CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-959

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Product: Orapred® ODT (prednisolone sodium phosphate ODT)
Sponsor: Biomarin
PIND: 70, 495 (N005)
Submission Date: 05/06/05
Purpose: Review of Sponsor's response regarding food-effect
Reviewer: Tapash K. Ghosh, Ph.D.

Background

In the meeting with the Agency on April 11, 2005, it was agreed upon that as food effect has not been mentioned in the labels of previous approved oral dosage forms of prednisolone, the Agency encourages sponsors to conduct food effect study on the ODT formulation. However, FDA and BioMarin agreed upon submitting the published literature to the PIND file for review prior to the NDA application. FDA agreed to contact BioMarin after reviewing the literature about whether a food effect study is still necessary for Orapred ODT and if the study may be initiated prior to filing the NDA.

In response to the above, the sponsor submitted several published articles regarding effect of food on the pharmacokinetics of prednisone/prednisolone.

Upon review of the articles, it appears that food does not affect the pharmacokinetics of prednisone/prednisolone when administered as conventional dosage forms.

Comments: Based on the assumption that bioequivalence (BE) between Orapred® ODT and the reference listed drug (RLD) can be established, food-effect study on Orapred® ODT will not be necessary. However, if BE can not be established, the sponsor needs to conduct food effect study on Orapred® ODT.

Tapash K. Ghosh, Ph.D.
Pharmacokineticist

Concurrence:

Edward D. Bashaw, Pharm. D./TL/HFD 880

CC: IND 70, 495
HFD-550/Div File; HFD-550/CSO/Clark; HFD-880/Lazor/Selen; To DFS

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/s/

Tapash Ghosh
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BIOPHARMACEUTICS

Dennis Bashaw
6/21/05 11:48:18 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-959	Submission Date: 7/29/05
Submission Type; Code:	505(b)(2)
Brand/Code Name:	Orapred ODT™
Generic Name:	Prednisolone Sodium Phosphate Orally Disintegrating Tablets
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	CPB 2
ORM Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	Medicis Pediatrics, Inc.
Relevant IND(s):	70,495
Reference NDA	Pediapred (NDA 19-157; Celltech Pharms)
Formulation; Strength(s):	10, 15 and 30 mg prednisolone base ODT (Equivalent to 13.44 mg, 20.16 mg and 40.32 mg of Prednisolone Sodium Phosphate)
Proposed Indication:	
Proposed Dosage Regimen:	The initial dose of Orapred may vary from [redacted] to 60 mg (prednisolone base) per day, depending on the specific disease entity being treated...The initial dosage should be maintained or adjusted until a satisfactory response is noted...**IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT...**It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; If after long term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly. In the treatment of acute exacerbations of multiple sclerosis, daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day or 4 to 8 mg dexamethasone every other day for one month have been shown to be effective. In pediatric patients, the initial dose of Orapred may vary depending on the specific disease entity being treated. The range of initial doses is 0.14 to 2 mg/kg/day in three or four divided doses (4 to 60 mg/m^2bsa/day).

The standard regimen used to treat nephrotic syndrome in pediatric patients is 60 mg/m^2/day given in three divided doses for 4 weeks, followed by 4 weeks of single dose alternate-day therapy at 40 mg/m^2/day.

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1 Executive Summary

Medicis Pediatrics, Inc, a wholly owned subsidiary of Medicis Pharmaceutical Corp, has submitted NDA 21-959 for Orapred ODT™, 10 mg, 15 mg and 30 mg Prednisolone Orally Disintegrating Tablets (Equivalent to 13.44 mg, 20.16 mg and 40.32 mg of Prednisolone Sodium Phosphate). It should be noted that the Applicant has Orapred

Solution (prednisolone sodium phosphate oral solution) currently on the market; each 5 mL (teaspoonful) of Orapred Solution contains 20.2 mg prednisolone sodium phosphate (15 mg prednisolone base) in a palatable, aqueous vehicle.

Orapred ODT was developed to provide another option for convenient dosing (e.g., the palatability and ease of administration of taking prednisolone with or without water; Orapred ODT seeks the same indications as the currently marketed prednisolone sodium phosphate oral solutions Pediapred and Orapred.

This submission relies on the Agency's previous findings of safety and effectiveness of the reference listed drug Pediapred Oral Solution, 6.7 mg/5mL (Prednisolone Base 5 mg/ 5 mL), via cross reference to NDA 19-157. No clinical efficacy studies were conducted.

However, the Applicant submitted the results of two relative bioavailability studies (OPD-001-01 and OPD-002-01), that compared the bioequivalency of Orapred ODT with the reference listed drug Pediapred (and Orapred Solution), and the relative bioavailability of Orapred ODT™ with and without water, respectively. To-be-marketed formulation was used in the BE studies. The studies were conducted using only the 30 mg prednisolone base equivalent strength of Orapred ODT. The 10 mg, 15 mg and 30 mg tablet formulation proposed in this Application are compositionally proportional. Since the ODT tablet formulations are proportionally similar, in vivo BE demonstration of the lower strengths can be waived based on dissolution tests and an in vivo study on the highest strength. (Refer to March 2003 Guidance and FDA Pre-NDA meeting minutes.)

Based on the findings of the Study OPD-001-01, the proposed Orapred ODT product is bioequivalent to the reference listed drug, Pediapred Solution. In addition, Orapred ODT was bioequivalent to Orapred Solution. Study OPD-002-01 demonstrated that Orapred ODT can be taken with or without water.

With respect to safety, the two BE studies did not show any AEs that were different from AEs already described in the current package insert for prednisolone sodium phosphate. In study OPD–001–01, three subjects (14%) reported 6 treatment–emergent adverse events (AEs); these AEs (face edema, swelling face, pharyngolaryngeal pain, blood in stool, eye irritation, eye edema) were not considered severe or serious. All 6 AEs occurred in Orapred ODT formulation group. No adverse events (AEs) occurred in study OPD–002–01.

Orapred ODT was not studied in pediatric population; the Division of Pediatric Drug Development did not recommend conducting a pediatric study (April 11, 2005 Pre-NDA meeting).

With respect to dissolution, the data supports the following dissolution specification: NLT [redacted] % (Q) in 30 minutes, rather than NLT [redacted]% (Q) in 30 minutes. This revised specification was communicated to and accepted by the sponsor via the ONDQA information request letter dated 3/15/2006.

The DSI inspection team recommends to accept the study OPD-001-01 (singed off date 5/15/06). With respect to Labeling, the Agency proposes to delete all references to [redacted] (see Section 3, Detailed Labeling Recommendations).

Overall, the information submitted in this NDA is acceptable pending a mutual agreement can be reached with the Applicant with respect to Orapred ODT Labeling.

1.1 Recommendations

From Office of Clinical Pharmacology and Biopharmaceutics point of view, the information contained in the Application is acceptable pending a satisfactory agreement can be reached with the Applicant regarding the Labeling for Orapred ODT formulation.

It is recommended that all references to [redacted] be deleted in the proposed Package Insert. Texts are deleted (~~crossed out~~) and added in red fonts, especially under the Clinical Pharmacology and the Dosage and Administrations sections (See Section 3 of this review, Detailed Labeling Recommendations).

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CPB Findings

The purpose of study OPD–001–01 was to determine the bioequivalence of a single 30 mg prednisolone base equivalent dose Orapred ODT to the Reference Listed Drug (RLD), Pediapred, and to examine the relative bioavailability of Orapred ODT to already marketd Orapred Solution. The results indicated that Orapred ODT is BE to both Pediapred Solution and Orapred Solution.

Treatments (Dose,Dosage Form, Route) [Product ID]	**Subjects (No.(M/F) type Age: mean (range)**	**Mean Parameters (+/– SD)**				
		Cmax (ng/mL)	**Tmax (h)**	**AUC (ng*h/mL)**	**T1/2 (h)**	**kel (1/h)**
Orapred ODT, 30 mg, oral	21 (17/4) Healthy volunteers 26 y (19-42)	420.905 ± 78.2847	1.3275 ± 0.55146	2408.1 ± 361.48	2.615 ± 0.2667	0.2678± 0.02874
Pediapred solution		461.333 ± 77.9393	0.8959 ± 0.33949	2426.1 ± 359.95	2.611 ± 0.3291	0.2697± 0.03540
Orapred solution		501.190 ± 86.2668	0.6429 ± 0.18661	2547.9 ± 388.89	2.815 ± 0.3080	0.2492± 0.02792

Ratios : (90% Confidence Intervals)

Parameter	Prednisolone Orapred° ODT (A) vs Celltech Pediapred (B)
AUC 0-t	99.0% (96.5 – 101.6%)
AUCinf	99.3% (96.7 – 102.0%)
Cmax	90.2% (85.7 – 95.1%)

Parameter	Prednisolone Orapred° ODT (A) vs Orapred° oral solution (C)
AUC 0-t	94,5% (92.1 – 97.0%)
AUCinf	94.5% (92.0 – 97.0%)
Cmax	83.8% (79.6 – 88.3%)

Study OPD-002-01 was a relative bioavailability study comparing the administration of Orapred ODT with and without water. The study results indicated that Orapred ODT can be taken with or without water.

Treatments (Dose,Dosage Form, Route) [Product ID]	**Subjects (No.(M/F) type Age: mean (range)**	**Mean Parameters (+/– SD)**				
		Cmax (ng/mL)	**Tmax (h)**	**AUC (ng*h/mL)**	**T1/2 (hr)**	**kel (1/h)**
Orapred ODT, 30 mg, oral with 240 mL water	14 (12/2) Healthy volunteers 30 y (20–45)	431.429 ± 77.5090	1.1455 + 0.47527	2555.2 ± 634.34	2.723 ± 0.2907	0.2571 ± 0.02618
Orapred ODT, 30 mg, oral without water		458.643 ± 111.8561	1.2679 ± 0.64647	2652.9 ± 797.17	2.806 ± 0.3479	0.2503 ± 0.02868

Ratios : (90% Confidence Intervals)

Parameter	Prednisolone Ora red° ODT without water (B) vs Ora red° ODT with 240 mL water (A)
AUC 0-t	102.8% (100.1 – 105.6%)
AUCinf	103.0% (100.2 – 106.0%)
Cmax	105.2% (99.3 – 111.4%)

The Applicant did not conduct food effect study in this Application. The Agency concluded that there is no food effect on conventional dosage forms of prednisolone, based on the published information submitted to the IND 70,495 on 05/06/2005 (serial # 005). This IND submission was reviewed on 6/21/05 by Dr. Tapash Ghosh and the Applicant was notified on 6/20/05 that no food effect study was needed if BE is established between the prednisolone ODT and the reference listed drug product.

The Applicant proposed the following dissolution method and specification. It is noted that prednisolone sodium phosphate is freely soluble in water (**PEDIAPRED®, prednisolone sodium phosphate, USP, Oral Solution)**). The Applicant's dissolution method is acceptable. However, the dissolution specification should be "NLT— % (Q) in 30 minutes" based on the submitted data. This revised specification was communicated to and accepted by the sponsor via the ONDQA information request letter dated 3/15/2006.

