)	126 ± 18 (12)	7610 ± 1711 (11)	ND	ND
	BIV		Norbuprenorphine	44 ± 9 (10)	26 ± 3 (10)	685 ± 170 (9)	ND	ND
	BTDS 20	7	Norbuprenorphine	136 ± 14 (9)	141 ± 13 (9)	20434 ± 3282 (9)	ND	ND
	BIV		Norbuprenorphine	51 ± 6 (8)	30 ± 2 (8)	919 ± 205 (8)	ND	ND
BP98-0201	BTDS 10	1	Buprenorphine	168 ± 34 (12)	30 ± 2.2 (12)	5017 ± 1218 (12)	9223 ± 1595 (6)	18 ± 2.6 (6)
	BTDS 10	2	Buprenorphine	157 ± 29 (11)	49 ± 0.3 (11)	6390 ± 1272 (11)	8923 ± 1516 (7)	16 ± 1.8 (7)
	BTDS 10	3	Buprenorphine	157 ± 16 (12)	70 ± 2.7 (12)	8554 1062 (12)	10330 1517 (8)	16 ± 2.4 (8)
	BTDS 10	4	Buprenorphine	159 ± 23 (11)	82 ± 7.3 (11)	10289 ± 1435 (11)	12288 ± 1609 (9)	20 ± 2.8 (9)
	BTDS 10	5	Buprenorphine	172 ± 17 (12)	92 ± 9.1 (12)	15385 ± 1857 (12)	18417 ± 2144 (9)	23 ± 4.9 (9)
	BTDS 10	6	Buprenorphine	188 ± 27 (12)	84 ± 6.1 (12)	17050 ± 1985 (12)	21330 ± 2553 (8)	28 ± 5.9 (8)
	BTDS 10	7	Buprenorphine	213 ± 28 (11)	86 ± 11 (11)	23088 ± 3271 (11)	26426 ± 4201 (8)	16 ± 1.9 (8)

(Cross-references: Tables 14.4.6 in CSR BP97-0501; Tables 14.4.3 and 14.4.4 in CSR BP98-0201.)

Clinical Pharmacology – Single Application Study
Mean (SD) Pharmacokinetic Metrics

Study No.	Dose (mg)	Days	Analyte	N	Cmax (pg/mL)	T max (min)	AUC (pg·min/mL)	AUC∞ (pg·min/mL)	T½ (min)	Cltot (mL/min)	Vd(ss) (L)
BP97-0112	Buprenex® 0.3 mg/mL IV (Healthy)	1	Buprenorphine	12	11770 ± 6983	11 ± 2	342299 ± 80042	415873 ± 113917	759 ± 456	779 ± 247	430 ± 288
	Buprenex® 0.3 mg/mL IV (Hepatically Impaired)	1	Buprenorphine	12	5798 ± 3310	12 ± 3	316790 ± 84773	427908 ± 112705	902 ± 426	741 ± 174	639 ± 392
	Buprenex® 0.3 mg/mL IV (Healthy)	1	Norbuprenorphine	12	75 ± 33	14 ± 6	12723 ± 21479	44230 ± 79802	550 ± 1093	ND	ND
	Buprenex® 0.3 mg/mL IV (Hepatically Impaired)	1	Norbuprenorphine	10	53 ± 22	33 ± 36	17893 ± 20819	119610 ± 184932	3160 ± 4248	ND	ND

(Cross-reference: Table 14.4.3 in CSR BP97-0112.)

Clinical Pharmacology – Multiple Application Studies
Summary of Pharmacokinetic Metrics (Mean ± 1 SE)

Study No.	Dose (mg)	Days	Analyte	N	Cmin (pg/mL)	AUC (pg·h)/ml	Cavg (pg/mL)
BP99-0204	BTDS 5 (Week 1)	7	Buprenorphine	27	53 ± 6	9459 ± 901	56 ± 5
	BTDS 5 (Week 2)	7	Buprenorphine	27	58 ± 6	11482 ± 914	68 ± 5
	BTDS 5 (Week 3)	7	Buprenorphine	27	57 ± 5	15827 ± 1385	94 ± 8

(Cross-reference: Table 14.4.2 in CSR BP99-0204.)

Clinical Pharmacology – Multiple Application Studies
Summary of Pharmacokinetic Metrics (Mean ± SE)

Study No.	Dose (mg)	Days	Analyte	N	Cmax (pg/mL)	Tmax (h)	AUC (pg·h/mL)	AUC∞ (pg·h/mL)	T½ (h)
BP97-0303	BTDS 5, 10 & 20 (Young Healthy)	13	Buprenorphine	11	722 ± 82	178 ± 5	86026 ± 7808	87485 ± 8867	29 ± 3
	BTDS 5, 10 & 20 (Elderly Healthy)	13	Buprenorphine	10	562 ± 78	181 ± 6	78674 ± 7707	81129 ± 8034	33 ± 4
	BTDS 5, 10 & 20 (Elderly Hypertension)	13	Buprenorphine	11	610 ± 58	208 ± 13	94022 ± 4242	99087 ± 4481	42 ± 2
	BTDS 5, 10 & 20 (Young Healthy)	13	Norbuprenorphine	11	191 ± 21	240 ± 16	31359 ± 3447	33535 ± 3945	45 ± 7
	BTDS 5, 10 & 20 (Elderly Healthy)	13	Norbuprenorphine	10	158 ± 18	257 ± 14	26210 ± 3102	30913 ± 3976	48 ± 5
	BTDS 5, 10 & 20 (Elderly Hypertension)	13	Norbuprenorphine	11	260 ± 40	295 ± 13	37695 ± 4023	ND	ND

(Cross-references: Tables 14.4.3 and 14.4.4 in CSR BP97-0303.)

Appendix 3

Proposed Dissolution Specifications

Test Point	Percent Buprenorphine Dissolved
0.5	(b) (4)
2	
24	

Batch Analysis Table for BTDS 5, 10, and 20 mg

Test	Method No.	Batch Number		
		Batch # 7/01081/8		
Dissolution		5 mg	10 mg	20 mg
0.5 Hour[a]		(b) (4)		
2 Hours				
24 Hours				
		Batch # 7/00499/6		
Dissolution		5 mg	10 mg	20 mg
0.5 Hour[a]		(b) (4)		
2 Hours				
24 Hours				
		Batch # 7/01508/6		
Dissolution		5 mg	10 mg	20 mg
0.5 Hour[a]		(b) (4)		
2 Hours				
24 Hours				
		Batch # 7/00067/7		
Dissolution		5 mg	10 mg	20 mg
0.5 Hour[a]		(b) (4)		
2 Hours				
24 Hours				

(Cross-references: LST Stability Report [Tables 1-4, 11-14, and 21-24].)

NT = Not tested as per protocol.

[a]The 0.5 hour time interval was not tested as per protocol.

[b]At the time of testing, no specification for individual values was in place, therefore, no additional testing was required.

Appendix 4

9 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix 5

NDA: **21-306/ Study BP96-0803** **Study Date**: **Oct-Nov 1996**

Type of Submission: **Single Dose PK Study**

Study **BP96-0803** is entitled,

*"A PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF BUPRENORPHINE TDS 25 μg/hr SINGLE APPLICATION TO DETERMINE THE PHARMACOLOGIC ACTIONS AND DURATION OF WEAR FOR THE 12.5 μg/hr PLACEBO, 25 μg/hr ACTIVE, AND THE 50 μg/hr PLACEBO BTDS IN HEALTHY ADULT VOLUNTEERS"***.**

Objectives

- To determine the pharmacokinetics of the BTDS 10 applied as a single dose over a 7-day period.

Study Design

Healthy young adult subjects (n = 24 (12 males and 12 females), Age 22-42 yrs, Wt 56-88 kg) wore one of 3 BTDS applications (single BTDS 10, single small placebo TDS and single large placebo TDS) for 7 days. The study was conducted in an open-label, single-treatment, single-period fashion. In each treatment arm, blood samples were drawn for determination of buprenorphine at 0 (pre-dose), 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126, 132, 138, 144, 150, 156, 162 and 168 hrs post-dose. The pharmacodynamic markers were assessed according to the same schedule.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml. Residual buprenorphine were determined by an HPLC/UV method validated over a linear range of 2-160 μg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$. Equivalence of the reference treatment, BTDS 10, and the two test treatments BTDS 5 & 20 was assessed by comparison of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} using one-way ANOVA**.** In addition, 90% confidence intervals were estimated around ratios of least squares means of log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Pharmacodynamics

A visual analog scale (VAS) of 0 to 100 was used to quantify the extent of the opioid side effects (overall drug effect, nausea, dizziness and sleepiness) experienced by each subject.

Results

Table 2. Summary of the primary pharmacokinetic parameters for buprenorphine

Metric	n	Arithmetic Mean (SD)
AUC (pg·h/mL)	18	14,140 (7279)
Cmax (ng/mL)	24	142 (57)
tmax (h)	24	107 (26)

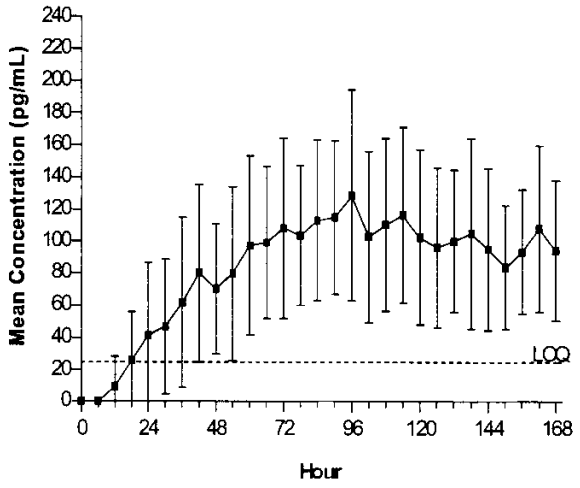


Fig. 7. Mean plasma conc-time profile for buprenorphine following BTDS 10 administration

Reviewer's Comments

- **Administration of BTDS 10 over a 7-day period appeared to be safe and tolerated.**
- **The mean 7-day flux for BTDS 10 system, as determined by residual analysis in the study, was 7.3 μg/hr.**
- **Pharmacokinetic-pharmacodynamic relationships were not explored via modeling due to high inter-subject variability in the measured pharmacodynamic markers. However, the mean VAS for overall drug effect and opioid side effects was higher for the BTDS 20 treatment.**
- **Hypotension was observed in 12 subjects for the 2 X BTDS 5 treatment, 15 subjects for the BTDS 10 treatment and 23 subjects for the BTDS 20 treatment.**

NDA: **21-306/ Study BP97-0501** **Study Date**: **Mar-May 1998**

Type of Submission: **Bioavailability Study**

Study **BP97-0501** is entitled,

"A RANDOMIZED, CROSSOVER, PHARMACOKINETIC STUDY TO CHRACTERIZE THE ABSOLUTE BIOAVAILABILITY OF BUPRENORPHINE TDS".

Objectives

- To determine the absolute bioavailability of buprenorphine administered as BTDS in 5, 10 and 20 mg strengths for 7-day application.

Study Design

Healthy subjects (36 males and females; 3 groups of 12 subjects each, Age 21-44 yrs, Wt 49-92 kg) wore 1 of 3 BTDS (BTDS 5, BTDS 10 or BTDS 20) for 7 days in one treatment period, and received buprenorphine I.V. at an infusion rate of 25 µg/hr for 24 hrs in the other treatment period. Each subject was randomly assigned to one of the two sequences. A 2-10 day washout period separated the treatment periods. The study was conducted in a randomized, two treatment, two period, crossover fashion. Blood samples were drawn for determination of buprenorphine and norbuprenorphine at the following time points:

(for BTDS) 0 (pre-dose), 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 108, 120, 132, 144, 156, 168, 168.25, 168.5, 168.75, 169, 170, 171, 172, 174, 180, 192, 216, 240, 264, 288, 312 and 336 hrs post-dose.

(for buprenorphine I.V.) 0, 5, 10, 20 and 30 min, 1, 2, 4, 8, 12, 18 and 24 hrs (after start of infusion), 2, 5, 10, 20 and 30 min, 1, 1.5, 2, 4, 6, 8 and 12 hrs (after stopping infusion). Pharmacodynamics were not assessed in the current study.

Analytical Assay

Plasma samples were analyzed for buprenorphine and norbuprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for both healthy subjects and patients with mild to moderate hepatic impairment: **F (absolute bioavailability),** $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$.

Results

Table 3. Summary of the primary pharmacokinetic parameters of **buprenorphine**

Metric	BTDS 5 (N = 12)		BTDS 10 (N = 12)		BTDS 20 (N = 11)	
	BTDS	BIV	BTDS	BIV	BTDS	BIV
	Arithmetic Mean ± SE (N)					
AUC (pg·h/mL)	12647 ± 2015 (12)	9543 ± 486 (12)	24311 ± 2355 (12)	9887 ± 575 (11)	51106 ± 6156 (9)	9043 ± 487 (8)
AUC∞ (pg·h/mL)	12087 ± 1839 (6)	10753 ± 772 (8)	27035 ± 2444 (10)	10669 ± 554 (9)	54294 ± 6919 (8)	9929 ± 540 (8)
Cmax (pg/mL)	176 ± 34 (12)	438 ± 29 (12)	191 ± 19 (12)	443 ± 27 (11)	471 ± 77 (9)	461 ± 49 (8)
tmax (h)	107 ± 10 (12)	24 ± 0.01 (12)	99 ± 12 (12)	24 ± 1.4 (11)	90 ± 13 (9)	24 ± 0.04 (8)
t½ (h)	17 ± 4 (6)	8 ± 1 (8)	26 ± 4 (10)	6 ± 1 (9)	35 ± 4 (8)	9 ± 1 (8)
Absolute bioavailability (F)	0.16 ± 0.02 (12)		0.15 ± 0.02 (11)		0.16 ± 0.02 (8)	

(Cross-reference: Table 11.2.1A in CSR BP97-0501.)
Absolute bioavailability values in this table were calculated from AUC data.