Proposed methodology by the Applicant:

Apparatus:	USP 2, paddles
Medium:	22 mM sodium acetate buffer, pH 4.5
Medium Volume:	500 mL
Medium Temperature:	37.0 °C ± 0.5 °C
Paddle Speed:	50 rpm
Sampling Time Point (single):	30 minutes
Sampling Time Points (profile):	5, 15, 30, 45, and 60 minutes
Sampling Volume:	5 mL

Proposed specification by the Applicant:

Dissolution Specification:		NLT [redacted] % (Q) in 30 minutes
	Stage 1)	NMT 0 Tablets less than [redacted] % (n=6)
	Stage 2)	Average NLT [redacted] %; NMT 0 Tablets < [redacted] % (n=12)
	Stage 3)	Average NLT [redacted] %; NMT 2 Tablets < [redacted] %, and NMT 0 Tablets < [redacted] % (n=24)
Method:		USP 2 at 50 rpm in pH 4.5 buffer, ATM-638

With respect to safety, during the study OPD–001–01, three subjects (14%) reported 6 treatment–emergent adverse events (AEs); these AEs (face edema, swelling face, pharyngolaryngeal pain, blood in stool, eye irritation, eye edema) were not considered severe or serious. All 6 AEs occurred in Orapred ODT formulation group. No adverse events (AEs) occurred during the study OPD–002–01. The subjects completing Study OPD–001–01 received three such doses, and the subjects completing Study OPD–002–01 received two such doses.

2 QBR

2.1 General Attributes of the Drug

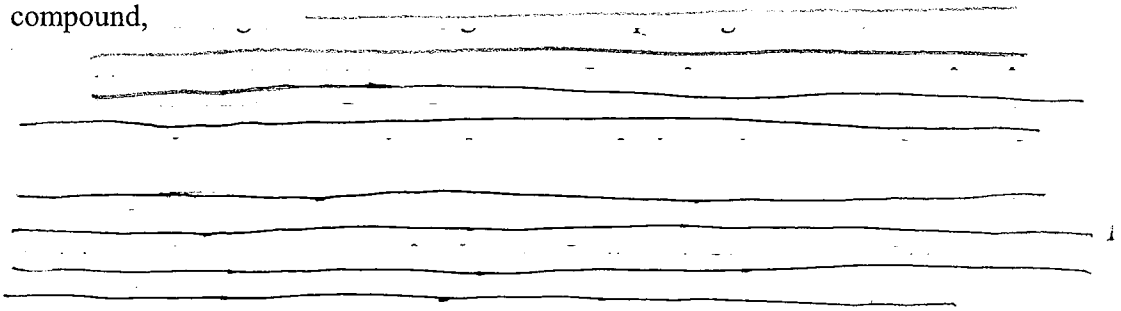
2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Orapred ODT was developed to provide another option for convenient dosing (the palatability and ease of administration) of oral prednisolone; Orapred ODT seeks the same indications as the currently marketed prednisolone sodium phosphate oral solutions Pediapred and Orapred.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The process developed for Orapred ODT is based on CIMA's proprietary drug delivery technology OraSolv. The drug substance, prednisolone sodium phosphate is a very bitter

compound,



Orapred ODT are provided as white, round, flat faced, beveled–edge tablets in prednisolone dosage strengths of 10 mg, 15 mg and 30 mg per tablet. The 10 mg, 15 mg and 30 mg tablet formulation are compositionally proportional. Each tablet is debossed with "ORA" on one side of the tablet and the dosage strength on the on the other side of the tablet (e.g., "10" for the 10 mg prednisolone dosage strength).

The composition of Coated PSP is provided in the following Table 1.

Table 1. Composition of coated prednisolone sodium phosphate

Component	Quality Standard	mg/g	Function
Prednisolone Sodium Phosphate	USP		Drug substance

The composition of each dosage strength is provided in Table 2.

Table 2: Composition of Orapred ODT. 10mg, 15 mg and 30 mg

The essential characteristic of the molecule and the most relevant physicochemical properties are summarized:

Property	**Observation**
Empirical Formula	C21H27Na2O8P
Molecular weight	484.4
Appearance	White or practically white crystalline powder
Solubility	Freely Soluble in Water, Soluble in Methanol Slightly soluble in Alcohol and Chloroform Very slightly soluble in Acetone and Dioxane
Description	Hygroscopic
Water content	NMT – %

Overages (Prednisolone ODT):

The intended commercial formulation for Orapred ODT. 10mg, 15 mg and 30 mg (Final Product) does not include any manufacturing overage.

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

Prednisolone sodium phosphate belongs to the class of synthetic adrenocortical steroids, with predominantly glucocorticoid activity. This drug is used for its potent anti–inflammatory effects in disorders of many organ systems (endocrine, rheumatic and hematologic disorders), dermatologic, ophthalmic, gastrointestinal, respiratory and neoplastic diseases, allergic and edematous states. Prednisolone may also be used as the replacement therapy for secondary adrenocortical insufficiency and congenital adrenal hyperplasia. The initial dose ranges from [redacted] mg to 60 mg per day depending upon the condition being treated. Initial daily doses of 200 mg of prednisolone have been used in the treatment of acute exacerbations of multiple sclerosis. With respect to adverse events (AEs), the majority AEs are derived from the drug's immunomodulatory properties, as well as from alternations in normal exocrine and endocrine function.

2.1.4 What are the proposed dosage and route of administration?

Orapred ODT is an immediate-release solid, orally disintegrating tablet formulation containing drug substance, Prednisolone Sodium Phosphate.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

No clinical safety and efficacy studies were conducted.

2.3 Intrinsic Factors

2.3.1.1 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?

Orapred ODT was not studied in pediatric population; the Division of Pediatric Drug Development did not recommend conducting a pediatric study (April 11, 2005 Pre-NDA meeting).

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

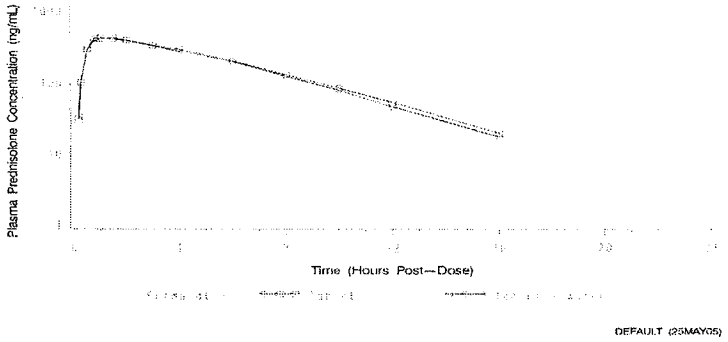
2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The to-be-marketed ODT formulation was used in the two BE studies. Division of Scientific Investigations audited study OPD-001-01 and recommended acceptance of the data for Regulatory Decision making.

Study OPD–001–01

Study OPD–001–01 was a three way crossover comparing the single dose oral bioavailability of a 30 mg prednisolone base equivalent dose of the test drug Orapred ODT with equivalent doses of Pediapred oral solution and Orapred oral solution.

Mean Plasma Prednisolone Concentrations



Orapred ODT was found to be bioequivalent to Pediapred oral solution. Orapred ODT and Orapred oral solution also displayed similar overall extent of absorption of prednisolone.

Treatments (Dose,Dosage Form, Route) [Product ID]	Subjects (No.(M/F) type Age: mean (range)	Mean Parameters (+/– SD)				
		Cmax (ng/mL)	Tmax (h)	AUC (ng*h/mL)	T1/2 (h)	kel (1/h)
Orapred ODT, 30 mg, oral	21 (17/4) Healthy volunteers 26 y (19-42)	420.905 ± 78.2847	1.3275 ± 0.55146	2408.1 ± 361.48	2.615 ± 0.2667	0.2678± 0.02874
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Cmax	90.2% (85.7 – 95.1%)

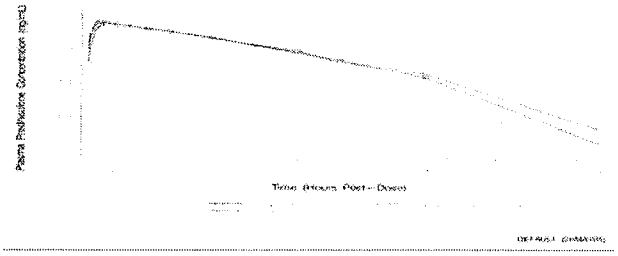
Parameter	Prednisolone Orapred° ODT (A) vs Orapred° oral solution (C)
AUC 0-t	94,5% (92.1 – 97.0%)
AUCinf	94.5% (92.0 – 97.0%)
Cmax	83.8% (79.6 – 88.3%)

Study OPD–002–01

The Orapred ODT water study, OPD–002–01, was a two way crossover comparing the relative bioavailability of a single 30 mg prednisolone base equivalent dose of Orapred ODT given with 240 mL water versus the same dose given without water.

Orapred ODT (prednisolone sodium phosphate) shows comparable bioavailability when administered with or without water.

Mean Plasma Prednisolone Concentrations



Treatments (Dose,Dosage Form, Route) [Product ID]	Subjects (No.(M/F) type Age: mean (range)	Mean Parameters (+/– SD)				
		Cmax (ng/mL)	Tmax (h)	AUC (ng*h/mL)	T1/2 (hr)	kel (1/h)
Orapred ODT, 30 mg, oral with 240 mL water	14 (12/2) Healthy volunteers 30 y (20–45)	431.429 ± 77.5090	1.1455 + 0.47527	2555.2 ± 634.34	2.723 ± 0.2907	0.2571 ± 0.02618
Orapred ODT, 30 mg, oral without water		458.643 ± 111.8561	1.2679 ± 0.64647	2652.9 ± 797.17	2.806 ± 0.3479	0.2503 ± 0.02868

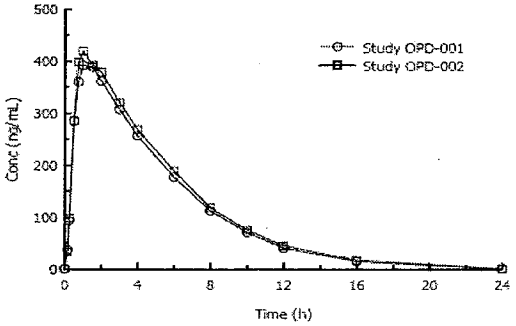
Ratios : (90% Confidence Intervals)

Parameter	Prednisolone Orapred° ODT without water (B) vs Ora red° ODT with 240 mL water (A)
AUC 0-t	102.8% (100.1 – 105.6%)
AUCinf	103.0% (100.2 – 106.0%)
Cmax	105.2% (99.3 – 111.4%)

Comparison of two studies

The plasma prednisolone levels from dosing with the Orapred ODT with 240 mL water in OPD–001–01 and OPD–002–01 were comparable across the various pharmacokinetic parameters.

Mean Plasma Prednisolone Concentrations



Comparison of Pharmacokinetic Parameters of Orapred ODT Given With 240 mL Water Between Studies OPD–001–01 and OPD–002–01

	AUC 0–t (ng*h/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	Half–life (h)	Kel (1/h)
OPD–001–01	2499.1 ± 633.23	2555.2 ± 634.34	431.429 ± 77.509	1.1455 ± 0.47527	2.723 ± 0.2907	0.2571 ± . 02618
OPD–002–01	2352.5 ± 342.42	2408.1 ± 361.48	420.905 ± 78.2847	1.3275 ± 0.55146	2.615 ± 0.2667	0.2678 ± 0.02874

2.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The food effect study was not conducted. In April 11, 2005, Pre-NDA meeting, the Agency conveyed to the Applicant that they need to conduct food effect study. During the discussion the Applicant agreed to submit a summary of the published literature on effect of food to the PIND file for review prior to the NDA application. Upon reviewing the information (Reviewer: Tapash K. Ghosh, Ph.D., June 2005), the Agency concluded that food does not affect the pharmacokinetics of prednisone/prednisolone.

2.5.3 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The Applicant conducted a comprehensive dissolution method development, which included different paddle speeds, and media. Prednisolone is freely soluble in water.

Proposed methodology:

Apparatus:	USP 2, paddles
Medium:	22 mM sodium acetate buffer, pH 4.5
Medium Volume:	500 mL
Medium Temperature:	37.0 °C ± 0.5 °C
Paddle Speed:	50 rpm
Sampling Time Point (single):	30 minutes
Sampling Time Points (profile):	5, 15, 30, 45, and 60 minutes
Sampling Volume:	5 mL

Proposed specification:

Dissolution Specification:		NLT ~ % (Q) in 30 minutes
	Stage 1)	NMT 0 Tablets less than ~% (n=6)
	Stage 2)	Average NLT ~ %; NMT 0 Tablets < ~% (n=12)
	Stage 3)	Average NLT ~%; NMT 2 Tablets < ~%, and NMT 0 Tablets < ~% (n=24)
Method:		USP 2 at 50 rpm in pH 4.5 buffer, ATM-638

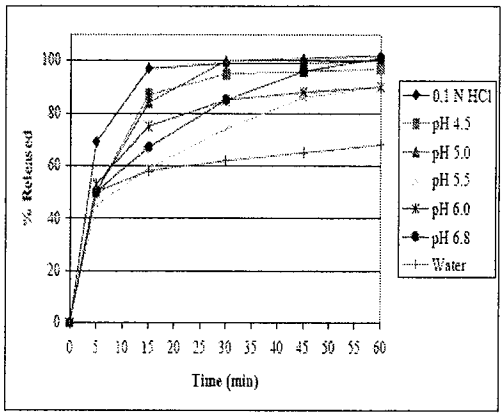
Dissolution support information

pH effect:

Table 1. Dissolution Profiles of Prednisolone ODT 30 mg, Development Lot LB1392-71 in Various Media (See Figure below)

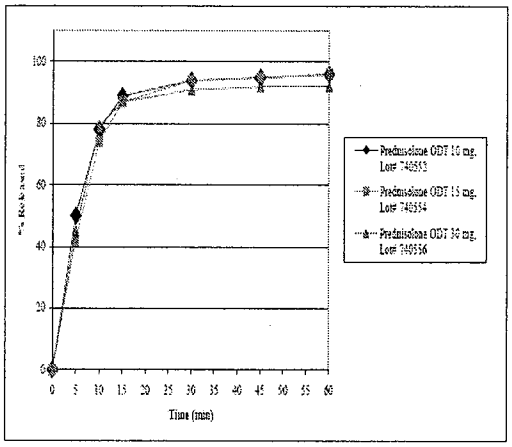
	Average % Released (n = 3)						
Time (min)	**0.1 N HCl**	**pH 4.5**	**pH 5.0**	**pH 5.5**	**pH 6.0**	**pH 6.8**	**Water**
0	0	0	0	0	0	0	0
5	69	50	50	45	53	50	50
15	97	87	84	59	75	67	58
30	99	95	100	74	85	85	62
45	99	96	101	86	88	96	65
60	100	97	102	90	90	101	68

Figure 1. Dissolution Profiles of Prednisolone ODT 30 mg, Development Lot LB1392-71 in Various Media



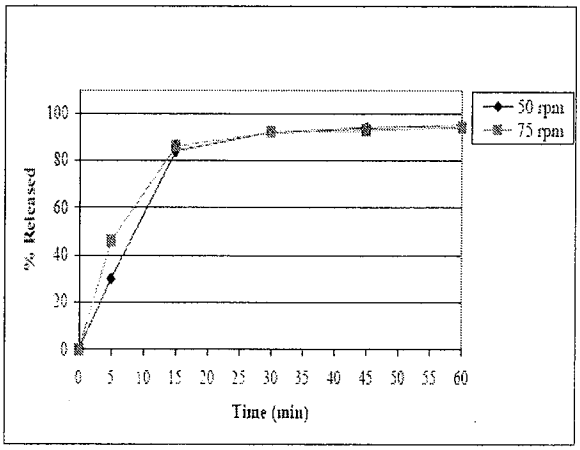
Dissolution data for all three strengths with the chosen medium

Figure 2. Prednisolone ODT Dissolution Results in pH 4.5 Medium



Paddle speed effect:

Figure 3. Effect of Paddle Speed on Prednisolone ODT 30 mg, Development Lot LB1392-74



2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?

Human plasma samples containing the analyte and internal standard are extracted using an online extraction method. The extracted samples are analyzed by an HPLC equipped with a [redacted] mass spectrometer. Positive ions are monitored in the selected reaction–monitoring (SRM) mode. Quantitation was determined using a weighted linear regression analysis (1/X2) of peak area ratios of the analyte and internal standard.

2.6.2 What is the range of the standard curve? What curve fitting techniques are used?

The analytical range for prednisolone in plasma was 4.00 – 1000 ng/mL. Quantitation was determined using a weighted linear regression analysis (1/X2) of peak area ratios of the analyte and internal standard.

2.6.3 What is the accuracy, precision and selectivity at these limits?

Precision was less than or equal to 7.3%. Accuracy ranged from 95.2% to 104.2%.

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

The freeze-thaw samples showed 1.3 – 1.6 % differences compared to the original stock solution.

2.6.4 What is the QC sample plan?

QC samples at four different concentrations (12.0 ng/mL, 250 ng/mL, 500 ng/mL, and 800 ng/mL) were prepared and utilized.

3 Detailed Labeling Recommendations

Sponsor is proposing [redacted] In the meantime, since the ODT information submitted in this supplement can stand on its own, it is recommended that all references to [redacted] be deleted. Texts are edited with deletion (~~crossed-out~~) and added in red fonts. Specifically, under the Clinical Pharmacology section, the following recommendation is proposed:

[redacted]

14 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

4.2 Individual Study Review

Study OPD-001-01

Comparative, Randomized, Single-Dose 3-way Crossover Relative Bioavailability Study of Orapred Orally Disintegrating Tablet (Prednisolone Sodium Phosphate) 40.3mg (Equivalent to 30mg Prednisolone Base) vs Celltech Pediapred (Prednisolone Sodium Phosphate) Oral Solution 6.7mg/5mL (Equivalent to 5mg Prednisolone Base/5 mL) and Orapred (Prednisolone Sodium Phosphate) Oral Solution 20.2mg/5mL (Equivalent to 15mg Prednisolone Base/5mL) in Healthy Volunteers under Fasting Conditions

[redacted] (Study Start Date): 14/Mar/2005 (date of last com leted): 30/Mar/2005

Objectives: The primary objective of this study was to compare the single-dose relative bioavailability of:

1. Orapred ODT (prednisolone sodium phosphate) 40.3mg (equivalent to 30mg prednisolone base) to Celltech Pediapred° (prednisolone sodium phosphate) oral solution 6.7mg/SmL (equivalent to 5 mg prednisolone base/5 mL)
2. Orapred ODT and Orapred° (prednisolone sodium phosphate) oral solution 20.2mg/5mL (equivalent to 15mg prednisolone base/5mL) under fasting conditions.

Methodology: The study subjects were healthy male and female adult volunteers. The study was a randomized, 3-way crossover, comparative bioavailability study under fasting conditions. All subjects in the study received a single 30 mg prednisolone base equivalent dose of the test formulation and an equivalent dose of each reference formulation (one Orapred° ODT tablet or 30 mL Pediapred° or 10 mL Orapred° oral solution). There was a 7-day washout between dosing periods.

Within 28 days of dosing, medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), elbow breadth were recorded. Each subject had a physical examination, vital signs (heart rate, blood pressure, temperature 4 respiratory rate), 12-lead ECG, and the laboratory tests including hematologic, hepatic and renal function tests.

Subjects were admitted to the study unit at least 10 hours prior to the scheduled dose. They remained in the unit until completion of the 24-hour post-dose blood sample.

Subjects were required to fast overnight for at least 10 hours before dosing and for at least 4 hours thereafter. Water was not permitted from 1 hour before until 1 hour after dosing, but was allowed at all other times. Standard meals were provided at approximately 4.5 and 9 hours after dosing, and at appropriate times thereafter. During housing, post-dose meal plans were identical for all periods.

Safety was evaluated by monitoring adverse events throughout the entire study, vital signs (heart rate, blood pressure, temperature and respiratory rate) at check-in and check-out in each period and clinical laboratory tests at the end of the study.

Number of Subjects (planned and analysed): 24 healthy adult subjects (20 males and 4 females) were dosed, and 21 subjects (17 males and 4 females) completed at least 2 periods. All 24 subjects were included in the safety assessment. Pharmacokinetic parameters were calculated for the 21 subjects that completed at least 2 periods.

Inclusion Criteria:

- Healthy adult male or female volunteers, 19-45 years of age;
- Weighing at least 52 kg for males and 45 kg for females and within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983);
- Medically healthy subjects with clinically normal laboratory profiles and ECGs; as deemed by the Principal Investigator;
- Females of childbearing potential should either be sexually inactive (abstinent) for 3 months prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) 6 months minimum;
    b. IUD in place for at least 3 months;
    c. barrier methods (condom, diaphragm) with spermicide for at least 3 months prior to the first dose and throughout the study;

d. surgical sterilization of the partner (vasectomy for 6 months minimum);
Other birth control methods may be deemed acceptable. Postmenopausal women with amenorrhea for at least 2 years will be eligible.

- Voluntarily consent to participate in the study.

Exclusion criteria:

- History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease.
- In addition, history or presence of:
  - alcoholism or drug abuse within the past 2 years;
  - hypersensitivity or idiosyncratic reaction to prednisolone or other corticosteroids.
- Female subjects who are pregnant or lactating.
- Subjects who received any form of injectable corticoids in the 12 weeks preceding the first dose or any oral forms of corticoids for the 30 days preceding the first dose.
- Subjects who have used any drugs or substances known to be strong inhibitors of CYP enzymes (formerly known as cytochrome P450 enzymes) within 10 days prior to the first dose.
- Subjects who have used any drugs or substances known to be strong inducers of CYP enzymes (formerly known as cytochrome P450 enzymes) within 28 days prior to the first dose.
- Subjects who have been on a special diet (for whatever reason) during the 28 days prior to the first dose and throughout the study.
- Females who are taking hormonal contraceptives or are on hormonal replacement therapy during the 28 days prior to the first dose and throughout the study.
- Subjects who have made any donation of blood within 56 days of study initiation.
- Subjects who have made a plasma donation within 7 days prior to the study.
- Subjects with hemoglobin less than 12.0 g/dL.
- Subjects who have participated in another clinical trial within 28 days prior to the first dose.
- Subjects who are currently using or have used nicotine-containing products within 30 days prior to entering the study.