Table 4. Summary of the primary pharmacokinetic parameters of **norbuprenorphine**

Metric	BTDS 5 (N = 12)		BTDS 10 (N = 12)		BTDS 20 (N = 11)	
	BTDS	BIV	BTDS	BIV	BTDS	BIV
	Arithmetic Mean ± SE (N)					
AUC (pg·h/mL)	4248 ± 1507 (11)	882 ± 113 (12)	7610 ± 1711 (11)	685 ± 170 (9)	20434 ± 3282 (9)	919 ± 205 (8)
Cmax (pg/mL)	52 ± 10 (12)	50 ± 3 (12)	64 ± 11 (12)	44 ± 9 (10)	136 ± 14 (9)	51 ± 6 (8)
tmax (h)	116 ± 19 (12)	30 ± 2 (12)	126 ± 18 (12)	26 ± 3 (10)	141 ± 13 (9)	30 ± 2 (8)

(Cross-reference: Table 11.2.1D in CSR BP97-0501.)

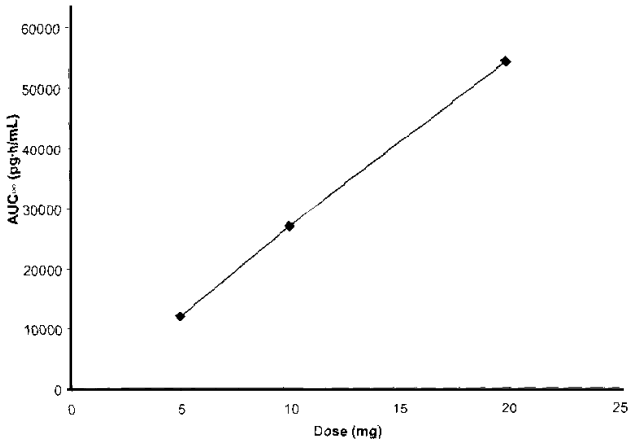


Fig. 8. Mean buprenorphine AUC vs. BTDS dose

Reviewer's Comments

- **Dose-adjusted mean ratios (AUC_{BTDS}/AUC_{BIV}) for BTDS 5, 10 and 20 were similar at 0.16, 0.15 and 0.16, respectively.**
- **AUC increased linearly with increasing dose, while deviations from linearity were observed for C_{max}. Dose proportionality was demonstrated for AUC across the 3 BTDS strengths evaluated, but not for C_{max}.**
- **The mean flux for the three BTDS strengths, as determined by 4 methods including residual analysis in the study, appeared to support nominal fluxes of 5, 10 and 20 μg/hr, respectively.**

NDA: **21-306/ Study BP96-0304** **Study Date**: **Sep-Oct 1996**

Type of Submission: **Bioequivalence & Dose Proportionality Study**

Study **BP96-0304** is entitled,

"A RANDOMIZED, CROSSOVER, ANALYTICALLY BLINDED SINGLE DOSE BIOEQUIVALENCE AND DOSE PROPORTIONALITY STUDY OF THREE STRENGTHS OF BUPRENORPHINE TRANSDERMAL SYSTEM IN NORMAL, HEALTHY, ADULT VOLUNTEERS".

Objectives

- To assess bioequivalence of two BTDS 5 systems vs. a single BTDS 10
- To assess the dose proportionality of the BTDS 10 and the BTDS 20

Study Design

Healthy male and female subjects (n = 28 (16 males & 12 females), age 23-45 years, Wt 62-95 kg) wore each of the BTDS 5, 10 & 20 treatments for 3 days. The study was conducted in a randomized, crossover fashion with a 10-day washout period separating successive BTDS applications. In each treatment period, blood samples were drawn for determination of buprenorphine at –0.5, 3, 6, 9, 12, 16, 24, 30, 36, 48, 60, 72 (before system removal), 72.25, 72.5, 72.75, 73, 75, 78, 84, 96, 108, 120, 132 and 144 hrs post-dose. The pharmacodynamic markers were assessed according to the same schedule.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml. Residual buprenorphine were determined by an HPLC/UV method validated over a linear range of 2-160 μg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: t_{max}, C_{max}, $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$. Equivalence of the reference treatment, BTDS 10, and the two test treatments BTDS 5 & 20 was assessed by comparison of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} using one-way ANOVA. In addition, 90% confidence intervals were estimated around ratios of least squares means of log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Pharmacodynamics

A visual analog scale (VAS) of 0 to 100 was used to quantify the extent of opioid side effects (overall drug effect, nausea, dizziness and sleepiness) experienced by each subject.

Results

Table 5. Summary of the primary pharmacokinetic parameters for buprenorphine

	Arithmetic Mean (SD); n		
Metric	**2 x BTDS 5**	**BTDS 10**	**BTDS 20 [a]**
AUC (pg·h/mL)	12070 (5065); 16	14028 (5182); 15	20467 (7178); 17
Cmax (pg/mL)	190 (66); 16	222 (91); 15	307 (99); 17
tmax (h)	70 (13); 16	68 (13); 15	71 (9); 17
t½ (h)	25 (10); 16	26 (9); 15	24 (7); 17

	LSM Ratio [b] (90% Confidence Interval) [c]	
Test/Reference	**AUC (pg·h/mL)**	**Cmax (pg/mL)**
2 x BTDS 5/BTDS 10	89% (67% to 118%)	93% (70% to 123%)
BTDS 20/BTDS 10	76% (58% to 101%)	72% (55% to 95%)

(Cross-reference: Table 11.2.1B in CSR BP96-0304.)

[a]Individual subject metrics for the BTDS 20 treatment period were dose-adjusted to BTDS 10 by dividing the value by 2. The mean AUC and Cmax were then calculated for comparison with BTDS 10.

[b]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUC and Cmax.

[c]90% confidence interval (CI) around the least squares means ratio.

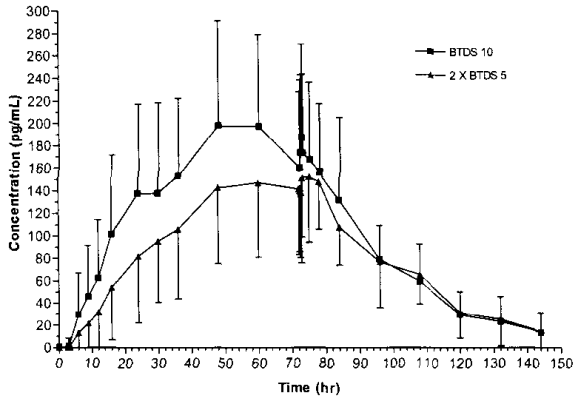


Fig. 9. Plasma conc-time profiles for BTDS 10 vs. 2 X BTDS 5

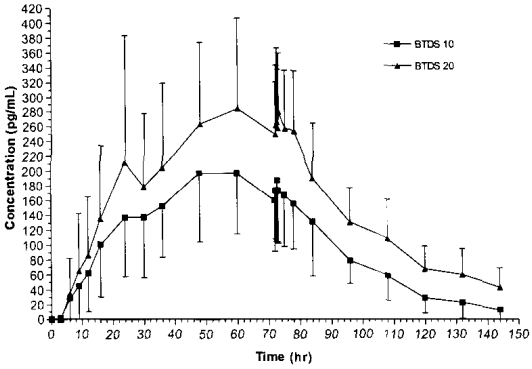


Fig. 10. Plasma conc-time profiles for BTDS 10 vs. 2 X BTDS 5

Reviewer's Comments

- **Dose adjusted exposure metrics indicated that BTDS 5 and BTDS 10 were similar, while large differences were evident between BTDS 10 and BTDS 20. Bioequivalence was not demonstrated between any two of the BTDS applications.**
- **Within 1 hr after system removal, mean buprenorphine plasma concentrations rose from 6-17% in proportion to the application dose strength.**
- **The mean flux for the three BTDS systems, as determined by residual analysis in the study, was 6 μg/hr for BTDS 5, 17 μg/hr for BTDS 10 and 34 μg/hr for BTDS 20.**
- **Pharmacokinetic-pharmacodynamic relationships were not explored via modeling due to high inter-subject variability in the measured pharmacodynamic markers. However, the mean VAS for overall drug effect and opioid side effects was higher for the BTDS 20 treatment.**
- **Hypotension was observed in 12 subjects for the 2 X BTDS 5 treatment, 15 subjects for the BTDS 10 treatment and 23 subjects for the BTDS 20 treatment.**

NDA: **21-306/ Study BP99-0204** **Study Date**: **May-Jun 1999**

Type of Submission: **Multiple Dose PK Study**

Study **BP99-0204** is entitled,

"AN OPEN-LABEL STUDY TO DETRMINE THE APPARENT TIME TO STEADY-STATE PLASMA CONCENTRATIONS FOLLOWING THE APPLICATION OF BUPRENORPHINE TRANSDERMAL SYSTEM (BTDS) AND THE EFFECTS OF LOCAL HEAT ON THE PLASMA CONCENTRATIONS OF BUPRENORPHINE AFTER BTDS REMOVAL".

Objectives

- To determine the time to steady state plasma concentrations following the application of BTDS 5 to healthy subjects.
- To determine effects on plasma buprenorphine concentrations of local heating in the first 3 hrs after removal of the third BTDS 5.

Study Design

Healthy young adult subjects (28 males and females, Age 18-43 yrs, Wt 48-98 kg) wore 3 sequential BTDS 5 applications for 7 days each. After BTDS 5 removal at the end of week 3, a subset of subjects received local heat application (3 hrs at 38°C). The study was conducted in an open-label, randomized, repeated-application, 3-period parallel fashion. In each treatment arm, blood samples were drawn for determination of buprenorphine at the following time points:

First BTDS 5 application: 0 (pre-dose), 1, 2, 3, 4 hrs post-dose on day 1, at 24, 48, 72, 96, 120, 144 and 168 hrs post-dose on days 2, 3, 4, 5, 6, 7 and 8.

Second BTDS 5 application: 168, 169, 170, 171 and 172 hrs, then at 192, 216, 240, 264, 288, 312 and 336 hrs post-dose on days 9, 10, 11, 12, 13, 14 and 15.

Third BTDS 5 application: 336, 337, 338, 339 and 340 hrs, at 360, 384, 408, 432, 456, 480 and 504 hrs post-dose on days 16, 17, 18, 19, 20, 21 and 22, and following removal of BTDS 5 removal on day 23 at 505, 506, 507, 508, 510, 512, 516 and 528 hrs.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$.

Results

Table 6. Summary of the primary pharmacokinetic parameters for buprenorphine

Metric	Arithmetic Mean (±1 SE)		
	Week 1 (0-168 h)	Week 2 (168-336 h)	Week 3 (336-504 h)
Cmin (pg/mL)	53 (6)	58 (6)	57 (5)
AUC (pg·h/mL)	9459 (901)	11482 (914)	15827 (1385)
Cavg (pg/mL)	56 (5)	68 (5)	94 (8)

(Cross-reference: Table 11.2.1B in CSR BP99-0204.)
Note: Cavg is AUC0-t divided by the length of BTDS 5 application (168 hours).

Table 7. Summary of AUC data following removal of the third BTDS 5 along with local heat treatment

Metric	Arithmetic Mean (±1 SE)		
	All Subjects (N = 27)	BTDS 5 + Heat (N = 14)	BTDS + No Heat (N = 13)
Before Heat Treatment			
AUC(336-504) (pg·h/mL)	15287 (1385)	17785 (2108)	13718 (1655)
After Heat Treatment			
AUC(504-528)[a] (pg·h/mL)	776 (101)	828 (165)	719 (116)
AUC(504-inf)[b] (pg·h/mL)	1621 (237)	1749 (340)	1416 (312)

(Cross-reference: Table 14.4.3 in CSR BP99-0204.)
[a]Twenty-five subjects met criteria for evaluation of AUC(504-528), 12 in the no heat group and 13 in the heat group.
[b]Thirteen subjects met criteria for evaluation of AUC(504-inf), 5 in the no heat group and 8 in the heat group.

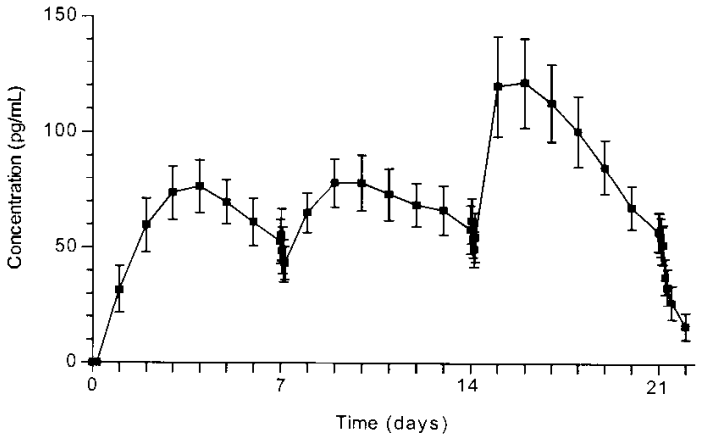
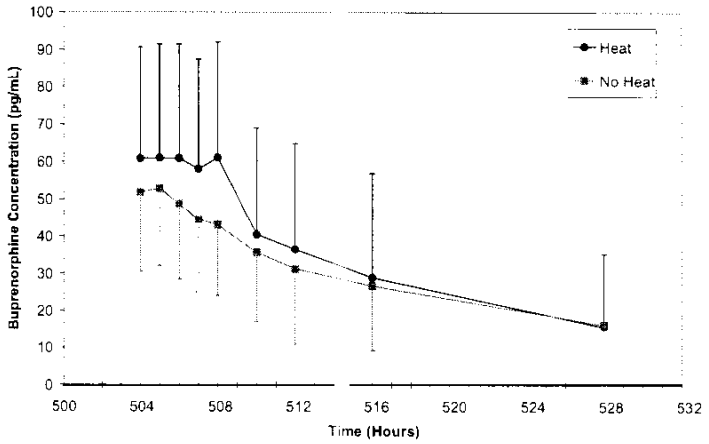


Fig. 11. Mean buprenorphine conc-time profile following repeated administration of BTDS 5



Note: Heat applied after BTDS removal (hour 504) in the heat group only

Fig. 12. Mean buprenorphine conc-time profiles after BTDS removal with and without application of a heat pad.