Duration of Treatment: Each treatment was administered once to each subject and was separated by a 7-day washout period: Period 1 dosing: 15/Mar/2005; Period 2 dosing: 22/Mar/2005; Period 3 dosing: 29/Mar/2005

Treatments, Dose, Mode of Administration, and Batch Number: Subjects randomized to Treatment C received 10 mL of Orapred° 15 mg/5 mL oral solution followed by 240 mL of water.

Test Treatment:	A.	Orasolv® Prednisolone 30 mg (Equivalent to Prednisolone Sodium Phosphate 40.3 mg) tablet Manufactured by Cima Labs Inc. Lot No.: 740556 Expiration date: Not provided Manufacture date: Oct-2004
Reference Treatment:	B.	Pediapred® (Prednisolone Sodium Phosphate 6.7 mg/5 mL) Prednisolone 5 mg/5 mL oral solution Manufactured by Celltech Pharmaceuticals Inc. Lot No.: 40173 Expiration date: Jan-2006 Manufacture date: Not provided
Reference Treatment:	C.	Orapred® (Prednisolone Sodium Phosphate 20.2 mg/5 mL) Prednisolone 15 mg/5 mL oral solution Manufactured by [redacted] Lot No.: RM0414 Expiration date: Sep-2007 Manufacture date: Not provided

Blood sampling: Blood samples were collected before dosing (1 x 10 mL) and at the following times: 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing (1 x SmL). Plasma concentrations of prednisolone were measured by a validated LC/MS/MS method ([redacted]. The analytical range for prednisolone in plasma was 4.00 – 1000 ng/mL.

Criteria for Evaluation: Study endpoints were the 90% confidence intervals of the ratio of least-squares means of the pharmacokinetic parameters AUC0-t, AUCinf and Cmax of the test to reference formulations. The primary comparison of interest was Orapred° ODT vs Pediapred°. Orapred° ODT was also compared to Orapred° oral solution.

Statistical Methods: Descriptive Statistics Arithmetic means, standard deviations, and coefficients of variation were calculated for the pharmacokinetics parameters listed above. Additionally, geometric means were calculated for AUC0-t, AUCinf and Cmax. Analysis of Variance Analyses of variance (ANOVA) were performed on the ln-transformed AUC0-t, AUCinf and Cmax. The ANOVA model included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term at a 10% level of significance. Each ANOVA included calculation of least-squares means (LSM), the difference between formulation LSM, and the standard error associated with this difference. The above statistical analyses were done using the SAS° GLM procedure.

Ratios and Confidence Intervals Ratios of least-squares means were calculated using the exponentiation of the LSM from the analyses on the ln-transformed AUC0-t, AUCinf and Cmax. These ratios were expressed as a percentage relative to the reference formulation. Consistent with the two one-sided test for bioequivalence, 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed AUC0-t, AUCinf and Cmax. The confidence intervals were expressed as a percentage relative to the reference formulation.

9.7.1.2.2 Analyses of Variance

Analyses of variance were performed on the ln-transformed AUC 0-t, AUCinf, and Cmax. The ANOVA model included sequence, formulation and period as fixed effect, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term, at a 10% level of significance. Each ANOVA included calculation of LSM, the difference between formulation LSM, and the standard error associated with this difference. The above statistical analyses were performed using the SAS® GLM procedure.

9.7.1.2.3 Ratios and Confidence Intervals

Ratios of LSM were calculated using the exponentiation of the LSM from the analyses on the ln-transformed AUC 0-t, AUCinf, and Cmax pharmacokinetic parameters. These ratios were expressed as a percentage relative to the reference formulation.

Consistent with the two one-sided test for bioequivalence[7], 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed AUC 0-t, AUCinf, and Cmax. The confidence intervals were expressed as a percentage relative to the reference formulation.

9.7.1.2.4 Intrasubject Variability

The intrasubject variability for the AUC 0-t, AUCinf and Cmax pharmacokinetic parameters, which reflects the residual variability after accounting for differences between subjects, periods and formulations, was derived from the analyses of the ln-transformed data. It is a major determinant of sample size, power and the width of confidence intervals for crossover studies.

9.7.1.2.5 Formulae

The following formulae were used for the ratio of the LSM, 90% confidence interval and intrasubject variability calculations derived from the ANOVA.

	Ln-transformed Parameters
Ratio of LSM:	$100 \times e^{\left(LSM_t - LSM_r\right)}$
90% Confidence Interval[8]:	$100 \times e^{\left(LSM_t - LSM_r \pm t_{df,0.05} \times SE_{t-r}\right)}$
Intrasubject CV%:	$100 \times \sqrt{e^{MSE} - 1}$

Note: $t_{df,\alpha}$ is the value of the Student's t distribution with df degrees of freedom (i.e. degrees of freedom for the error term from the analysis of variance) and a right-tail fractional area of α.

LSM_T and LSM_R are the least-squares mean of the test and reference formulation, respectively, as computed by the LSMEANS statement of the SAS® GLM procedure.

MSE is the mean square error from the analysis of variance.

SE_{T-R} is the standard error of the adjusted difference between the formulation means, as computed by the ESTIMATE statement in the SAS® GLM procedure.

Results:

1. Withdrawals

There were three subjects who were withdrawn/discontinued from the study:

Subject No.	Date	Reason
8	21-Mar-2005	Subject withdrew for personal reasons.
18	21-Mar-2005	Subject withdrew for personal reasons.
22	22-Mar-2005	Subject withdrew for personal reasons.

2. Assay

Calibration Curve Standards and Quality Control Samples - A set of 9 non-zero calibration standards ranging from 4.00 ng/mL to 1000 ng/mL and QC samples at four different concentrations (12.0 ng/mL, 250 ng/mL, 500 ng/mL, and 800,ng/mL) were prepared and subsequently stored at a nominal temperature of -20°C.

Study samples were analyzed without exceeding short term, freeze-thaw stability, post-preparative stability or processed sample integrity. The following evaluations have been conducted:

Long-term Stability: 99 days at -20°C
Short-term Stability: 30.8 hours at ambient temperature
Freeze-thaw Stability: 3 cycles at -22°C
Post-preparative Stability: 55.7 hours at ambient temperature
Processed Sample Integrity: 223.9 hours at ambient temperature

Quality Control Sample Analyses (Between-Batch Precision and Accuracy) - Precision was less than or equal to 7.3%. Accuracy ranged from 95.2% to 104.2%.

Table 2. Quality Control Sample Data (Between-batch Precision and Accuracy) for Prednisolone in Human Plasma (EDTA)

Batch	*QC A 12.0 ng/mL*	*QC D 250 ng/mL*	*QC B 500 ng/mL*	*QC C 800 ng/mL*
7	11.3	258	491	822
	11.1	273	518	811
	14.3	260	495	776
	13.6	263	487	810
8	13.6	250	465	735
	12.8	256	486	775
	13.8	270	478	757
	14.4	258	454	749
9	12.5	247	466	760
	12.9	244	471	772
	12.7	256	456	769
	12.3	260	476	759
10	10.8	244	501	748
	11.7	255	487	774
	12.2	256	479	769
	12.2	252	480	741
11	13.3	258	458	759
	13.5	255	480	756
	12.9	242	475	766
	11.9	259	473	754
12	12.8	247	461	779
	11.7	255	476	832
	12.7	256	461	762
	12.0	254	457	806
13	12.3	249	465	758
	12.1	245	463	777
	11.7	262	481	773
	12.1	255	476	780
Mean	12.5	255	476	772
S.D.	0.913	7.38	14.8	24.2
%CV	7.3	2.9	3.1	3.1
%Theoretical	104.2	102.0	95.2	96.5
n	28	28	28	28

Calibration Standard Concentrations – Accuracy ranged from -5.4% to 6.5%.

Table 3. Back-calculated Calibration Curve Standard Concentrations of Prednisolone in Human Plasma (EDTA)

Batch	*STD B 4.00 ng/mL*	*STD C 8.00 ng/mL*	*STD D 20.0 ng/mL*	*STD E 100 ng/mL*	*STD F 300 ng/mL*	*STD G 436 ng/mL*	*STD H 600 ng/mL*	*STD I 850 ng/mL*	*STD J 1000 ng/mL*
7	4.05	7.83	19.3	111	337	443	563	786	962
8	3.80	8.41	22.1	110	313	442	549	789	925
9	3.96	8.09	20.2	108	307	449	601	802	942
10	4.01	7.68	21.6	102	300	460	581	835	963
11	3.85	8.27	22.0	101	318	437	585	820	926
12	3.94	7.96	21.6	104	312	426	586	829	957
13	3.91	*6.38	22.0	105	310	443	571	780	945
Mean	3.93	8.04	21.3	106	314	443	577	806	946
S.D.	0.0871	0.275	1.08	4.04	11.6	10.4	17.1	22.2	15.9
%CV	2.2	3.4	5.1	3.8	3.7	2.3	3.0	2.8	1.7
%Bias	-1.8	0.5	6.5	6.0	4.7	-1.6	-3.8	-5.2	-5.4
n	7	6	7	7	7	7	7	7	7

Reason Deactivated
* Rejected

Precision and accuracy:

Table 2. Inter- and Intra-batch Precision and Accuracy for Prednisolone in Human Plasma (EDTA)

Batch	LLOQQC 4.00 ng/mL	QC A 12.0 ng/mL	QC D 250 ng/mL	QC B 500 ng/mL	QC C 800 ng/mL
2	2.93	11.8	244	476	796
	3.34	11.9	247	485	790
	3.91	11.7	245	480	777
	3.61	12.0	247	473	768
	4.32	11.0	260	475	776
	3.58	12.3	256	479	777
	3.89	11.2	263	478	786
	4.03	10.9	254	486	793
	3.76	11.7	252	475	764
	3.43	12.0	249	477	757
	2.76	12.0	247	489	787
	3.36	12.5	244	480	856
Intrarun Mean	3.58	11.8	251	479	786
Intrarun SD	0.448	0.493	6.36	4.93	25.2
Intrarun %CV	12.5	4.2	2.5	1.0	3.2
Intrarun %Bias	-10.5	-1.7	0.4	-4.2	-1.8
n	12	12	12	12	12
6	3.42	12.2	261	490	799
	3.37	12.2	254	494	792
	3.41	13.4	257	483	794
	3.58	13.9	255	487	780
	3.73	12.3	249	495	801
	3.08	13.3	255	483	789
	3.91	11.4	254	535	773
	3.80	12.6	252	472	792
	3.81	10.6	260	481	779
	2.75	12.6	249	485	784
	4.36	12.4	253	488	794
	3.86	12.8	251	491	783
Intrarun Mean	3.59	12.4	254	490	788
Intrarun SD	0.422	0.776	3.81	15.4	8.55
Intrarun %CV	11.8	6.3	1.5	3.1	1.1
Intrarun %Bias	-10.3	3.3	1.6	-2.0	-1.5
n	12	12	12	12	12

Long-term Stability: 99 days at -20°C

Table 6. Long-term Stability of Prednisolone in Human Plasma (EDTA) at -20°C

Extraction date: 04-May-2004
Preparation date: 27-Jan-2004
Long-term stability period: 99 days

Batch	QC A LT 12.00 ng/mL	QC C LT 799.00 ng/mL
12	10.90	735.64
	11.17	688.90
	11.56	703.32
	11.03	727.91
	11.69	715.83
	11.97	728.33
	11.42	716.37
	10.93	705.28
	10.56	707.09
Mean	11.24	714.52
S.D.	0.46	14.59
%CV	4.1	2.0
%Theoretical	93.7	89.4
n	9	9

Acceptance Criteria:
The mean of the low and high QCs is within ±15% of the respective nominal concentration and the precision is ≤ 15%

This data was evaluated under [redacted] study 013051-RTF.

Short-term Stability: 30.8 hours at ambient temperature

Table 7. Short-term Stability of Prednisolone in Human Plasma (EDTA) at Ambient Temperature

Short-term stability period: 30.8 hours

Curve Code: QMU-11
Date of Assay: 18-Oct-01

		QUALITY CONTROL SAMPLES			
		STABILITY SAMPLES		FRESHLY SPIKED SAMPLES	
Preparation Date		11-Oct-01		18-Oct-01	
Nominal Concentration:	ng/mL	12.06	803.84	12.06	803.84
		10.36	723.15	9.78	815.59
		11.20	802.30	11.70	936.32
		9.53	766.38	11.49	799.12
		11.72	829.78	11.87	896.86
		11.42	802.08	10.36	908.93
		11.36	839.06	10.89	826.82
Mean		10.932	793.792	11.015	863.940
n		6	6	6	6
%Difference		0.8	-8.1	N/AP	N/AP

% Difference = (Mean Stability Samples - Mean Freshly Spiked Samples) / Mean Freshly Spiked Samples × 100

Acceptance criteria:
% Difference ± 15%

This data was evaluated under [redacted] project 73053/QMU.

Freeze-thaw Stability: 3 cycles at -22°C

Table 8. Stability of Prednisolone in Human Plasma (EDTA) Following Freeze and Thaw Cycles (-22°C)

Freeze and thaw stability: 3 cycles

Curve Code: QMU-11
Date of Assay: 18-Oct-01

		QUALITY CONTROL SAMPLES			
		STABILITY SAMPLES		FRESHLY SPIKED SAMPLES	
Preparation Date:		11-Oct-01		18-Oct-01	
Nominal Concentration:	ng/mL	12.06	803.84	12.06	803.84
		10.57	812.30	9.78	815.59
		11.10	876.14	11.70	936.32
		10.43	848.25	11.49	799.12
		10.78	756.41	11.87	896.86
		11.33	910.66	10.36	908.93
		11.02	899.19	10.89	826.82
Mean		10.872	850.492	11.015	863.940
n		6	6	6	6
%Difference		-1.3	-1.6	N/AP	N/AP

% Difference = Mean Stability Samples - Mean Freshly Spiked Samples x 100
Mean Freshly Spiked Samples

Acceptance criteria:
% Difference ± 15%

This data was evaluated under [redacted] project 73053/QMU.

Post-preparative Stability: 55.7 hours at ambient temperature

Table 9. Post-preparative Stability of Prednisolone in Human Plasma (EDTA) at Ambient Temperature

Extraction end date & time: 19-Apr-2005, 16:20 h
Injection end date & time: 22-Apr-2005, 00:02 h
Post-preparative stability period: 55.7 hours

Batch	*QC APP 12.0 ng/mL*	*QC CPP 800 ng/mL*
7	12.2	699
	12.0	695
	11.5	690
	12.2	690
	10.8	- 678
	11.1	684
Mean	11.6	689
S.D.	0.596	7.53
%CV	5.1	1.1
%Theoretical	96.7	86.1
n	6	6

Flagged Value
- >15% Theoretical

Acceptance Criteria:
The mean of the low and high QCs is within ±15% of the respective nominal concentration and the precision is ≤ 15%

Processed Sample Integrity: 223.9 hours at ambient temperature

Table 13. Processed Sample Integrity of Prednisolone in Human Plasma (EDTA) at Ambient Temperature

Processed sample integrity period: 223.9 hours

	Initial Curve QMU-09				Re-injection Curve QMU-12			
	Date of initial injection: 18-Oct-01				Date of re-injection: 26-Oct-01			
	Extraction end time: 20:20hrs				Re-injection end time: 04:16hrs			
	Quality Control Samples (ng/mL)				Quality Control Samples (ng/mL)			
	QC A	QC B	QC C	QC D	QC A	QC B	QC C	QC D
	12.06	502.40	803.84	4.01	12.06	502.40	803.84	4.01
	12.03	476.76	820.43	4.07	13.96	533.77	881.78	5.00
	12.84	530.59	826.09	4.09	11.25	530.08	C	3.71
	10.34	583.96	830.17	4.32	10.74	610.34	837.38	3.51
	11.45	585.69	905.38	4.38	15.93	605.59	868.28	3.23
	14.44	522.51	806.66	4.18	15.06	529.33	791.68	4.12
	11.18	526.70	821.01	4.66	10.52	518.99	738.86	3.23
Mean	12.047	537.702	834.957	4.283	12.910	554.683	823.596	3.800
n	6	6	6	6	6	6	5	6
%CV	12.0	7.7	4.2	5.2	18.3	7.5	7.1	17.8
%Nominal	99.9	107.0	103.9	106.8	107.0	110.4	102.5	94.8

Acceptance Criteria:

Precision (%CV) for LOQ and low QC ≤ 20% Accuracy (%Nominal) for LOQ and low QC within 80 - 120%

Precision (%CV) for medium and high QC ≤ 15% Accuracy (%Nominal) for medium and high QC within 85 - 115%

C – Poor Chromatography

This data was evaluated under [redacted]: project 73053/QMU.

3. Demographics

The study population consisted of 24 healthy adult volunteers (20 males and 4 females) with a mean age of 26 years (range of 19 - 42 years). The mean height and weight of the subjects was 174 cm (range of 152 – 191 cm) and 70.5 kg (range 58.0 – 86.6 kg), respectively.

	Male	Female	Overall
Age (Years)			
Mean	26.0	27.8	26.3
Median	23.5	25.0	24.0
S.D.	6.2	9.9	6.7
Minimum	19	19	19
Maximum	42	42	42
N	20	4	24
Sex			
Female		4 (100%)	4 (16.7%)
Male	20 (100%)		20 (83.3%)
Race			
Black	8 (40%)		8 (33.3%)
Caucasian	6 (30%)	1 (25%)	7 (29.2%)
Hispanic	6 (30%)	3 (75%)	9 (37.5%)
Frame			
Medium	15 (75%)	2 (50%)	17 (70.8%)
Small	5 (25%)	2 (50%)	7 (29.2%)

	Male	Female	Overall
Weight (kg)			
Mean	71.5	65.6	70.5
Median	71.5	65.4	71.0
S.D.	7.4	7.7	7.6
Minimum	61.5	58.0	58.0
Maximum	86.6	73.7	86.6
N	20	4	24
Height (cm)			
Mean	175.6	163.6	173.6
Median	175.5	165.7	174.6
S.D.	6.8	8.3	8.3
Minimum	161	152	152
Maximum	191	173	191
N	20	4	24

4. Pharmacokinetic and Statistical Results:

Parameters:

28-May-2005 14:52

Table 14.2.
Project No:
Summary of Results - Prednisolone in Plasma
Pharmacokinetic Parameters (N = 21)

	ln AUC 0-t* (ng-h/mL)	ln AUCinf* (ng-h/mL)	ln Cmax* (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)
Cingrel CUT (A)						
Mean	2327.53	2381.02	413.8581	1.3275	2.615	0.2678
CV	15.3	15.7	29.2	41.5	10.2	10.7
n	21	21	21	21	21	21
Pediapred (B)						
Mean	2355.00	2401.72	455.3320	0.8959	2.611	0.2697
CV	14.2	14.5	36.7	37.9	12.6	13.1
n	21	21	21	21	21	21
Cingrel solution (C)						
Mean	2469.98	2519.55	494.0699	0.6429	2.815	0.2492
CV	15.3	15.7	37.6	39.0	10.9	11.2
n	22	21	21	21	21	21
Least-Squares Means						
Cingrel CUT (A)	2321.93	2375.09	410.1086			
Pediapred (B)	2345.60	2391.82	454.4260			
Cingrel solution (C)	2466.38	2514.44	489.3450			
Ratio of Least-Squares Means						
(A/B)%	99.0	99.3	90.2			
(A/C)%	94.5	94.5	83.8			
90% Confidence Intervals						
(A/B)%						
Lower limit:	96.5%	96.7%	85.7%			
Upper limit:	101.6%	102.0%	95.1%			
(A/C)%						
Lower limit:	92.1%	92.0%	79.6%			
Upper limit:	97.0%	97.0%	88.3%			
p-Value (2000A)						
A vs B	0.5220	0.6502	0.0020			
A vs C	0.0007	0.0006	0.0001			
Period	0.4807	0.5324	0.1960			
Sequence	0.6872	0.7162	0.4284			
Intrasubject CV%	4.9	5.1	9.9			

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Section 9.1.7 of Report for details on calculation of parameters.
WinNonlin Pro 2.1-000

26-May-2005 08:02

Table 14.2.1
Project Number:
Prednisolone in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Cingrel CUT (A)

Subject ID	Period	AUC 0-t (ng-h/mL)	AUCinf (ng-h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	1	2165	2215	97.7	394.00	1.500	2.58	0.268	10.00	16.00
2	1	2477	2529	97.9	373.00	1.000	2.66	0.260	8.00	16.00
3	3	2691	2793	96.4	316.00	1.500	2.90	0.239	10.00	16.16
4	3	2654	2845	98.5	347.00	2.000	2.29	0.302	10.00	16.00
5	2	2478	2563	96.7	390.00	1.000	3.01	0.230	6.00	16.00
6	2	2708	2803	97.1	451.00	1.500	2.83	0.245	8.00	16.13
7	3	2088	2128	98.1	395.00	1.500	2.56	0.271	6.00	16.00
8	3	2084	2121	98.3	336.00	1.500	2.96	0.234	6.00	16.00
9	1	1677	1725	97.2	238.00	1.500	2.86	0.242	8.00	16.00
10	2	2183	2203	99.1	477.00	1.000	2.12	0.327	8.00	16.00
11	2	2670	2757	96.8	507.00	1.000	2.64	0.263	10.00	16.00
12	3	2426	2459	98.6	490.00	1.000	2.33	0.297	8.00	16.00
13	1	2600	2677	97.2	519.00	0.500	2.81	0.247	8.00	16.00
14	2	2775	2843	97.6	445.00	1.000	2.77	0.250	8.00	16.00
15	3	2656	2720	97.6	519.00	1.500	2.74	0.253	6.00	16.00
16	1	2537	2602	98.4	483.00	0.750	2.31	0.300	6.00	16.00
17	3	2554	2612	97.8	563.00	3.000	2.50	0.277	8.00	16.00
18	1	2947	3042	96.9	572.00	1.000	3.01	0.230	8.00	16.00
19	1	3196	3423	97.2	368.00	2.000	2.79	0.249	8.00	16.11
20	3	2348	2386	98.3	360.00	1.228	2.48	0.280	6.28	16.00
21	3	1722	1738	99.1	312.00	1.500	2.14	0.323	8.00	16.00
24	2	2253	2306	97.7	371.00	1.000	2.76	0.251	6.00	16.00
Arithmetic Mean		2352.5	2408.1	97.76	429.905	1.3275	2.615	0.2678		
± SD		342.43	361.48	0.756	78.2967	0.55146	0.2667	0.02874		
CV%		14.6	15.0	0.8	18.6	41.5	10.2	10.7		
n		21	21	21	21	21	21	21		