Reviewer's Comments

- **The mean C_{min} values were similar over weeks 1-3. However, C_{ave} increased from the first to second week and from the second to the third week of BTDS 5 application. The sponsor is currently conducting a study to explain the observed increase in systemic buprenorphine levels with multiple dose BTDS applications.**
- **Application of local heat following removal of the third BTDS 5 did not result in increased plasma concentration or AUC.**
- **A subset of individuals with low body weight exhibited larger increases in C_{ave} during the third week than the other subjects. Analysis conducted by the sponsor pointed to a trend for increased exposure with a decrease in subject weight and height.**

NDA: **21-306/ Study BP96-0501** **Study Date**: **Sep-Oct 1996**

Type of Submission: **Relative Bioavailability Study from Different Body Regions**

Study **BP96-0501** is entitled,

"A RANDOMIZED, CROSSOVER, PHARMACOKINETIC PHARMACODYNAMIC STUDY OF BUPRENORPHINE TDS 25 μG/HOUR SINDGLE DOSE TO DETRMINE THE RELATIVE BIOAVAILABILITY FROM DIFFERENT BODY REGIONS IN HEALTHY ADULT VOLUNTEERS".

Objectives

- To assess bioequivalence of BTDS 10 applied to 3 test application sites (upper outer arm, upper chest, upper back) using application to the midaxillary line as the reference treatment.

Study Design

Healthy male and female subjects (n = 24 (12 males & 12 females), age 23-44 years, Wt 55-89 kg) wore a BTDS 10 application on each of 4 application sites (upper outer arm, upper chest, upper back and midaxillary line) for 7 days. The study was conducted in a randomized, open-label, four-treatment, four-period, crossover fashion with a 10-day washout period separating successive BTDS applications. In each treatment period, blood samples were drawn for determination of buprenorphine at 0 (pre-dose), 8, 16, 24, 36, 48, 72, 96, 120, 144, 168, 176, 184 and 192 hrs post-dose. The pharmacodynamic markers were assessed according to the same schedule.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml. Residual buprenorphine were determined by an HPLC/UV method validated over a linear range of 2-160 μg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$. Equivalence of the reference treatment, BTDS 10, and the two test treatments BTDS 5 & 20 was assessed by comparison of $\mathbf{AUC_{0-t}}$, $\mathbf{AUC_{0-\infty}}$ and $\mathbf{C_{max}}$ using one-way ANOVA**.** In addition, 90% confidence intervals were estimated around ratios of least squares means of log-transformed $\mathbf{AUC_{0-t}}$, $\mathbf{AUC_{0-\infty}}$ and $\mathbf{C_{max}}$.

Pharmacodynamics

A visual analog scale (VAS) of 0 to 100 was used to quantify the extent of opioid side effects (overall drug effect, nausea, dizziness and sleepiness) experienced by each subject.

Results

Table 8. Summary of the primary pharmacokinetic parameters of buprenorphine

	Arithmetic Mean (± SD)			
Metric	**Midaxillary Line**	**Upper Outer Arm**	**Upper Chest**	**Upper Back**
AUC (pg·h/mL)	21731 (10191)	25250 (10726)	22647 (9668)	25706 (8357)
Cmax (pg/mL)	178 (78)	199 (88)	188 (91)	207 (63)
tmax (h)	95 (32)	115 (34)	84 (35)	100 (32)
	LSM Ratio[a] (90% Confidence Interval)[b]			
Test/Reference	**Cmax (ng/mL)**		**AUC (ng·h/mL)**	
Upper outer arm/midaxillary line	112% (96% to 131%)		118% (102% to 137%)	
Upper chest/midaxillary line	106% (91% to 124%)		107% (93% to 125%)	
Upper back/midaxillary line	123% (106% to 143%)		126% (108% to 146%)	

(Cross-references: Tables 11.2.1B and 11.2.1C in CSR BP96-0501.)

[a]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUC, and Cmax.

[b]90% confidence interval (CI) around the least squares means ratio.

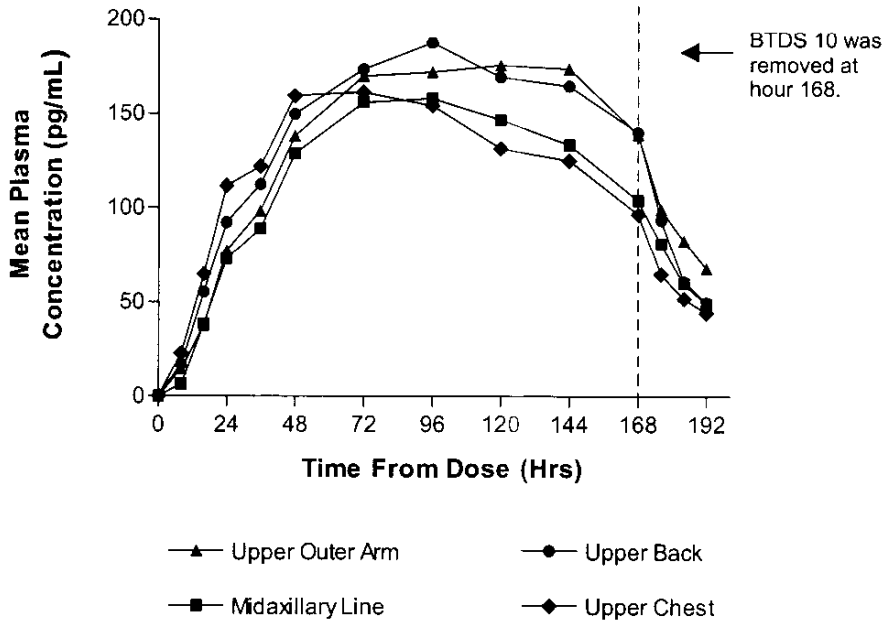


Fig 13. Mean plasma buprenorphine conc-time profiles following administration of BTDS 10 to four different application sites on the body

Reviewer's Comments

- **BTDS 10 application to the upper chest was bioequivalent to the reference treatment (midaxillary line). Peak and total exposures to the upper outer arm and upper back were similar but not bioequivalent to the reference treatment.**
- **The 7-day flux, estimated by residual buprenorphine analysis, ranged from 9.48 to 10.01 μg/hr across application sites.**

NDA: **21-306/ Study BP98-0201** **Study Date**: **Apr-May 1998**

Type of Submission: **PK Study for Applications with Varying Durations**

Study **BP98-0201** is entitled,

"A PARALLEL GROUP STUDY TO EVALUATE THE ABOSRPTION AND DISPOSITION OF BUPRENORPHINE DELIVERED BY A TRANSDERMAL SYSTEM APPLIED FOR VARYING DURATIONS IN YOUNG, HEALTHY VOLUNTEERS".

Objectives

- To evaluate the absorption and disposition kinetics of buprenorphine after 1 to 7 days of BTDS 10 application.

Study Design

Healthy subjects (84 males and females; 7 groups of 12 subjects each, Age 21-48 yrs, Wt 42-95 kg) were randomized to one of 7 treatment groups: one BTDS 10 applied for 1, 2, 3, 4, 5, 6 or 7 days. The study was conducted in a open-label, single-dose, randomized, one period, parallel fashion. Blood samples were drawn for determination of buprenorphine at the following time points: 0 (pre-dose), 2, 4, 6, 8, 10, 12 and 18 hrs post-dose. Blood samples were also collected following the 18-hr time point at 6-hr intervals for all groups other than one-day application. Additional blood samples were also collected upon application removal at: 0 (at removal), 0.25, 0.5, 0.75, 1, 2, 4, 8, 16, 24, 36, 48, 72, 96, 120 and 144 hrs.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS 10 treatment: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$.

Results

Table 9. Summary of the primary pharmacokinetic parameters for buprenorphine by treatment group

Metric	Arithmetic Mean ± 1 SE						
	Group 1 (1 Day)	Group 2 (2 Days)	Group 3 (3 Days)	Group 4 (4 Days)	Group 5 (5 Days)	Group 6 (6 Days)	Group 7 (7 Days)
AUC (pg·h/mL)	5017 ± 1218 (n = 12)	6390 ± 1272 (n = 11)	8554 ± 1062 (n = 12)	10289 ± 1435 (n = 11)	15385 ± 1857 (n = 12)	17050 ± 1985 (n = 12)	23088 ± 3271 (n = 11)
AUC∞ (pg·h/mL)[a]	9223 ± 1595 (n = 6)	8923 ± 1516 (n = 7)	10330 ± 1517 (n = 8)	12288 ± 1609 (n = 9)	18417 ± 2144 (n = 9)	21330 ± 2553 (n = 8)	26426 ± 4201 (n = 8)
Cmax (pg/mL)	168 ± 34 (n = 12)	157 ± 29 (n = 11)	157 ± 16 (n = 12)	159 ± 23 (n = 11)	172 ± 17 (n = 12)	188 ± 27 (n = 12)	213 ± 28 (n = 11)
tmax (h)	30 ± 2.2 (n = 12)	49 ± 0.3 (n = 11)	70 + 2.7 (n = 12)	82 ± 7.3 (n = 11)	92 + 9.1 (n = 12)	84 + 6.1 (n = 12)	86 ± 11 (n = 11)
t½ (h)[a]	18 ± 2.6 (n = 6)	16 ± 1.8 (n = 7)	16 ± 2.4 (n = 8)	20 ± 2.8 (n = 9)	23 ± 4.9 (n = 9)	28 ± 5.9 (n = 8)	16 ± 1.9 (n = 8)
Normalized by Duration (AUC/Days of Application)[b]							
AUC (pg·h/mL)	5017 ± 1218 (n = 12)	3195 ± 636 (n = 11)	2851 ± 354 (n = 12)	2572 ± 359 (n = 11)	3077 ± 371 (n = 12)	2842 ± 331 (n = 12)	3298 ± 467 (n = 11)

(Cross-reference: Table 11.2.1A in CSR BP98-0201.)

Note: Twelve subjects per treatment group. n = number of subjects evaluable.

[a]If R^2 of the terminal slope was less than 0.85, t½ was considered inestimable, and accordingly the corresponding AUC∞ could not be reported. As a result, reportable values for t½ and AUC∞ were available for only 6-9 subjects per treatment group.

[b]Normalized by duration of system application: LS mean (adjusted mean) divided by number of treatment days.

Reviewer's Comments

- **Plasma concentrations continued to increase for 24-48 hrs after system application.**
- **Total buprenorphine exposure (AUC) increased with increasing duration of BTDS 10 application over the 7-day application period. When normalized to duration of system application, total exposure appeared to be similar across treatment groups.**

NDA: **21-306/ Study BP96-1102** **Study Date**: **Jan-Mar 1998**

Type of Submission: **Effect of elevated body temperature on absorption**

Study **BP96-1102** is entitled,

"A PHARMACOKINETIC STUDY TO DETERMINE THE EFFECT OF INREASED CORE BODY TEMPERATURE ON BUPRENORPHINE ABSORPTION FROM THE 25 μg/hr (10 mg) BUPREORPHINE TDS IN NORMAL VOLUNTEERS".

Objectives

- To assess the effect of elevated body temp on buprenorphine bioavailability from the BTDS 10.

Study Design

Healthy young adult subjects (22 males), Age 24-45 yrs, Wt 60-95 kg) wore BTDS 10 on day 1 and either endotoxin or placebo on day 2 during each period. The study was conducted in a randomized, single dose, two-treatment, two-period, crossover fashion. Each BTDS was applied for 3 days with a 10-day washout period separating treatment periods. In each treatment period, blood samples were drawn for determination of buprenorphine at 0 (pre-dose), 2, 4, 8, 12, 18, 24, 26, 28, 30, 32, 36, 48, 60, 72, 72.25, 72.5, 73, 74, 75, 78, 84, 96 and 108 hrs post-dose. Pharmacodynamics were assessed in the current study.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml. Residual buprenorphine were determined by an HPLC/UV method validated over a linear range of 2-160 µg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$. Equivalence of the reference treatment, BTDS 10, and the two test treatments BTDS 5 & 20 was assessed by comparison of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} using one-way ANOVA**.** In addition, 90% confidence intervals were estimated around ratios of least squares means of log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Results

Table 10. Summary of the primary pharmacokinetic parameters for buprenorphine

	Arithmetic Mean (SD)	
Metric	**Endotoxin**	**Placebo**
AUC (pg·h/mL)	6144 (4029)	6209 (4957)
AUC∞ (pg·h/mL)	8731 (4576)	8523 (5268)
Cmax (pg/mL)	138 (99)	131 (84)
t½ (h)	68 (11)	71 (6)
tmax (h)	39 (40)	39 (50)
	LSM Ratio[a] (90% Confidence Interval)[b]	
Test/Reference	**Cmax (pg/mL)**	**AUC (pgh/mL)**
Endotoxin/placebo	102% (86% to 121%)	104% (86% to 124%)

(Cross-references: Table 14.4.5 and Table 14.4.5.1 in CSR BP96-1102.)
[a]Ratio (%) (test/reference) of least squares mean (ANOVA) derived from logarithmic-transformed values of AUC, and Cmax.
[b]90% confidence interval (CI) around the least squares means ratio.