26-May-2005 08:02

Table 14.2.
Project Number:
Prednisolone in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Pediapred (B)

Subject ID	Period	AUC 0-t (ng-h/mL)	AUCinf (ng-h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	1	1996	2032	98.2	441.00	0.750	2.63	0.263	6.00	16.17
2	1	2724	2799	97.3	475.00	0.750	2.70	0.257	10.00	16.00
3	1	2826	2946	99.3	421.00	1.000	3.18	0.218	10.00	28.00
4	3	2113	2137	98.9	467.00	0.750	2.28	0.304	8.00	16.15
5	1	2355	2419	97.4	366.00	2.000	2.85	0.244	6.99	16.00
6	1	2320	2355	98.5	537.00	0.750	2.42	0.286	6.00	16.00
7	2	2315	2146	98.6	419.00	0.750	2.40	0.289	8.00	16.00
8	1	1887	1951	96.7	314.00	1.000	3.03	0.228	6.00	16.00
9	1	2393	2448	99.2	446.00	1.500	2.06	0.336	8.00	16.00
10	2	3095	3196	96.9	627.00	0.500	2.92	0.237	8.00	16.00
11	2	2389	2422	98.6	531.00	1.000	2.36	0.293	8.12	16.00
12	1	2528	2605	97.1	496.00	0.774	2.77	0.250	10.00	16.00
13	1	2396	2426	98.8	467.00	1.000	2.28	0.304	8.00	16.00
14	3	2397	2440	98.2	457.00	0.798	2.61	0.266	6.00	16.00
15	3	2085	2118	98.5	475.00	0.750	2.52	0.275	6.00	16.00
16	2	2463	2517	97.8	462.00	0.500	2.76	0.251	6.00	16.00
17	2	3071	3177	96.6	547.00	0.500	3.18	0.218	6.00	16.00
18	3	2567	2645	97.2	446.00	1.000	2.80	0.248	8.00	16.00
23	2	2119	2150	98.1	385.00	1.000	2.60	0.266	8.00	16.00
22	2	1860	1875	99.2	385.00	1.000	1.97	0.352	10.00	16.00
24	1	2296	2342	98.0	443.00	0.750	2.50	0.278	10.00	16.00
Arithmetic Mean		2377.7	2426.1	98.06	461.333	0.8959	2.611	0.2697		
± SD		342.25	359.96	0.842	77.9393	0.33949	0.3291	0.03540		
CV%		14.4	14.8	0.9	16.9	37.9	12.6	13.1		
n		21	21	21	21	21	21	21		

26-May-2005 Table 14.2.[redacted] 06:02

Project Number: [redacted]
Prednisolone in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Orapred solution (C)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC%AUCinf (%)	Cmax (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	2	2144	2188	98.0	430.00	0.500	2.65	0.261	6.00	16.00
2	3	2692	2759	97.5	547.00	0.500	2.81	0.246	6.00	16.17
3	2	2807	2829	99.2	481.00	0.500	3.24	0.214	8.00	24.00
4	1	2130	2176	97.9	410.00	1.000	2.63	0.263	8.00	16.00
5	3	2541	2606	97.5	655.00	0.750	2.81	0.246	8.00	16.12
6	2	2953	2626	97.2	573.00	0.500	2.95	0.235	6.00	16.00
7	3	2049	2072	98.9	429.00	1.000	2.90	0.301	6.00	16.11
8	1	1899	1951	97.3	343.00	0.750	2.74	0.253	10.00	16.00
9	1	2602	2643	98.5	647.00	0.500	2.47	0.280	8.00	16.00
10	1	3357	3387	99.1	582.00	0.500	3.26	0.213	10.00	24.00
11	2	2530	2568	98.5	484.00	0.750	2.53	0.287	8.00	16.00
12	3	2674	2777	96.3	654.00	0.500	3.17	0.219	8.00	16.00
13	2	2683	2761	97.2	485.00	0.750	2.71	0.256	10.00	16.00
14	1	2549	2607	97.8	451.00	0.750	2.75	0.252	6.00	16.00
15	3	2186	2238	97.7	544.00	0.500	2.86	0.243	6.00	16.00
16	3	2555	2634	97.0	547.00	0.500	2.98	0.232	8.00	16.00
17	1	3160	3280	96.3	559.00	1.000	3.14	0.221	8.00	16.00
18	2	2653	2763	95.9	442.00	0.500	3.31	0.209	6.07	16.00
19	3	2406	2462	97.7	498.00	0.500	2.61	0.265	10.00	16.00
20	1	1827	1952	93.8	365.07	0.750	2.35	0.295	6.00	16.00
21	3	2256	2330	96.8	454.00	0.500	3.03	0.229	8.00	16.00
Arithmetic Mean		2488.2	2547.9	97.68	501.190	0.6429	2.815	0.2492		
± SD		377.72	388.96	0.911	86.2668	0.18661	0.3290	0.02792		
CV%		15.2	15.3	1.0	17.2	29.0	10.9	11.2		
n		21	21	21	21	21	21	21		

26-May-2005 Table 14.2.[redacted] 08:04

Project Number: [redacted]
Prednisolone in Plasma
Ratio Analysis - AUC 0-t (ng·h/mL)

Subject	(A)	(B)	(C)	(A/B)%	(A/C)%
1	2165	1996	2144	108.5	101.0
2	2477	2724	2692	90.9	92.0
3	2691	2826	2807	95.2	95.9
4	2014	2113	2130	95.3	94.5
5	2478	2352	2541	105.4	97.5
6	2788	2330	2553	120.2	109.2
7	2088	2115	2049	98.7	101.9
8	1677	1887	1899	88.8	88.3
9	2183	2130	2602	102.5	83.9
10	2670	3056	3357	86.6	79.5
11	2426	2389	2530	101.6	95.9
12	2600	2528	2674	102.9	97.2
13	2575	2396	2683	107.5	96.0
14	2656	2197	2549	118.8	104.2
15	2037	2065	2186	97.7	93.2
16	2554	2461	2555	103.8	100.0
17	2720	2400	3160	96.0	93.3
18	2947	3071	2951	91.8	88.9
19	2356	2567	2406	96.7	85.1
20	2688	2118	1827	92.6	94.2
21	1722	1860	2256	98.0	99.8
Arithmetic Mean	2352.5	2377.7	2488.2	99.14	94.83
± SD	342.43	342.25	377.72	8.156	7.037
CV%	14.6	14.4	15.2	8.2	7.4
n	21	21	21	21	21

Orapred ODT (A) vs Prednisone (B)
Orapred ODT (A) vs Orapred solution (C)

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26-May-2005 Table 14.[redacted] 08:04

Project Number: [redacted]
Prednisolone in Plasma
Ratio Analysis - AUCinf (ng·h/mL)

Subject	(A)	(B)	(C)	(A/B)%	(A/C)%
1	2215	2032	2188	109.0	101.2
2	2529	2709	2759	93.3	91.6
3	2793	2846	2829	98.1	98.8
4	2045	2137	2176	95.7	94.0
5	2563	2419	2606	106.0	98.4
6	2865	2355	2626	121.7	109.1
7	2128	2166	2072	99.2	102.7
8	1725	1951	1951	88.5	88.4
9	2203	2368	2643	93.8	83.3
10	2737	3196	3387	85.6	80.8
11	2460	2422	2568	101.5	95.8
12	2677	2609	2777	102.9	96.4
13	2641	2426	2761	108.9	95.7
14	2720	2446	2607	111.5	104.3
15	2062	2118	2238	97.4	92.1
16	2612	2517	2634	103.8	99.2
17	3043	3177	3280	95.7	92.7
18	2623	2641	2763	99.3	94.9
19	2085	2159	2462	96.5	84.7
20	1738	1875	1952	92.7	89.1
21	2306	2342	2330	98.5	99.0
Arithmetic Mean	2468.1	2426.1	2547.9	99.48	94.76
± SD	365.48	359.95	388.96	8.580	7.111
CV%	15.0	14.8	15.3	8.6	7.5
n	21	21	21	21	21

Orapred ODT (A) vs Prednisone (B)
Orapred ODT (A) vs Orapred solution (C)

PhAST RDMS 2.3-000 DEFAULT

26-May-2005 Table 14.2.1 08:04
Project Number: [redacted]
Prednisolone in Plasma
Ratio Analysis - Cmax (ng/mL)

Subject	(A)	(B)	(C)	(A/B)%	(A/C)%
1	354.00	441.00	430.00	80.3	82.3
2	473.00	475.00	547.00	99.6	86.5
3	376.00	421.00	483.00	89.3	77.8
4	347.00	467.00	410.00	74.3	84.6
5	390.00	366.00	615.00	106.6	63.4
6	451.00	537.00	577.00	84.0	78.2
7	395.00	419.00	429.00	94.3	92.1
9	276.00	314.00	343.00	87.9	80.5
10	477.00	448.00	647.00	106.5	73.7
11	507.00	627.00	582.00	80.9	87.1
12	496.00	532.00	484.00	93.3	101.2
13	539.00	496.00	654.00	104.8	79.4
14	445.00	467.00	445.00	95.3	100.0
15	510.00	457.00	451.00	111.6	113.1
16	483.00	475.00	544.00	101.7	88.8
17	363.00	442.00	547.00	82.1	66.4
19	572.00	647.00	559.00	88.4	102.3
20	368.00	446.00	442.00	82.5	83.3
21	360.00	385.00	499.00	93.5	72.1
23	312.00	385.00	383.00	81.0	81.5
24	371.00	443.00	454.00	83.7	81.7
Arithmetic Mean	420.905	463.333	501.190	91.45	84.57
± SD	78.2847	77.9393	86.2668	10.454	12.113
CV%	18.6	16.9	17.2	11.4	14.3
n	21	21	21	21	23

Orapred ODT (A) vs Pediapred (B)
Orapred ODT (A) vs Orapred solution (C)

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Ratios of LSM (90% Confidence Intervals)

Parameter	Prednisolone Orapred° ODT (A) vs Celltech Pediapred (B)
AUC 0-t	99.0% (96.5 – 101.6%)
AUCinf	99.3% (96.7 – 102.0%)
Cmax	90.2% (85.7 – 95.1%)

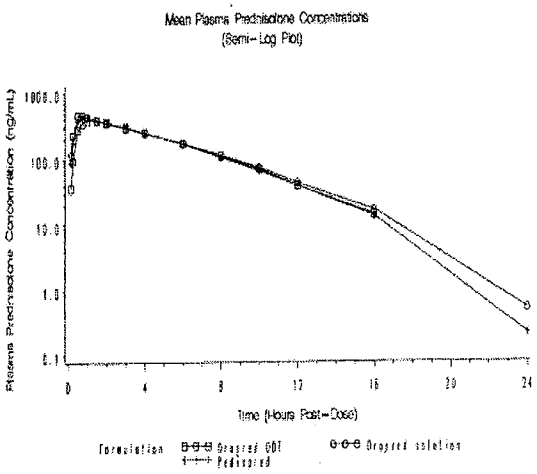
Parameter	Prednisolone Orapred° ODT (A) vs Orapred° oral solution (C)
AUC 0-t	94,5% (92.1 – 97.0%)
AUCinf	94.5% (92.0 – 97.0%)
Cmax	83.8% (79.6 – 88.3%)

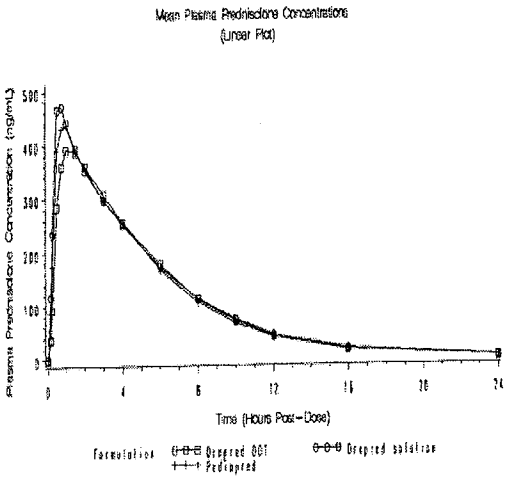
The mean tmax values of prednisolone for the Orapred° ODT, Pediapred° and Orapred° solution treatments were 1.3275, 0.8959 and 0.6429 hour, respectively.

Safety Results: No severe or serious adverse events occurred during this study, and no subject was withdrawn due to an AE. Three subjects (12.5%) reported 6 treatment-emergent adverse events during this study. Four adverse events were mild, and 2 were moderate. All 6 adverse events occurred in Treatment A (face edema, swelling face, pharyngolaryngeal pain, blood in stool, eye irritation, eye edema). Two were considered unrelated to the study medication, and 4 were judged possibly treatment-related.

All formulations of prednisolone sodium phosphate (Orapred 40.3 mg tablets, Celltech Pediapred° 6.7 mg/5 mL oral solution and Orapred° 20.2 mg/5 mL oral solution) appeared to be equally safe and well tolerated when administered as single oral doses in this group of healthy men and women.

5. Figures





Conclusion:

The 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC O-t, AUCinf and Cmax for prednisolone in plasma for the comparison A vs B were within the 80-125% range. Therefore, Orapred° ODT was found to be bioequivalent to the reference listed drug, Pediapred°.

The Orapred° ODT (prednisolone sodium phosphate) 40.3 mg (equivalent to 30 mg prednisolone base) and the Celltech Pediapred (prednisolone sodium phosphate) oral solution 6.7 mg/5 mL (equivalent to 5 mg prednisolone base/SmL) displayed similar rate and extent of absorption of prednisolone.

The 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t and AUCinf for prednisolone in plasma for the comparison A vs C were within the 80-125% range. The ratio of least-squares means derived from the analyses of the ln-transformed pharmacokinetic parameter Cmax was within the 80-125% range but the lower 90% confidence interval was below 80% (79.6%). Therefore, the extent of absorption of prednisolone is similar between both treatments, but the rate of absorption appears to be slightly lower as supported by the observed delay in tmax.

Software: The following software were used to generate the report, tables and figures for this study: Microsoft0 Word 2000, MicrosoftOR Excel 2000, PhAST 2.3-001 and SAS0 S tem for Windows™ release 6.12 and SAS version 8.2 for 0 en VMS VAX v.7.2-1.

Study OPD-002-01

Title of Study: Comparative, Randomized, Single-Dose 2-way Crossover Bioavailability Study of Orapred° Orally Disintegrating Tablet (Prednisolone Sodium Phosphate) 40.3mg (Equivalent to 30mg Prednisolone Base) Administered with 240 mL Water and Without Water in Healthy Volunteers under Fasting Conditions

Investigator: [redacted] Study Center: [redacted]

Study Period: Phase of development: 1; (Study Start Date): 21/Mar/2005; (date of last com leted): 30/Mar/2005

Objectives: The primary objective was to compare single dose bioavailability of the test drug, Orapred° Orally Disintegrating Tablet (ODT) administered with 240 mL of water and Orapred° ODT administered without water.

Methodology: The study subjects were healthy male and female adult volunteers. The study was a randomized, 2-way crossover, comparative bioavailability study under fasting conditions. All subjects received a single 30 mg prednisolone base equivalent dose of the test formulation with 240 mL of water and a single 30 mg prednisolone base equivalent dose of the same formulation without water. There was a 7-day washout between dosing periods.

Within 28 days of dosing, medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), elbow breadth were recorded. Each subject had a physical examination, vital signs (heart rate, blood pressure, temperature 8c respiratory rate), 12-lead ECG, and the laboratory tests including hematologic, hepatic and renal function tests.

Hematology: Hemoglobin, Hematocrit, Total and differential leukocyte count, Red blood cell count, Platelet count.

Serum Chemistry: BUN, Creatinine, Total bilirubin, Alkaline phosphatase, AST, ALT, Sodium, Potassium, Glucose fasting

Urinalysis: pH, Specific gravity Protein, Glucose, Ketones, Bilirubin, Blood, Nitrite, Urobilinogen, Leukocytes

Additional Tests: HIV test HbsAg, HCV Urine drug screen, Cocaine, Cannabinoids, Alcohol, Amphetamines, Serum Pregnancy Test (for females only)

Repeat/End of Study Laboratory Tests

See Laboratory Tests table above:

- To be repeated at the end of the study.
- To be repeated at each check-in

- To be performed at screening and repeated within 24h prior to each check-in.

Vital signs (heart rate, blood pressure, temperature and respiratory rate) were performed at check-in and check-out for each period.

Subjects were admitted to the clinical study unit at least 10 hours prior to the scheduled dose. They remained in the unit until completion of the 24-hour post-dose blood sample.

Subjects were required to fast overnight for at least 10 hours before dosing and for at least 4 hours thereafter. Water was not permitted from 1 hour before until 1 hour after dosing, but was allowed at all other times. Standard meals were provided at approximately 4 and 9 hours after dosing, and at appropriate times thereafter. During housing, post-dose meal plans were identical for both periods.

Safety was evaluated by monitoring adverse events throughout the entire study, vital signs (heart rate, blood pressure, temperature and respiratory rate) at check-in and check-out in each period and clinical laboratory tests at the end of the study.

Number of Subjects (planned and analysed): Fourteen healthy adult subjects (12 males and 2 females) were dosed, and all subjects completed the study. All 14 subjects were included in the safety assessment. Pharmacokinetic parameters were calculated for the 14 subjects.

Inclusion Criteria:
• Healthy adult male or female volunteers, 19-45 years of age;
• Weighing at least 52 kg for males and 45 kg for females and within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Cornpany, 1983);
• Medically healthy subjects with clinically normal laboratory profiles and ECGs; as deemed by the Principal Investigator;
• Females of childbearing potential should have either been sexually inactive (abstinent) for 3 months prior to the first dose and throughout the study or been using one of the following acceptable birth control methods:
a. surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) 6 months minimum; b. IUD in place for at least 3 months; c. barrier methods (condom, diaphragm) with spermicide for at least 3 months prior to the first dose and throughout the study; d. surgical sterilization of the partner (vasectomy for 6 months minimum); Other birth control methods may have been deemed acceptable. Postmenopausal women with amenorrhea for at least 2 years were eligible.
• Voluntarily consent to participate in the study.

Exclusion Criteria:
• History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastraintestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease.

• In addition, history or presence of:
• alcoholism or drug abuse within the past 2 years;
• hypersensitivity or idiosyncratic reaction to prednisolone or other corticosteroids.
• Female subjects who were pregnant or lactating.
• Subjects who received any form of injectable corticoids in the 12 weeks preceding the first dose or any oral forms of corticoids for the 30 days preceding the first dose.
• Subjects who had used any drugs or substances known to be strong inhibitors of CYP enzymes (formerly known as cytochrome P450 enzymes) within 10 days prior to the first dose.
• Subjects who had used any drugs or substances known to be strong inducers of CYP enzymes (formerly known as cytochrome P450 enzymes) within 28 days prior to the first dose.
• Subjects who had been on a special diet (for whatever reason) during the 28 days prior to the first dose and throughout the study.
• Females who were taking hormonal contraceptives or were on hormonal replacement therapy during the 28 days prior to the first dose and throughout the study.
• Subjects who had made any donation of blood within 56 days of study initiation.
• Subjects who had made a plasma donation within 7 days prior to the study.
• Subjects with hemoglobin less than 12.0 g/dL.
• Subjects who had participated in another clinical trial within 28 days prior to the first dose.
• Subjects who were currently using or had used nicotine-containing products within 30 days prior to entering the study.

Blood sampling: Blood samples were collected in blood collection tubes containing EDTA before dosing (1 x 10 mL) and at the following times: 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing (1 x 5 mL). Plasma concentrations of prednisolone were measured by a validated LC-MS/MS method. The analytical range for prednisolone in plasma was 4.00 – 1000 ng/mL.

Test Product: Treatment A (administered with 240 mL water) and Treatment B (administered without water): Orasolv° Prednisolone 30 mg (Equivalent to Prednisolone Sodium Phosphate 40.3 mg) tablet Manufactured by Cima Labs Inc. Lot No.: 740556 Expiration date: Not provided Manufacture date: Oct-2004
Although the label of the test treatment provided by the Sponsor was "Orasolv° Prednisolone 30 mg (Equivalent to Prednisolone Sodium Phosphate 40.3 mg) tablet", the treatment name Orapred° ODT can be used interchangeably.

Subjects randomized to Treatments A and B received 1 tablet on the tongue, which was sucked on until it disintegrated; followed by either 240 mL of water (Treatment A) or no water (Treatment B).

Criteria for Evaluation: Study endpoints were the 90% confidence intervals of the ratio of least-squares means of the pharmacokinetic parameters AUC O-t, AUCinf and Cmax of the test formulation given with 240 mL water and without water.

Pharmacokinetic Parameters: prednisolone AUC0-t, AUC0-inf, and Cmax were calculated.

Statistical Methods: Descriptive Statistics Arithmetic means, standard deviations, and coefficients of variation were calculated for the pharmacokinetics parameters listed above. Additionally, geometric means were calculated for AUC0-t, AUCinf and Cmax.

Analysis of Variance Analyses of variance (ANOVA) were performed on the 1n-transformed AUC O-t, AUCinf and Cmax. The ANOVA model included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested usin sub'ect nested within se uence as the error term at a 10% level of significance.

Each ANOVA included calculation of least-squares means (LSM), the difference between formulation LSM, and the standard error associated with this difference. The above statistical analyses were done using the appropriate SAS° procedure.

Ratios and Confidence Intervals Ratios of least-squares means were calculated using the exponentiation of the LSM from the analyses on the 1n-transformed AUC O-t, AUCinf and Cmax. These ratios were expressed as a percentage relative to the test formulation administered with 240 mL water.