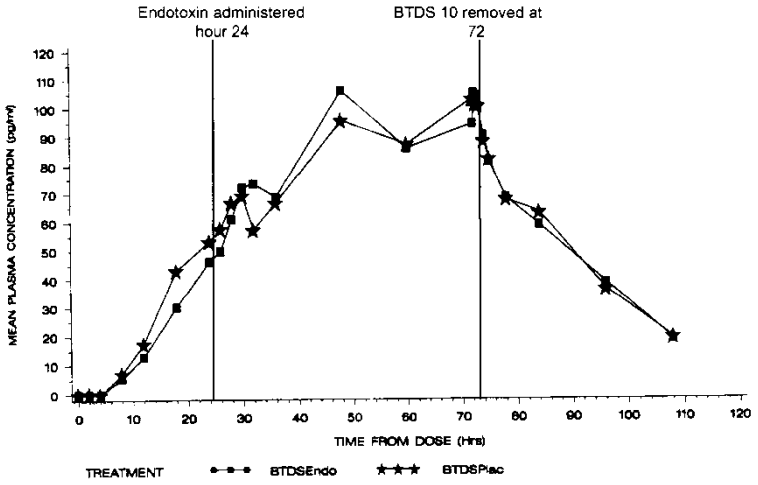


Fig. 14. Mean plasma buprenorphine conc-time profile following administration of BTDS 10 with and without endotoxin

Reviewer's Comments

- **19 of 20 subjects developed fever in response to endotoxin with peak response observed 2-8 hrs after administration.**
- **The primary pharmacokinetic parameters for buprenorphine after BTDS 10 application were similar between the endotoxin and placebo treatments. Thus, elevated systemic temperature did not appear to influence the pharmacokinetics of BTDS 10.**
- **The mean flux for BTDS 10, as determined by residual analysis in the study, was 15.6 μg/hr for endotoxin and 14.3 μg/hr for placebo.**

NDA: **21-306/ Study BP98-1204** **Study Date**: **Sep-Nov 1999**

Type of Submission: **Effect of External Heat Application on Absorption**

Study **BP98-1204** is entitled,

"EVALUATION OF EFFECT OF EXTERNAL HEAT APPLICATION ON THE PLASMA CONCENTRATION TIME COURSE OF BUPRENORPHINE FROM BTDS IN HEALTHY SUBJECTS".

Objectives

- To assess the effect of the application of external heat on buprenorphine bioavailability from BTDS 10.

Study Design

Healthy young adult subjects (20 males and females, Age 21-55 yrs, Wt 51-98 kg) wore either BTDS 10 with intermittent external heat using a heating pad applied for three 2-hr periods on days 2 and 4 or BTDS 10 without external heat during each period. The study was conducted in a randomized, single dose, two-treatment, two-period, crossover fashion. Each BTDS was applied for 7 days with a 10-day washout period separating treatment periods. In each treatment period, blood samples were drawn for determination of buprenorphine at 0 (pre-dose), 1, 2, 3, 6, 9, 12, 16, 24 (pre-heat application), 24.5, 26, 27.5, 30, 32, 31, 31.5, 36, 48, 60, 72 (pre-heat application), 72. 5, 74, 75.5, 78, 79, 79.5, 84, 96, 108, 120, 144, 168, 168.25, 168.5, 168.75, 169, 171 and 174 hrs post-dose.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$.

Results

Table 11. Summary of the primary pharmacokinetic parameters for buprenorphine

Metric	BTDS 10 (No Heat)	BTDS 10 (Heat)
Across the Entire 174-Hour Treatment Period		
Cmax (pg/mL)	191 (55)	238 (80)
$Conc_{0-174}$ (pg/mL)	125 (40)	119 (36)
tmax (h)	111 (37)	73 (11)
AUC_{0-174} (pg·h/mL)	21,798 (6960)	20,624 (6199)
Heat Effect Intervals (12-Hour) Only		
$Conc_{24-36}$ (pg/mL)	83 (35)	130 (64)
$Conc_{0-174}$ (pg/mL)	156 (51)	193 (62)
AUC_{24-36} (pg·h/mL)	991 (418)	1562 (773)
AUC_{72-84} (pg·h/mL)	1870 (607)	2318 (742)

Test/Reference	LSM Ratio[a] (90% Confidence Interval)[b]			
	Cmax (pg/mL)	AUC_{0-174} (pg·h/mL)	AUC_{24-36} (pg·h/mL)	AUC_{72-84} (pg·h/mL)
BTDS heat/no heat	124% (107% to 143%)	96% (85% to 108%)	155% (129% to 186%)	126% (112% to 141%)

(Cross-reference: Table 11.2.1C in CSR BP98-1204.)

[a]Ratio (%) (test/reference) of least squares means (ANOVA derived from logarithmic-transformed values of AUC, and Cmax.

[b]90% confidence interval (CI) around the least squares means ratio.

$Conc_{0-174} = AUC_{0-174}/174$; $Conc_{24-36} = AUC_{24-36}/12$; $Conc_{72-84}/12$.

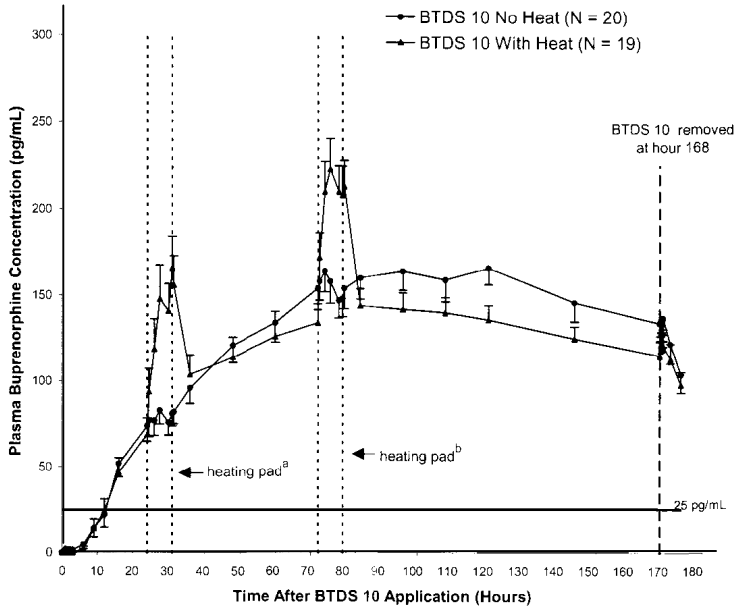


Fig. 15. Mean plasma conc-time profile by treatment following administration of BTDS 10

Reviewer's Comments

- **During the 7-hrs of intermittent heating pad application and up to 5 hrs later, mean plasma buprenorphine concentrations were 26-55% higher than in subjects not receiving heat.**
- **A clear increase in opioid-related adverse events was associated with the heating pad application. This is consistent with increased adverse events with increased plasma buprenorphine levels which were observed in other studies.**

NDA: **21-306/ Study BP96-0702** **Study Date**: **Jun 1997**

Type of Submission: **PK/PD Study in Elderly**

Study **BP96-0702** is entitled,

"A SINGLE DOSE PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF BUPRENORPHINE TRANSDERMAL SYSTEM (25 µg/hour, 10 mg/patch) IN HEALTHY ELDERLY AND YOUNG ADULT VOLUNTEERS".

Objectives

- To compare the pharmacokinetics and to assess the effect of age on the bioavailability of a single application of the BTDS 10 worn for 7 days in healthy elderly and young adults.
- To assess the duration of wear of a small and a large TDS and a BTDS 10 over a 7-day treatment period.

Study Design

Healthy elderly (n = 12, Age 65-77 yrs) and young (n = 12, Age 22-45 yrs) adult subjects wore 3 BTDS applications (single BTDS 10, single small placebo TDS and single large placebo TDS) for 7 days. The study was conducted in an open-label, single-treatment, single-period fashion. Blood samples were drawn for determination of buprenorphine at 0 (pre-dose), 6, 9, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 168.5, 169, 171, 174, 180, 186, 192, 198 and 204 hrs post-dose. The overall drug effect was assessed according to the same schedule.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of (b) (4) pg/ml. Residual buprenorphine were determined by an HPLC/UV method validated over a linear range of (b) (4) µg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for BTDS 10 application in elderly and young adults using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$. Equivalence of the reference treatment, BTDS 10 in elderly and young subjects was assessed by comparison of $\mathbf{AUC_{0-t}}$, $\mathbf{AUC_{0-\infty}}$ and $\mathbf{C_{max}}$ using one-way ANOVA**.** In addition, 90% confidence intervals were estimated around ratios of least squares means of log-transformed $\mathbf{AUC_{0-t}}$, $\mathbf{AUC_{0-\infty}}$ and $\mathbf{C_{max}}$.

Pharmacodynamics

A visual analog scale (VAS) of 0 to 100 was used to quantify the extent of the overall drug effect experienced by each subject.

Results

Table 12. Summary of the primary pharmacokinetic parameters of

Metric	Arithmetic Mean (SD)	
	Elderly (N = 12)	Young (N = 12)
AUC (pg·h/mL)[a]	18543 (6992)	20011 (7915)
Cmax (ng/mL)	152 (56)	170 (72)
tmax (h)	122 (45)	98 (36)
	LSM Ratio[a] (90% Confidence Interval)[b]	
Test/Reference	Cmax (pg/mL)	AUC (pgh/mL)
Elderly young	90% (69% to 116%)	93% (72% to 120%)

(Cross-references: Tables 11.2.1A and 11.2.1B in CSR BP96-0702.)

[a]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUC, and Cmax.

[b]90% confidence interval (CI) around the least squares means ratio.

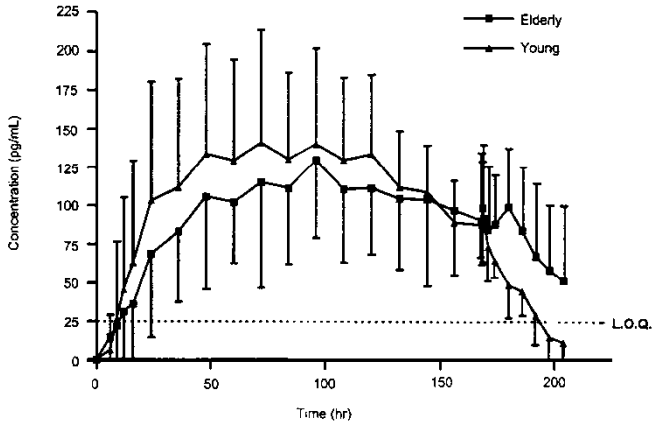


Fig. 16. Mean plasma conc-time profiles for young and elderly subjects following administration of BTDS 10

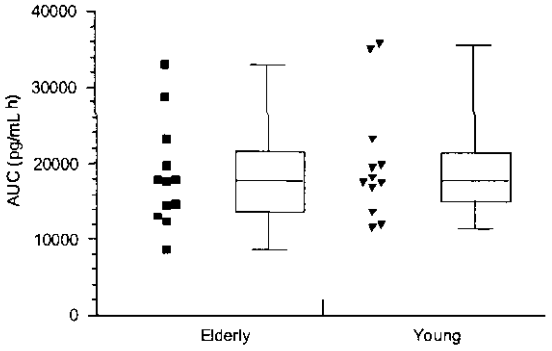


Fig. 17. AUC spread by age group

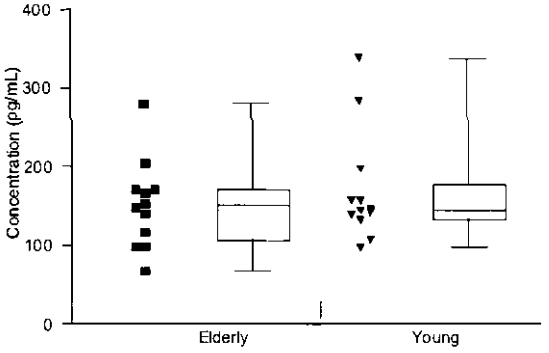


Fig. 18. C_{max} spread by age

Reviewer's Comments

- **AUC and Cmax values were similar, but not bioequivalent, for young and elderly subjects. The ratio of the least square means were 93% for AUC and 90% for C_{max}.**
- **The mean flux for the BTDS 10 system, as determined by residual analysis in the study, was 8.7 μg/hr in the elderly and 8.3 μg/hr in the young subjects.**
- **An increase in plasma buprenorphine concentrations was observed in 5 young subjects and 5 elderly subjects following the removal of BTDS 10 at the end of the study.**
- **Similar to other studies, the highest mean drug effect scores appeared to coincide with the steepest rise in mean buprenorphine concentrations following BTDS 10 administration. This points to a trend in increased drug effect with increased buprenorphine plasma levels.**
- **Hypotension and decreased pulse rate associated with BTDS 10 administration were particularly evident in elderly subjects, which may point to increased sensitivity to opioid effects in the elderly.**

NDA: **21-306/ Study BP97-0112** **Study Date**: **Jan-Mar 1998**

Type of Submission: **Hepatic Impairment Study**

Study **BP97-1102** is entitled,

"A SINGLE DOSE PHARMACOKINETIC STUDY OF BUPRENORPHINE IN HEALTHY ADULTS AND ADULT SUBJECTS WITH HEPATIC IMPAIRMENT".

Objectives

- To assess the effect of hepatic impairment on the pharmacokinetics of I.V. administered buprenorphine.

Study Design

Healthy and hepatic-impairment subjects (24 males and females, Age 36-70 yrs, Wt 50-103 kg, 12 healthy, 8 mild hepatic-impairment and 4 moderate hepatic-impairment) received 0.3 mg buprenorphine as a 10 min I.V. infusion. The study was conducted in an open label, single dose, parallel fashion. Blood samples were drawn for determination of buprenorphine and norbuprenorphine at 0 (pre-dose), 10 (end of infusion), 20, 15, 30 and 45 min, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 hrs post-dose. Pharmacodynamics was not assessed in the current study.

Analytical Assay

Plasma samples were analyzed for buprenorphine and norbuprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for both healthy subjects and patients with mild to moderate hepatic impairment: **Vdss**, **CL, $t_{1/2}$** and **AUC_{0-t}**.

Results

Table 13. Summary of the primary pharmacokinetic parameters for **buprenorphine**

	Arithmetic Mean (SD)		Median	
Metric	**Hepatically Impaired**	**Healthy**	**Hepatically Impaired**	**Healthy**
AUC (pg·min/mL)	316,790 (84,773)	342,299 (80,042)	334,233	326,827
Cmax (pg/mL)	5,798 (3,310)	11,770 (6,983)	4,845	11,400
tmax (min)	12 (3)	11 (2)	10	10
CLtot (mL/min)	741 (174)	779 (247)	765	747
Vd (ss)	639 (392)	430 (288)	483	306
	LSM Ratio[a] (90% Confidence Interval)[b]			
Test/Reference	**Cmax (pg/mL)**	**AUC (pg·h/mL)**	**AUC∞ (pg·h/ mL)**	
Hepatically impaired/healthy	51% (34% to 76%)	92% (76% to 110%)	104% (86% to 125%)	

(Cross-reference: Table 14.4.3 in CSR BP97-0112.)
[a]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUC, and Cmax.
[b]90% confidence interval (CI) around the least squares means ratio.

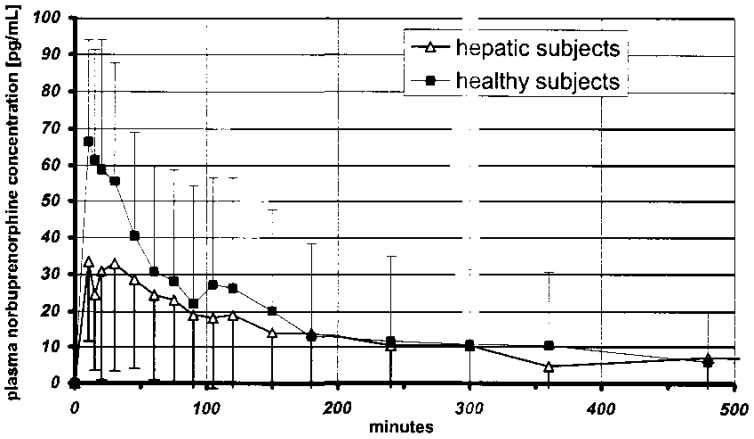


Fig. 19. Mean plasma buprenorphine conc-time profiles after adminisration of buprenorphine I.V. infusion (0.3 mg) in healthy subjects and patients with mild to moderate hepatic-impairment

Reviewer's Comments

- **The pharmacokinetics of buprenorphine did not seem to be different between healthy subjects and patients with mild to moderate hepatic impairment.**
- **The systemic exposure of norbuprenorphine did not seem to be significantly affected by chronic mild to moderate hepatic impairment, with the exception of 30% reduction in C_{max} and AUC. However, interpretation of the results is obscured by the high variability and low concentrations of norbuprenorphine.**
- **The impact of hepatic impairment on buprenorphine pharmacokinetics was not fully evaluated as patients with severe hepatic imapirment were not included in the study. In addition, the single buprenorphine dose studied was much smaller than what would be employed in the clinical setting (BTDS 5-20 mg) and in the absence of dose proportionality, the results might not be extrapolatable. The sponsor also analyzed the combined data for patients with mild- and with moderate- hepatic impairment, which obscures the overall interpretation of the results.**

NDA: **21-306/ Study BP96-0101** **Study Date**: **Nov 1996 -Nov 1997**

Type of Submission: **Multiple Dose PK Study in Patients**

Study **BP96-0101** is entitled,

*"A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO- AND ACTIVE-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF BUPRENORPHINE TDS 12.5, 25 AND 50 µg/hr APPLIED EVERY SIX DAYS vs. IR 5 mg OXYCODONE/325 mg ACETAMINOPHEN TABLETS q6h prn vs. PLACEBO IN PATIENTS WITH CHRONIC PAIN DUE TO OSTEOARTHRITIS"***.**

Objectives

- To evaluate the safety, efficacy and buprenorphine plasma concentration-dose relationship of the 3 dosage strengths of BTDS 12.5, 25 and 50 µg/hr given for 60 days vs. immediate –release 5 mg oxycodone/325 mg acetaminophen tablets given prn.

Study Design

Adult osteoarthritis patients (270 males and females, Age 29-90 yrs, Wt 47-147) were randomized to one of 5 treatment arms for 60 days: 1) Placebo, 2) IR 5 mg Oxycodone/325 mg acetaminophen 1-2 tablets q6h prn, 3) BTDS 5, 4) BTDS 10, 5) BTDS 20. The study was conducted in a double-blind, placebo- and active-controlled, randomized, five-treatment, parallel fashion. In each treatment arm, blood samples were drawn for determination of buprenorphine within 30 min prior to system placement on days 0, 9, 15, 30, 45 and 60.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The relationships between plasma buprenorphine concentrations and drug effect and pain scores were analyzed for each buprenorphine dose level.

Results

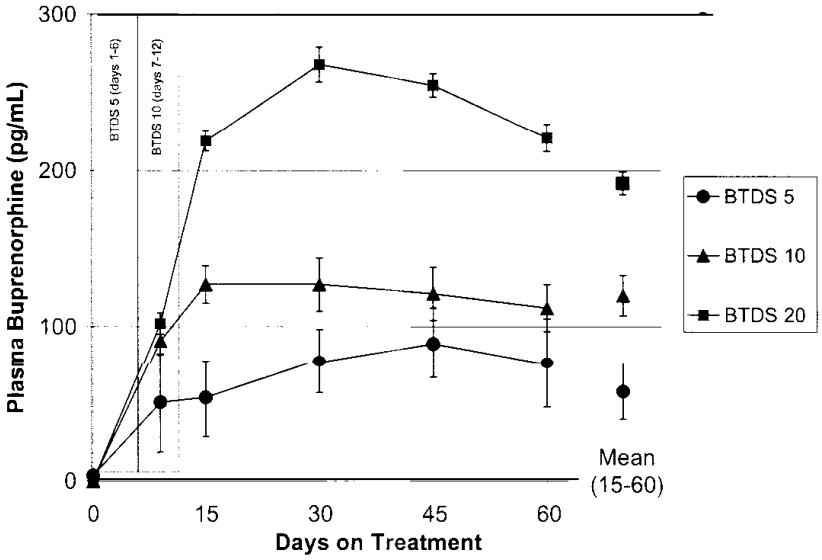


Fig. 20. Mean plasma buprenorphine conc-time profiles by day

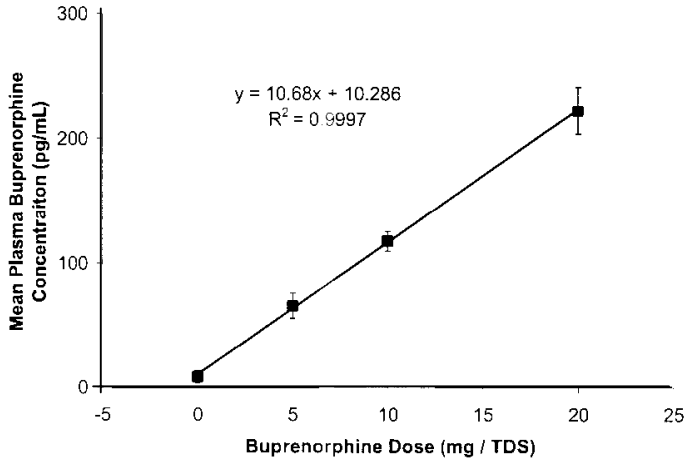


Fig. 21. Mean plasma buprenorphine concentrations vs. dose

Reviewer's Comments

- **The correlation of mean buprenorphine concentrations vs. dose was 0.997, which suggests dose proportionality of BTDS in this study.**
- **No unexpected accumulation was noted over the 60 day dosing period.**

NDA: **21-306/ Study BP96-0102** **Study Date**: **Apr 1997 -Jan 1998**

Type of Submission: **Multiple Dose PK Study in Patients**

Study **BP96-0102** is entitled,

*"SAFETY AND EFFICACY OF BUPRENORPHINE TDS 12.5, 25 AND 50 µg/hr APPLIED EVERY 7 DAYS FOR SIXTY DAYS vs. 5 mg OXYCODONE325 mg ACETAMINOPHEN TABLETS q6h prn vs. PLACEBO IN PATIENTS WITH CHRONIC LOWER BACK PAIN"***.**

Objectives

- To evaluate the safety, efficacy and buprenorphine plasma concentration-dose relationship of the 3 dosage strengths of BTDS 12.5, 25 and 50 µg/hr given for 60 days vs. immediate –release 5 mg oxycodone/325 mg acetaminophen tablets given prn.

Study Design

Adult patients with chronic lower back pain (270 males and females, Age 22-88 yrs, Wt 40-141 kg) were randomized to one of 5 treatment arms for 60 days: 1) Placebo, 2) IR 5 mg Oxycodone/325 mg acetaminophen 1-2 tablets q6h prn, 3) BTDS 5, 4) BTDS 10, 5) BTDS 20. The study was conducted in a double-blind, placebo- and active-controlled, randomized, five-treatment, parallel fashion. In each treatment arm, blood samples were drawn for determination of buprenorphine within 30 min prior to system placement on days 0, 9, 15, 30, 45 and 60.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-400 pg/ml.

Pharmacokinetics

The relationships between plasma buprenorphine concentrations and drug effect and pain scores were analyzed for each buprenorphine dose level.

Results

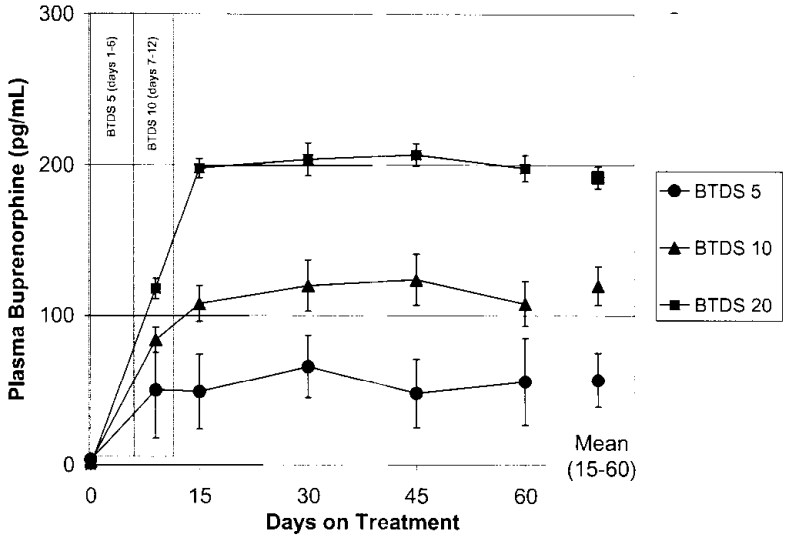


Fig. 22. Mean plasma buprenorphine conc-time profiles by day

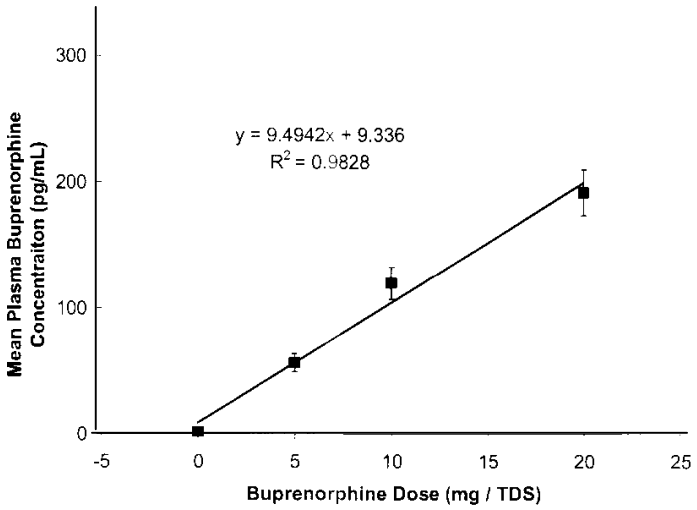


Fig. 23. Mean buprenorphine concentrations vs. dose

Reviewer's Comments

- **The correlation of mean buprenorphine concentrations vs. dose was 0.983, which suggests dose proportionality of BTDS in this study.**
- **No unexpected accumulation was noted over the 60 day dosing period.**

NDA: **21-306/ Study BP96-0104** **Study Date**: **Oct 1996 -Nov 1997**

Type of Submission: **Single Dose PK Study in Patients**

Study **BP96-0104** is entitled,

*"A SINGLE DOSE, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP OF THE SAFETY AND PHARMACOKINETICS OF BUPRENORPHINE TDS (12.5, 25, 50 μg/hr) vs. PLACEBO IN PATIENTS WITH MODERATE TO SEVERE PAIN FOLLOWING ORTHOPEDIC SUREGERY"***.**

Objectives

- To assess the safety and pharmacokinetics of BTDS 5, 10 and 20 for 72 hrs in patients following orthopedic surgery.

Study Design

Adult patients (110 males and females, Age 18-94 yrs) received one of 4 treatments: Placebo, BTDS 5, BTDS 10 and BTDS 20 for 172 hrs. The study was conducted in a double-blind, single-treatment, placebo-controlled, 4 treatment parallel fashion. In each treatment arm, blood samples were drawn for determination of buprenorphine at 0 (pre-dose), 2, 4, 6, 12, 24, 30, 36, 48, 54, 60, 72, and 78 hrs post-dose. The pharmacodynamic markers were assessed according to the same schedule.

Analytical Assay

Plasma samples were analyzed for buprenorphine using an LC/MS/MS method validated over a linear range of 25-600 pg/ml.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each BTDS application using non-compartmental analysis: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$. Equivalence of the reference treatment, BTDS 10, and the two test treatments BTDS 5 & 20 was assessed by comparison of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} using one-way ANOVA**.** In addition, 90% confidence intervals were estimated around ratios of least squares means of log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Results

Table 14. Summary of the primary pharmacokinetic parameters for buprenorphine

Parameter (unit)	(N) Mean ± SD					
	BTDS 5 (N = 33)		BTDS 10 (N = 33)		BTDS 20 (N = 33)	
AUC (pg·h/mL)	(24)	2066 ± 2394	(26)	4021 ± 3266	(27)	12279 ± 7763
Cmax (pg/mL)	(32)	51.1 ± 64.4	(32)	87.1 ± 61.3	(32)	259.8 ± 153.3
tmax (h)	(32)	37.7 ± 34.4	(32)	59.6 ± 25.5	(32)	61.9 ± 17.5

(Cross-reference: Table 11.2.1A in CSR BP96-0104.)
n = number of patients with sufficient data.

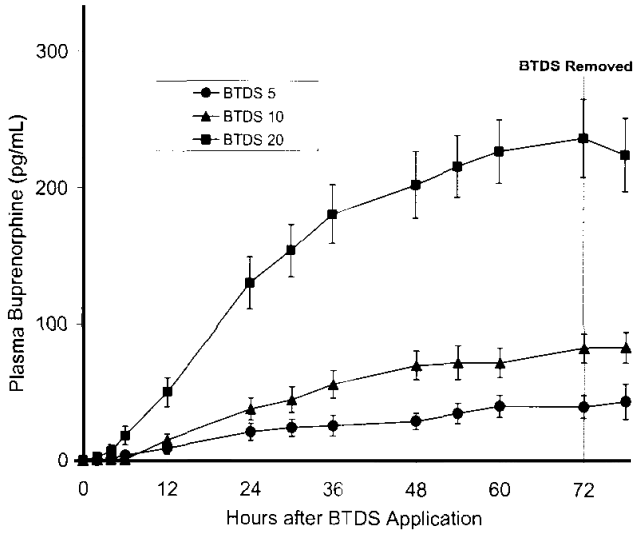


Fig. 24. Mean plasma buprenorphine conc-time profiles after application of BTDS 5, 10 and 20

Reviewer's Comments

- **For all BTDS treatment groups, the largest increase in mean plasma buprenorphine concentrations occurred between 12 and 24 hrs after BTDS application.**
- **Cmax and AUC values suggest dose linearity but not dose proportionality for the three BTDS strengths.**
- **The mean flux for the three BTDS systems, as determined by residual analysis in the study, was 7.54 μg/hr for BTDS 5, 15.77 μg/hr for BTDS 10 and 39.06 μg/hr for BTDS 20.**

NDA: **21-306/ Study BP97-0303** **Study Date**: **May-Dec 1998**

Type of Submission: **Pharmacodynamic Interaction Study**

Study **BP97-0303** is entitled,

"A PARALLEL GROUP STUDY TO EVALUATE THE EFFECTS OF BUPRENORPHINE TRANSDERMAL SYSTEM ON VITAL SIGNS AND OXYGEN SATURATION IN YOUNG HEALTHY VOLUNTEERS, ELDERLY HEALTHY VOLUNTEERS, AND ELDERLY PATIENTS WITH HYPERTENSION RECEIVING THIAZIDE DIURETICS".

Objectives

- To evaluate the tendency of buprenorphine transdermal system to cause orthostatic hypotension.
- To compare the pharmacokinetics of buprenorphine delivered by BTDS in healthy young and healthy elderly subjects, and elderly hypertensive patients treated with thiazide diuretics.

Study Design

Healthy subjects (36 males and females; 3 groups of 11-13 subjects each, Age 21-80 yrs, Wt 50-93 kg) wore BTDS 5 for 3 days, BTDS 10 for 3 days and BTDS 20 for 7 days. Each system was applied to the same area following removal of the previous system without any washout period. The study was conducted in an open-label, three-period, three-group, parallel fashion. Blood samples were drawn for determination of buprenorphine at the following time points:

(for BTDS 5 & 10) 0 (pre-dose), 23 and 47 hrs post-dose.

(for BTDS 20) 0 (pre-dose), 23, 47, 71, 119 and 143 hrs post-dose. Additional samples were collected post-system removal at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24, 48 and 72 hrs.

Analytical Assay

Plasma samples were analyzed for buprenorphine and norbuprenorphine using an LC/MS/MS method. The method was validated over a linear range of: 25-600 pg/ml for both analytes.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for each buprenorphine treatment: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$.

Pharmacodynamics

Respiratory rate and oxygen saturation were used to assess respiratory depression resulting from BTDS 5, 10 and 20 application in young healthy, elderly healthy and elderly hypertensive subjects.

Results

Table 15. Summary of the primary pharmacokinetic parameters for buprenorphine by treatment group

Metric	Least Squares Mean		% Ratio	90% CI*
	Young Healthy (N = 11)	Elderly Healthy (N = 10)	Young/Elderly Healthy	
AUC	82207	74122	111%	88 to 140
AUC∞	83177	76367	109%	86 to 138
Cmax	672	507	132%	97 to 181
	Young Healthy (N = 11)**	Elderly Hypertensive	Young/Elderly Hypertensive	
AUC	82207	92956	88%	71 to 111
AUC∞	83177	97986	85%	67 to 107
Cmax	672	581	116%	85 to 157

(Cross-reference: Table 11.2.1C in CSR BP97-0303.)

*Ratios and 90% CI were calculated from the ANOVA of the logarithmic-transformed values of AUC and Cmax.

**Ten subjects were evaluable for AUC∞.

NS = not statistically significant.

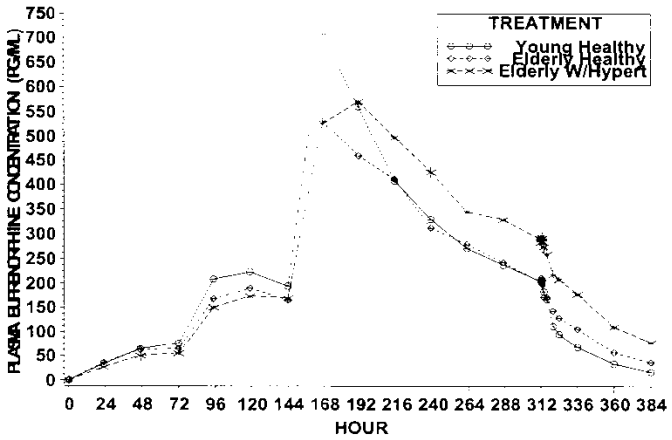


Fig. 25. Mean plasma conc-time profile for buprenorphine following BTDS application

Reviewer's Comments

- **Similar plasma buprenorphine conc-time profiles were observed in the elderly hypertensive group compared to the young and the healthy elderly groups.**
- **Total exposure to buprenorphine was greater in the young compared to the healthy elderly, and greater in the hypertensive elderly compared to the young.**
- **Maximum exposure was greater in the young compared to the two elderly groups.**

NDA: **21-306/ Study BP97-1001** **Study Date**: **Apr-May 1998**

Type of Submission: **Pharmacodynamic Interaction Study**

Study **BP97-1001** is entitled,

"A THIRD-PARTY BLIND, DOUBLE-DUMMY STUDY TO EVALUATE THE EFFECTS OF BUPRENORPHINE TRANSDERMAL SYSTEM (BTDS) PLUS MIDAZOLAM AND OF FENTANYL TRANSDERMAL (DURAGESIC®) PLUS MIDAZOLAM ON VITAL SIGNS AND OXYGEN SATURATION IN YOUNG HEALTHY VOLUNTEERS".

Objectives

- To evaluate the interaction between buprenorphien transdermal system BTDS 10 applied as a single dose over a 7-day period and midazolam (Versed®) 1 mg dose I.V. over 2 min.
- To evaluate the interaction between fentanyl transdermal (Duragesic®) 25 µg/hr applied over a 7-day period and midazolam (Versed®) 1 mg dosed I.V. over 2 min.

Study Design

Healthy subjects (36 males and females; 3 groups of 12 subjects each, Age 21-45 yrs, Wt 54-92 kg) were randomized to one of three treatment groups: (active BTDS 10 & medium placebo TDS), (active fentanyl (Duragesic®) patch & medium placebo TDS), and 2 medium placebo TDS. All subjects received midazolam 1 mg I.V. over 2 min on day 6. As the fentanyl patch is designed for 3-day application, the fentanyl patch was replaced on day 4. The study was conducted in a double-dummy, randomized, parallel fashion. Blood samples were drawn for determination of buprenorphine, fentanyl and midazolam at the following time points:

(for midazolam) 0 (pre-dose), 5, 15, 30 and 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hrs post-dose.

(for buprenorphine and fentanyl on days 5 & 6) 0, 2, 4, 6, 8, 12 and 24 hrs.

Analytical Assay

Plasma samples were analyzed for buprenorphine, fentanyl and midazolam using an LC/MS/MS method. The metahod was validated over a linear range of: 25-600 pg/ml for buprenorphine, 5-150 ng/ml for midazolam and 0.05-15 ng/ml for fentanyl.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for midazolam, fentanyl and buprenorphine treatments: **F (absolute bioavailability), t_{max}, C_{max}, $t_{1/2}$, AUC_{0-t}** and **$AUC_{0-\infty}$.**

Pharmacodynamics

Respiratory rate and oxygen saturation were used to assess respiratory depression resulting from BTDS 10 or transdermal fentanyl with concomitant midazolam.

Results

Table 16. Summary of the primary pharmacokinetic parameters for midazolam

	Arithmetic Mean ± 1 SE (N = 12)			
Metric	**BTDS 10**	**Fentanyl**	**Placebo**	***P* Value[a]**
Cmax (ng/mL)	36 ± 3.5	29 ± 2.4	29 ± 2.5	NS
AUC (ng·h/mL)	27 ± 2.9	21 ± 1.4	25 ± 2.7	NS
AUC∞ (ng·h/mL)	40 ± 4.7[b]	33 ± 1.9[b]	36 ± 3.6	NS
tmax (h)	0.10 ± 0.01	0.10 ± 0.01	0.14 ± 0.04	—
t½ (h)	1.5 ± 0.28[b]	1.4 ± 0.14[b]	1.4 ± 0.20	—

(Cross-reference: Table 11.2.1A in CSR BP97-1001.)

[a]*P* value from an ANOVA model with log-transformed data of the metric as the response variable and treatment as the predictor.

[b]Number of evaluable subjects = 11; NS = not statistically significant (ie, *P*>0.05).

— Statistical analysis was not perfumed.

Table 17. Summary of the primary pharmacokinetic parameters for buprenorphine

	Arithmetic Mean ± 1 SE (N = 12)		
Metric	**Day 5**	**Day 6**	**% Decrease**
AUC (pg·h/mL)	1988 ± 330	1896 ± 307	5
Cmax (pg/mL)	123 ± 12	107 ± 10	13
	LSM Ratio[a] (90% Confidence Interval)[a]		
Test/Reference	**AUC (pg·h/mL)**	**Cmax (pg/mL)**	
Day 6/Day 5	92% (73% to 114%)	88% (82% to 94%)	

(Cross-references: Tables 11.2.1C and D in CSR BP97-1001.)

[a]Adjusted mean, % ratio, and 90% confidence intervals, were calculated from the ANOVA model with log-transform of the PK metric as response variables and day as the predictor.

Table 18. Summary of the primary pharmacokinetic parameters for fentanyl

	Arithmetic Mean ± 1 SE (N = 12)		
Metric	**Day 5**	**Day 6**	**% Decrease**
AUC (ng·h/mL)	11.0 ± 1.0	7.5 ± 0.6	32
Cmax (ng/mL)	0.59 ± 0.06	0.45 ± 0.04	24
	LSM Ratio[a] (90% Confidence Interval)[a]		
Test/Reference	**AUC (pg·h/mL)**	**Cmax (pg/mL)**	
Day 6/Day 5	70% (64% to 76%)	80% (71% to 89%)	

(Cross-references: Tables 11.2.1E and F in CSR BP97-1001.)

[a]Adjusted mean, % ratio, and 90% confidence intervals, were calculated from the ANOVA model with log-transform of the PK metric as response variables and day as the predictor.

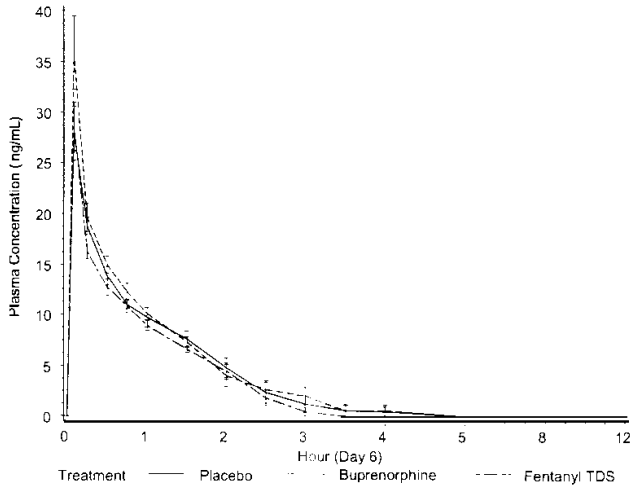


Fig. 26. Mean plasma conc-time profile for midazolam over day 6 by treatment group

Reviewer's Comments

- **Buprenorphine plasma concentrations were similar before and after concomitant administration of midazolam. As for the fentanyl group, , Cmax and AUC were significantly lower after midazolam dosing.**
- **BTDS 10 did not appear to be associated with a difference in respiratory suppression when coadministered with midazolam 1 mg I.V. in healthy subjects.**

NDA: **21-306/ Study BP98-0202** **Study Date**: **Apr-Jun 1998**

Type of Submission: **Pharmacodynamic Interaction Study**

Study **BP98-0202** is entitled,

"A THIRD-PARTY BLIND, DOUBLE-DUMMY STUDY TO EVALUATE THE EFFECTS OF BUPRENORPHINE TRANSDERMAL SYSTEM (BTDS 10) PLUS PROCHLORPERAZINE AND OF FENTANYL TRANSDERMAL (DURAGESIC®) PLUS PROCHLORPERAZINE ON VITAL SIGNS AND OXYGEN SATURATION IN YOUNG HEALTHY VOLUNTEERS".

Objectives

- To evaluate the interaction between buprenorphine transdermal system BTDS 10 applied as a single dose over a 7-day period and prochlorperazine.
- To evaluate the interaction between fentanyl transdermal (Duragesic®) 25 µg/hr applied over a 7-day period and prochlorperazine.

Study Design

Healthy subjects (36 males and females; 3 groups of 12 subjects each, Age 21-45 yrs, Wt 51-95 kg) were randomized to one of three treatment groups: (active BTDS 10 & medium placebo TDS), (active fentanyl (Duragesic®) patch & medium placebo TDS), and 2 medium placebo TDS. All subjects received prochlorperazine, 25 mg suppository on day 6. As the fentanyl patch is designed for 3-day application, the fentanyl patch was replaced on day 4. The study was conducted in a double-dummy, randomized, parallel fashion. Blood samples were drawn for determination of buprenorphine, fentanyl and prochlorperazine at the following time points:

(for prochlorperazine) 0 (pre-dose), 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hrs post-dose.

(for buprenorphine and fentanyl on days 5 & 6) 0, 2, 4, 6, 8, 12 and 24 hrs.

Analytical Assay

Plasma samples were analyzed for buprenorphine, fentanyl and midazolam using an LC/MS/MS method. The method was validated over a linear range of: (b) (4) pg/ml for buprenorphine, 5-1000 ng/ml for prochlorperazine and 0.05-15 ng/ml for fentanyl.

Pharmacokinetics

The following pharmacokinetic parameters were estimated for prochlorperazine, fentanyl and buprenorphine treatments: $\mathbf{t_{max}}$, $\mathbf{C_{max}}$, $\mathbf{t_{1/2}}$, $\mathbf{AUC_{0-t}}$ and $\mathbf{AUC_{0-\infty}}$.

Pharmacodynamics

Respiratory rate and oxygen saturation were used to assess respiratory depression resulting from BTDS 10 or transdermal fentanyl with concomitant midazolam.

Results

Table 19. Summary of the primary pharmacokinetic parameters for **buprenorphine**

	Arithmetic Mean ± 1 SE (N = 12)	
Metric	**Day 5**	**Day 6**
Cavg (pg/mL)	0.5 ± 0.05	0.4 ± 0.06
Cmax (pg/mL)	0.6 ± 0.06	0.6 ± 0.08
	LSM Ratio[a] (90% Confidence Interval)[a]	
Test/Reference	**Cavg (pg/mL)**	**Cmax (pg/mL)**
Day 6/Day 5	77% (70% to 86%)	90% (80% to 101%)

(Cross-references: Tables 11.2.1C and D in CSR BP98-0202.)
Note: Study began on Day 0. N = 12
[a]Adjusted mean, % ratio, and 90 % confidence intervals, and *P* values were calculated from the ANOVA model with log-transform of the PK metric as response variables and day as the predictor.

Table 20. Summary of the primary pharmacokinetic parameters for **fentanyl**

	Arithmetic Mean ± 1 SE (N = 12)	
Metric	**Day 5**	**Day 6**
Cavg (pg/mL)	0.5 ± 0.05	0.4 ± 0.06
Cmax (pg/mL)	0.6 ± 0.06	0.6 ± 0.08
	LSM Ratio[a] (90% Confidence Interval)[a]	
Test/Reference	**Cavg (pg/mL)**	**Cmax (pg/mL)**
Day 6/Day 5	77% (70% to 86%)	90% (80% to 101%)

(Cross-references: Tables 11.2.1C and D in CSR BP98-0202.)
Note: Study began on Day 0. N = 12
[a]Adjusted mean, % ratio, and 90 % confidence intervals, and *P* values were calculated from the ANOVA model with log-transform of the PK metric as response variables and day as the predictor.

Reviewer's Comments

- **BTDS 10 and fentanyl transdermal system did not appear to be associated with a difference in respiratory depression when coadministered with prochlorperazine in healthy subjects.**

NDA: **21-306/ Study PKDM-BUP-DM002**

Type of Submission: ***In Vitro* Metabolism**

Study **PKDM-BUP-DM002** is entitled,

*"IN VITRO METABOLISM AND DRUG INTERACTIONS OF BUPRENORPHINE FOLLOWING ITS INCUBATION WITH HUMAN LIVER MICROSOMES, RECOMBINANT HUMAN CYTOCHROME P450 ISOFORMS, AND HUMAN HEPATOCYTES"***.**

Objectives

- To determine *in vitro* metabolism of buprenorphine using human liver S9 fractions, microsomes, recombinant CYP isoforms and human hepatocytes.
- To determine if human skin microsomes can catalyze metabolism of buprenorphine.
- To evaluate potential *in vivo* drug-drug interactions.

Study Design

S9 fractions and microsomes were prepared by differential centrifugation of human liver and skin tissue homogenates using the method described by Lu and Levine. Human hepatocytes were isolated by a two-step collagenase perfusion of the liver samples (n = 10) as described by Li et al.

Analytical Assay

A reversed-phase HPLC method was used for analysis of buprenorphine and its metabolites. No details were provided regarding validation of the method.

Results and Discussion

- **Metabolism of buprenorphine in human S9 liver fraction, microsomes and isolated hepatocytes**

The results indicate that in both human liver S9 and microsomal fractions, buprenorphine is metabolized primarily to norbuprenorphine. In human hepatocytes, buprenorphine-2-O-glucuronide was additionally detected.
The Km and Vmax values for the formation of norbuprenorphine in human liver microsomes and hepatocyes were 66.61 µM, 343 ng/min/mg and 14.31 µM, 323 ng/min/mg respectively.

- **Buprenorphine metabolism by recombinant human CYP isoforms**

The results indicate that CYP3A4 is the major isoform responsible for the formation of norbuprenorphine with a rate of 2.4 pmol/min/pmol of P450. In addition, CYP2C8 was shown to catalyze some norbuprenorphine formation with a rate of 0.3 pmol/min/pmol of P450.

- **Buprenorphine metabolism in human skin microsomes**

No buprenorphine N-dealkylase activity was detected in skin microsomes. Also, with the exception of some CYP1A2 activity, no CYP3A4 activity was detected in skim microsomes. The results suggest that no first pass metabolism in skin takes place following administration of buprenorphine in humans.

- **Inhibition of buprenorphine by CYP3A4 inhibitors ketoconazole, ritonavir and indinavir**

Iribarne et al have demonstrated potent inhibition of norbuprenorphine formation in human liver microsomes by ketoconazole, ritonavir and indinavir. The current study evaluated inhibition of norbuprenorphine formation by those inhibitors in human hepatocytes. For all three evaluated CYP3A4 inhibitors, markedly weaker or no inhibition of norbuprenorphine formation was noted in hepatocytes relative to that in microsomes.

- **Inhibition of CYP isoforms by buprenorphine**

The effect of buprenorphine on 4 recombinant human CYP isoforms (CYP1A2, CYP2D6, CYP2A6 and CYP3A4) was determined. The results showed that buprenorphine is a weak inhibitor of CYP 1A2 (IC_{50} > 200 μM), CYP2A6 (IC_{50} > 100 μM) and CYP3A4 (IC_{50} ~ 25 μM). The results also showed that buprenorphine is a highly potent inhibitor of CYP2D6 with an IC_{50} of 0.05 μM. However, such buprenorphine concentrations are unlikely to be achieved clinically as they are 50-fold greater than buprenorphine concentrations noted with BTDS applications in humans.

NDA: **21-306**

Type of Submission: **Population PK Analysis**

Objectives

- To define a compartmental PK model that describes the plasma concentration-time relationship of buprenorphine after single and multiple doses via I.V. and transdermal routes of administration.
- To conduct a preliminary screen of covariate effects on transdermal absorption parameters in the PK model using data from 3 Phase I studies.

- To use the compartmental PK model to predict the expected plasma concentration-time curves after various dosing scenarios.

Study Design

A population PK analysis was conducted using pooled PK data from three studies (BP97-0501, BP97-0303, BP99-0204) using nonlinear mixed-effects modeling with the NonMem software. Model discrimination criteria included the likelihood ratio test, visual inspection of diagnostic scatter plots and evaluation of estimates of population fixed and random effect parameters.

In addition, parameter estimates obtained from the final population model were used to conduct Monte Carlo simulations of 1000 trials (96,000 subjects) for different single and multiple BTDS applications. The Monte Carlo technique was used to evaluate how well the population PK model predicted the entire plasma concentration-time profile and the range of concentrations at set time points of interest in both single and multiple BTDS applications. The predictive performance of the model was examined by comparing the plasma concentrations simulated by the model with the actual plasma concentrations measured at set time points.

Table 21. Summary of the PK studies used for constructing the population PK model

Study Type	Study Number	Description of Study
Single Dose	BP97-0501	BTDS, 5 (7-day duration), or BTDS, 10 (7-day duration), or BTDS 20 (7-day duration) Crossover with: Buprenorphine IV Infusion 0.6 mg/day (24-hour duration)
Multiple Dose	BP97-0303	BTDS Forced Dose Escalation: BTDS 5 (3-day duration) followed by BTDS 10 (3-day duration) followed by BTDS 20 (7-day duration)
	BP99-0204	BTDS 5 (7-day duration) (each period consisted of seven days for a total treatment period of 21 days)

Results and Conclusions

The following is a summary of the main assumptions incorporated into the base population PK model:

- The bioavailability of the 7-day BTDS was estimated at 15% and should be approximately twice that of 3-day BTDS.
- Drug release from BTDS was primarily through a zero-order process.
- The I.V. data are well characterized with a 3-compartment disposition model.

- Several individuals exhibited increased exposure upon repeat dosing.
- A local skin depot was postulated.

The final population PK model simultaneously fit data from 3 clinical studies which included buprenorphine administration by I.V. infusion (BP97-0501), single dose (BP97-0501) and multiple dose (BP97-0303 and BP99-0204) BTDS applications of 3- and 7-day durations.

The final model estimated the absolute bioavailabilities for the 3-day and 7-day BTDS applications at 16.1 and 7.7%, respectively. In addition, based on the model predictions, the transdermal absorption of buprenorphine was equally split between zero-order and first-order processes. The model also estimated that the first-order transdermal absorption rate for buprenorphine increased by 1.55 fold when BTDS was re-applied to the same skin site, relative to re-application to a new skin site.

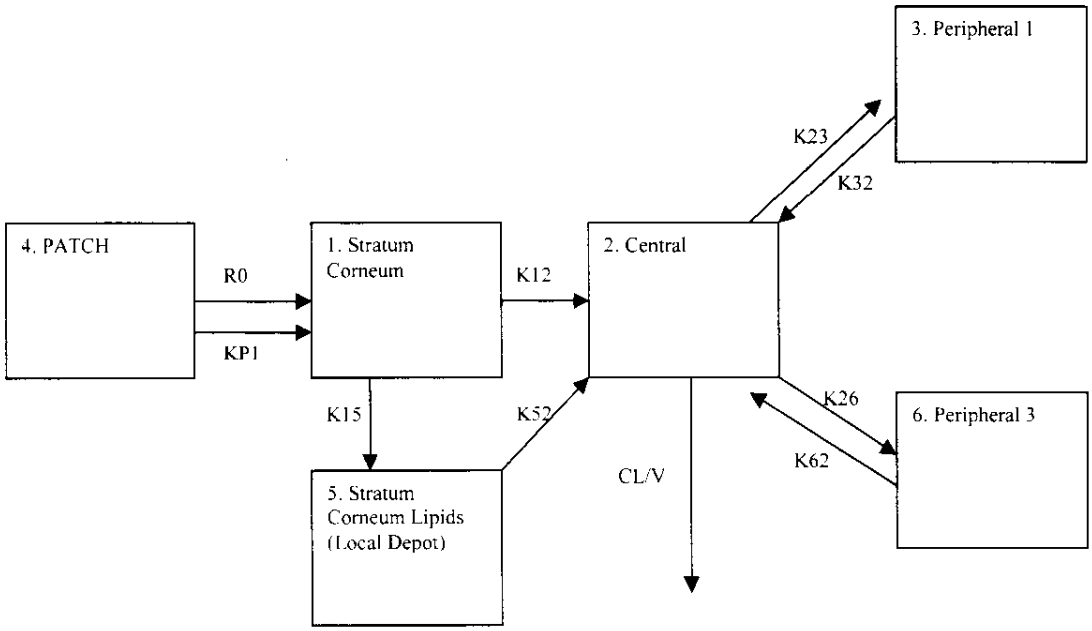


Fig. 27. A schematic of the final population PK model for BTDS

Table 22. Summary of the NonMem output generated using the final population PK

Parameter	Theta	Final Parameter Estimate	Standard Error of Estimate
Clearance (L/h)	1	55.1[a]	NE[b]
Volume of Central Compartment (L)	2	37.2[a]	NE
Volume of Peripheral Compartment 1(L)	3	68[a]	NE
Intercompartmental Clearance (between central and first peripheral compartments) (L/h)	4	132[a]	NE
Absolute Bioavailability of BTDS for 7-day application	5	0.15	0.00733
Lag time for zero order component of BTDS (h)	8	1.01	0.0101
First order rate constant (from stratum corneum to central compartment) (1/h)	9	1000[a]	NE
First order rate constant (from stratum corneum to stratum corneum lipid depot) (1/h)	10	3.000[a]	NE
First order rate constant (from stratum corneum lipid depot to central compartment) (1/h)	11	0.0265	0.00205
Volume of Peripheral Compartment 2 (L)	12	579[a]	NE
Intercompartmental Clearance (between central and second peripheral compartments) (L/h)	13	34.6[a]	NE
Zero order input fraction	14	.00000299	NE
Lag time for first order component of BTDS (h)	15	10.5	1.14
First order input rate (from BTDS to stratum corneum) (1/h)	16	0.0302	0.00339
Absolute Bioavailability of BTDS for 3-day application	17	0.0809	0.00666

[a] Fixed
[b] NE = Not Estimated
(Cross Reference: Appendix 9.3.2)

Interindividual Variability	OMEGA	Variance (%CV)	Standard Error of Estimate
Clearance (L/h)	1	0.0537[a]	0.0101
Volume of Central Compartment (L)	2	1.01	0.277
Absolute Bioavailability of BTDS for 7- day application	5	0.104	0.0189
Absolute Bioavailability of BTDS for 3-day application	6	0.0689	0.0285
First order rate constant (from stratum corneum lipid depot to central compartment) (1/h)	8	0.276	0.0918
First order input rate (from BTDS to stratum corneum) (1/h)	9	0.763	0.247

[a] root*100
(Cross Reference: Appendix 9.3.2)

Residual Variability	SIGMA	Variance	Standard Error of Estimate
Proportional component for IV treatment groups	1	0.0141	0.0117
Additive component for IV treatment groups	2	1570[a]	689
Proportional component for BTDS treatment groups	3	0.0363	0.0102
Additive component for BTDS treatment groups	4	329[a]	143

[a] SD = root
Additive error: SD = sqrt(variance)
Proportional error: % CV = sqrt(variance*100)
(Cross Reference: Appendix 9.3.2)

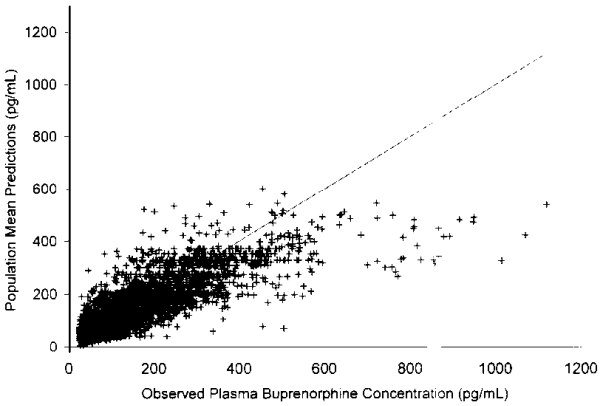


Fig. 28. **Population** mean prediction vs. observed buprenorphine plasma conc.

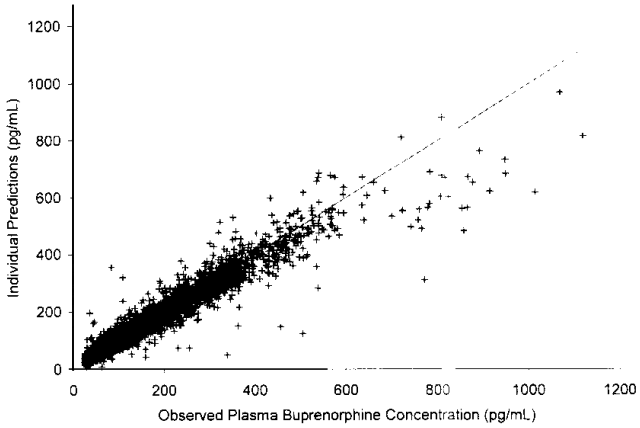


Fig. 29. **Individual** mean prediction vs. observed buprenorphine plasma conc.

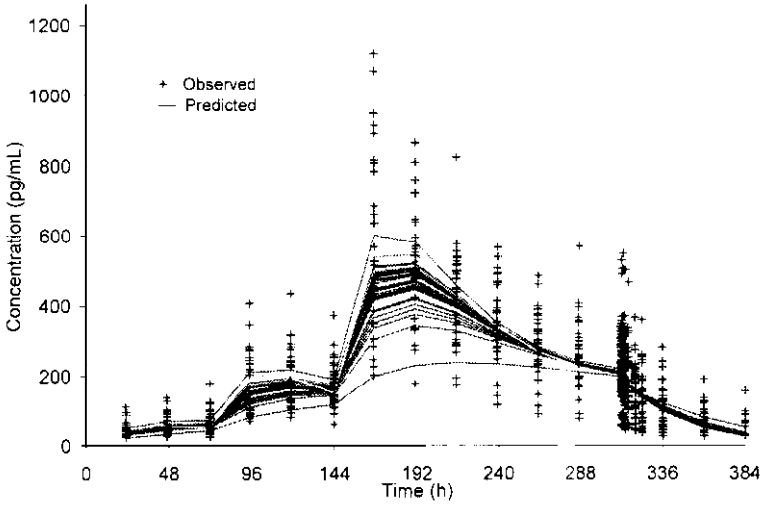


Fig. 30. Observed and predicted buprenorphine plasma conc.-time profiles (study BP97-0501).

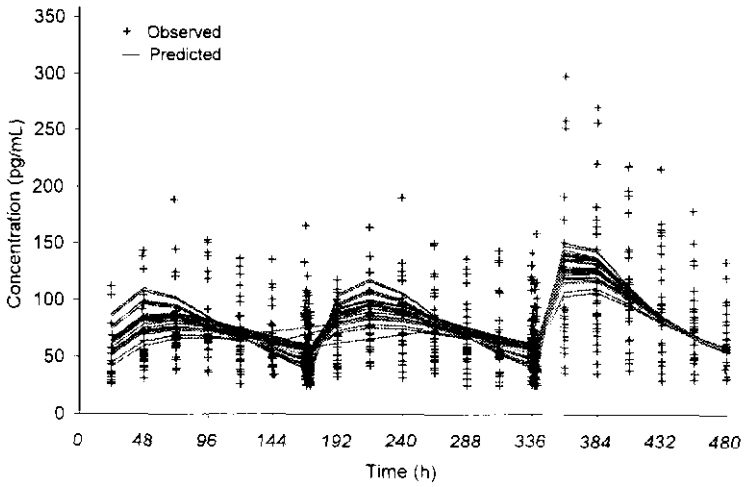


Fig. 31. Observed and predicted buprenorphine plasma conc.-time profiles (study BP97-0303).

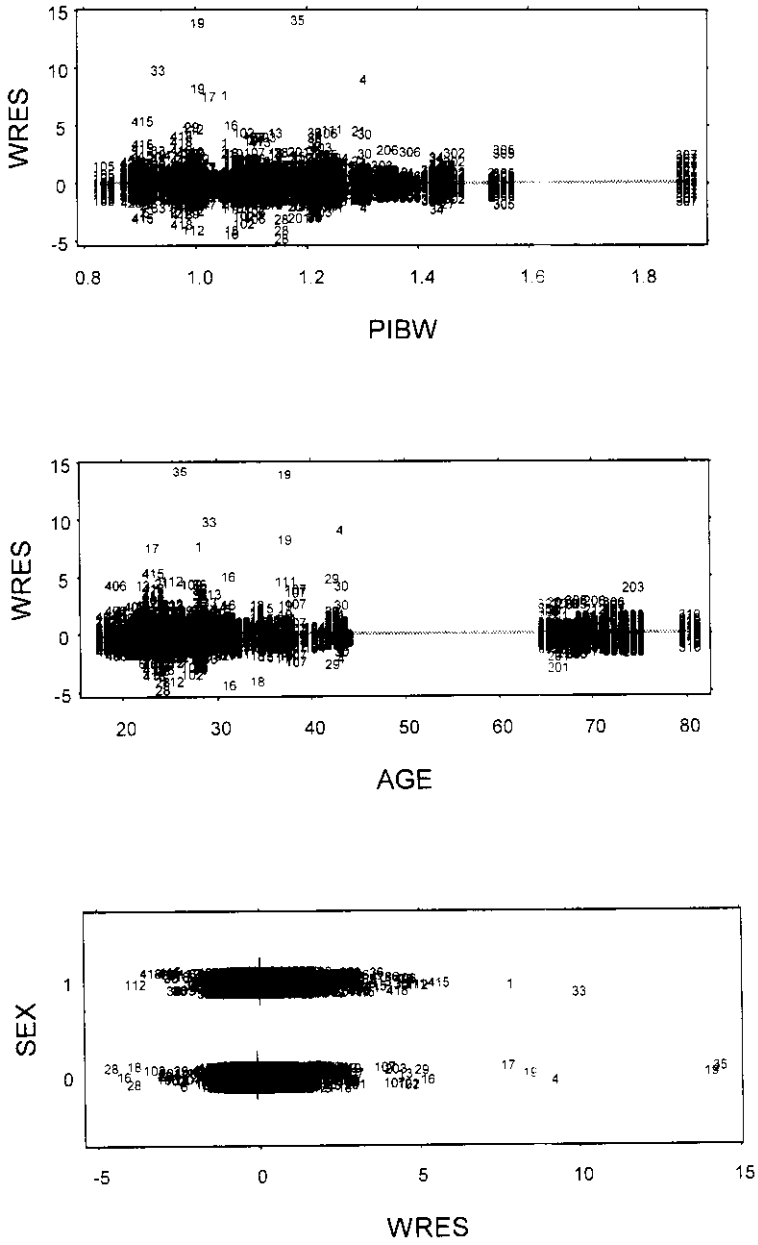


Fig. 32. Weighted residuals vs. covariates.

Fig. 23. Comparison of buprenorphine concentrations from actual and simulated clinical trials (single dose study).

		BTDS Dose (mg)					
		Observed Concentration(pg/mL)[a]			Simulated Concentration (pg/mL)		
	Percentile	5	10	20	5	10	20
48 hours after BTDS application	Median	84.6	146	331	75.9	140	285
	25th	56.4	112	233	50.2	93.1	192.7
	75th	119	204	438	109.9	200.9	419.7
24 hours after BTDS removal	Median	34.5	54.6	79.2	25.9	51.4	103
	25th	33.3	36.6	67.6	12.8	32.4	67.9
	75th	34.7	76.9	135	40	76.5	151.3

[a] Study BP97-0501

Fig. 24. Comparison of buprenorphine concentrations from actual and simulated clinical trials (multiple dose study).

	Time (h)					
Percentile	48	216	384	48	216	384
	Observed Concentration (pg/mL)[b]			Median Simulated Concentration (pg/mL)		
Median	55.5	76.5	106.0	74.4	88.0	112.7
25th	48.0	56.9	76.4	48.4	59.4	79.7
75th	82.0	107.0	160.0	110.2	127.3	155.9

[a] The concentrations shown are at 48 hours after first BTDS application (48), 24 hours after the second application (216), and 24 hours after the third application (384). Values shown are the median and the 25th and 75th percentiles.
[b] Study BP99-0204

Fig. 25. Comparison of buprenorphine concentrations from actual and simulated clinical trials (escalating BTDS applications).

	Time (h)					
Percentile	48	120	192	48	120	192
	Observed Concentration (pg/mL)[b]			Simulated Concentration (pg/mL)		
Median	50.5	176.5	534.0	52.1	160.7	412.0
25th	40.5	126.0	450.5	34.4	116.9	294.0
75th	83.5	250.5	618.0	74.3	217.5	565.8

[a] Concentrations shown are at 48 hours after the first BTDS 5 application (48), 24 hours after the second BTDS 10 application (120) and 24 hours after the third BTDS 20 application (192). The values shown are the median and the 25th and 75th percentiles.
[b] Study BP97-0303

Reviewer's Comments

- **The final population PK model seemed to predict reasonably well the plasma concentration of different subjects at set time points after single and multiple dose BTDS applications. However, it is noteworthy that the model failed to explain extreme buprenorphine plasma concentrations (i.e.-buprenorphine concentrations greater than 400 pg/ml).**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suliman Alfayoumi
7/13/01 11:05:23 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/15/01 07:11:29 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Filing Memorandum

NDA:	21-306	Priority Classification:	S
IND:		Indication:	Management of Pain
Brand Name:	Norspan	Date of Submission:	11/3/00
Generic Name:	Buprenorphine Transdermal System		
Sponsor:	Purdue Pharma L.P.	UFGD:	9/3/01
Division:	DACCADP	Medical Division:	DACCADP
Reviewer:	Suliman AlFayoumi	Team Leader:	Suresh Doddapaneni

Items included in NDA	*Yes*	*No*	*Request*
***Table of Contents present and sufficient to locate reports, tables, data, etc.**	X		
†Tabular Listing of All Human Studies (electronic and hard copies)	X		
†HPK Summary (electronic and hard copies)	X		
†Study Synopses (electronic and hard copies)	X		
†Labeling (electronic and hard copies)	X		
Human Bioavailability Studies	X		
***Bioequivalence Studies (if needed)**	X		
IVIVC Studies		X	
†Dissolution Profiles (electronic and hard copies)		X	
***Assay Validation Reports**	X		
Plasma Protein Binding Studies	X		
***In Vitro* Metabolism Studies**	X		
Pharmacokinetics Studies in Volunteers	X		
Pharmacokinetics Studies in Patients	X		
Sub-population Studies	X		
Population PK Studies		X	
Summary Table of PK/PD Studies	X		
PK/PD Studies in Volunteers	X		
PK/PD Studies in Patients	X		
Individual Datasets for all PK and PK/PD studies in electronic format	X		

*required for filing
†for these, indicate with an "h" or an "e" which is present /absent, and which will be requested. Use N/A if not applicable.

This application is filable
(if not filable, discuss why below:)

Comments to be sent to the Firm

Signature:

CC: NDA 21-306, HFD-850(Lesko, Lee, Metz), HFD-170(GDALPAN, SSHEPHERD)
HFD-870(PLEE, ALFAYOUMI, SDODDAPANENI, HMALINOWSKI)

45 DAY MEETING CHECKLIST

FILEABILITY

On initial overview of the NDA application: **YES**

BIOPHARMACEUTICAL:

(1) On its face, is the biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin? **YES**

(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? **YES**

(3) On its face, is the biopharmaceutical section of the NDA legible so that substantive review can begin? **YES**

(4) Are the Phase studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? **YES**

(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceuticals data to allow comparison between the product to be marketed and the product(s) used in the clinical development? **YES**

(6) From a biopharmaceuticals perspective, is the NDA fileable? If "no", please state below why it is not? **YES**

_____

Reviewing Biopharmaceutics Officer Date

_____

Supervisory Biopharmaceutics Officer Date

/s/

Suliman Alfayoumi
12/7/00 02:30:39 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
12/10/00 12:04:43 PM
BIOPHARMACEUTICS