Consistent with the two one-sided test for bioequivalence, 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the 1n-transformed AUC O-t, AUCinf and Cmax. The confidence intervals were expressed as a percentage relative to the test formulation administered with 240 mL water.

Results:

1. Demographics

	Male	Female	Overall
Age (Years)			
Mean	30.9	27.0	30.4
Median	26.5	27.0	27.0
S.D.	9.4	0.0	8.7
Minimum	20	27	20
Maximum	45	27	45
N	12	2	14
Sex			
Female		2 (100%)	2 (14.3%)
Male	12 (100%)		12 (85.7%)
Race			
Black	4 (33.3%)	1 (50%)	5 (35.7%)
Caucasian	2 (16.7%)		2 (14.3%)
Hispanic	6 (50.0%)	1 (50%)	7 (50.0%)
Frame			
Medium	4 (33.3%)		4 (28.6%)
Small	8 (66.7%)	2 (100%)	10 (71.4%)

	Male	Female	Overall
Weight (kg)			
Mean	76.4	60.4	74.1
Median	79.0	60.4	77.5
S.D.	7.8	10.5	9.7
Minimum	60.5	53.0	53.0
Maximum	86.2	67.9	86.2
N	12	2	14
Height (cm)			
Mean	177.7	160.7	175.2
Median	177.4	160.7	174.9
S.D.	6.4	4.5	8.6
Minimum	167.6	157.5	157.5
Maximum	189.2	163.8	189.2
N	12	2	14

2. Assay

Calibration Curve Standards and Quality Control Samples A set of 9 non-zero calibration standards ranging from 4.00 ng/mL to 1000 ng/mL and QC samples at four different concentrations (12.0 ng/mL, 250 ng/mL, 500 ng/mL, and 800 ng/mL) were prepared and subsequently stored at a nominal temperature of -20°C.

Study samples were analyzed without exceeding short term, freeze-thaw stability, post-preparative stability or processed sample integrity. The following evaluations have been conducted:

Stability Summary: See below

a. Long-term Stability: 99 days at -20°C

Table 6. Long-term Stability of Prednisolone in Human Plasma (EDTA) at -20°C

Extraction date: 04-May-2004
Preparation date: 27-Jan-2004
Long-term stability period: 99 days

Batch	QC A LT 12.00 ng/mL	QC C LT 799.00 ng/mL
12	10.80	735.64
	11.17	688.90
	11.56	705.32
	11.03	727.91
	11.69	715.83
	11.97	728.33
	11.42	716.37
	10.93	705.28
	10.56	707.09
Mean	11.24	714.52
S.D.	0.46	14.59
%CV	4.1	2.0
%Theoretical	93.7	89.4
n	9	9

Acceptance Criteria:
The mean of the low and high QCs is within ±15% of the respective nominal concentration and the precision is ≤ 15%

This data was evaluated under [redacted] study 013051-RTF.

b. Short-term Stability: 30.8 hours at ambient temperature

Table 7. Short-term Stability of Prednisolone in Human Plasma (EDTA) at Ambient Temperature

Short-term stability period: 30.8 hours

Curve Code: QMU-11
Date of Assay: 18-Oct-01

		QUALITY CONTROL SAMPLES			
		STABILITY SAMPLES		FRESHLY SPIKED SAMPLES	
Preparation Date		11-Oct-01		18-Oct-01	
Nominal Concentration:	ng/mL	12.06	803.84	12.06	803.84
		10.36	723.15	9.78	815.59
		11.20	802.30	11.70	936.32
		9.53	766.38	11.49	799.12
		11.72	829.78	11.87	896.86
		11.42	802.08	10.36	908.93
		11.36	839.06	10.89	826.82
Mean		10.932	793.792	11.015	863.940
n		6	6	6	6
%Difference		-0.8	-8.1	N/AP	N/AP

% Difference = $\frac{\text{Mean Stability Samples - Mean Freshly Spiked Samples}}{\text{Mean Freshly Spiked Samples}} \times 100$

Acceptance criteria:
% Difference ± 15%

This data was evaluated under [redacted] project 73053/QMU.

c. Freeze-thaw Stability 3 cycles at -22°C

Table 8. Stability of Prednisolone in Human Plasma (EDTA) Following Freeze and Thaw Cycles (-22°C)

Freeze and thaw stability: 3 cycles

Curve Code: QMU-11
Date of Assay: 18-Oct-01

		QUALITY CONTROL SAMPLES			
		STABILITY SAMPLES		FRESHLY SPIKED SAMPLES	
Preparation Date:		11-Oct-01		18-Oct-01	
Nominal Concentration:	ng/mL	12.06	803.84	12.06	803.84
		10.57	812.30	9.78	815.59
		11.10	876.14	11.70	936.32
		10.43	848.25	11.49	799.12
		10.78	756.41	11.87	896.86
		11.33	910.66	10.36	908.93
		11.02	899.19	10.89	826.82
Mean		10.872	850.492	11.015	863.940
n		6	6	6	6
%Difference		-1.3	-1.6	N/AP	N/AP

% Difference = Mean Stability Samples - Mean Freshly Spiked Samples x 100
Mean Freshly Spiked Samples

Acceptance criteria:
% Difference ± 15%

This data was evaluated under [redacted] project 73053/QMU.

d. Post-preparative Stability: 55.7 hours at ambient temperature

Table 9. Post-preparative Stability of Prednisolone in Human Plasma (EDTA) at Ambient Temperature

Extraction end date & time: 19-Apr-2005, 16:20 h
Injection end date & time: 22-Apr-2005, 00:02 h
Post-preparative stability period: 55.7 hours

Batch	*QC APP 12.0 ng/mL*	*QC CPP 800 ng/mL*
7	12.2	699
	12.0	695
	11.5	690
	12.2	690
	10.8	- 678
	11.1	684
Mean	11.6	689
S.D.	0.596	7.53
%CV	5.1	1.1
%Theoretical	96.7	86.1
n	6	6

Flagged Value
- >15% Theoretical

Acceptance Criteria:
The mean of the low and high QCs is within ±15% of the respective nominal concentration and the precision is ≤ 15%

e. Processed Sample Integrity: 223.9 hours at ambient temperature

Table 13. Processed Sample Integrity of Prednisolone in Human Plasma (EDTA) at Ambient Temperature

Processed sample integrity period: 223.9 hours

	Initial Curve QMU-09				Re-injection Curve QMU-12			
Date of initial injection:	18-Oct-01				Date of re-injection:	26-Oct-01		
Extraction end time:	20:20hrs				Re-injection end time:	04:16hrs		
	Quality Control Samples (ng/mL)				Quality Control Samples (ng/mL)			
	QC A	QC B	QC C	QC D	QC A	QC B	QC C	QC D
	12.06	502.40	803.84	4.01	12.06	502.40	803.84	4.01
	12.03	476.26	820.43	4.07	13.96	533.77	981.78	5.00
	12.84	530.59	826.09	4.09	11.25	530.09	C	3.71
	10.34	583.96	830.17	4.32	10.74	610.34	837.28	3.51
	11.45	585.69	905.38	4.38	15.93	605.59	868.28	5.23
	14.44	522.51	896.66	4.18	15.06	529.33	991.68	4.12
	11.18	526.70	821.01	4.66	10.52	518.99	738.86	3.23
Mean	12.067	533.702	834.957	4.281	12.910	554.683	823.596	3.800
n	6	6	6	6	6	6	5	6
%CV	12.0	7.7	4.2	5.2	18.3	7.5	7.1	17.8
%Nominal	99.9	107.0	103.9	106.8	107.0	110.4	102.5	94.8

Acceptance Criteria:
Precision (%CV) for LOQ and low QC ≤ 20%
Precision (%CV) for medium and high QC ≤ 15%
Accuracy (%Nominal) for LOQ and low QC within 80 - 120%
Accuracy (%Nominal) for medium and high QC within 85 - 115%

C - Poor Chromatography

This data was evaluated under [redacted] project 73052/QMU.

Quality Control Sample Analyses (Between-Batch Precision and Accuracy): Precision was less than or equal to 6.9%. Accuracy ranged from 96.4% to 102.0%.

Quality Control Sample Data (Between-batch Precision and Accuracy) for Prednisolone in Human Plasma (EDTA)

Batch	*QC A 12.0 ng/mL*	*QC D 250 ng/mL*	*QC B 500 ng/mL*	*QC C 800 ng/mL*
1	11.3	254	467	819
	11.0	255	457	832
	12.1	254	491	775
	12.7	252	494	794
2	11.6	260	464	770
	-10.1	260	492	795
	11.3	250	486	802
	12.0	264	494	779
3	12.1	250	484	772
	11.1	255	473	775
	12.5	248	502	751
	11.1	252	477	780
4	11.9	262	490	772
	13.0	253	468	765
	11.7	252	480	794
	10.3	264	485	791
Mean	11.6	255	482	785
S.D.	0.805	5.11	13.7	20.5
%CV	6.9	2.0	2.6	2.6
%Theoretical	96.7	102.0	96.4	98.1
n	16	16	16	16

Calibration Standard Concentrations: Accuracy ranged from -8.4% to 6.0%.

Table 3. Back-calculated Calibration Curve Standard Concentrations of Prednisolone in Human Plasma (EDTA)

Batch	*STD B 4.00 ng/mL*	*STD C 8.00 ng/mL*	*STD D 20.0 ng/mL*	*STD E 100 ng/mL*	*STD F 300 ng/mL*	*STD G 450 ng/mL*	*STD H 600 ng/mL*	*STD I 850 ng/mL*	*STD J 1000 ng/mL*
1	3.85	8.39	21.3	102	289	475	602	771	973
2	4.05	7.64	20.8	108	310	452	587	775	991
3	3.87	8.33	21.0	104	306	462	586	769	971
4	4.03	7.58	21.8	106	307	459	567	799	973
Mean	3.95	7.99	21.2	105	303	462	586	779	977
S.D.	0.105	0.434	0.435	2.58	9.49	9.63	14.3	13.9	9.38
%CV	2.7	5.4	2.1	2.5	3.1	2.1	2.4	1.8	1.0
%Bias	-1.3	-0.1	6.0	5.0	1.0	2.7	-2.3	-8.4	-2.3
n	4	4	4	4	4	4	4	4	4

Standard Curve Parameters:

Standard curve parameters from 4 successful analytical batches, are provided in Table 4. A representative calibration curve is illustrated in Figure 1. The coefficient of determination (R-squared) was greater than or equal to 0.9966.

3. Parameters:

	ln AUC 0-t* (ng-h/mL)	ln AUCinf* (ng-h/mL)	ln Cmax* (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)
Tablet with 240 mL water (A)						
Mean	2641.93	2698.30	426.3500	1.1355	2.733	0.2573
CV	21.1	21.1	17.4	45.6	16.2	16.2
n	14	14	14	14	14	14
Tablet without water (B)						
Mean	2570.66	2576.16	447.9565	1.2678	2.806	0.2501
CV	20.1	23.9	22.6	61.6	12.4	13.6
n	14	14	14	14	14	14
Least-Squares Means						
Tablet with 240 mL water (A)	2641.93	2698.30	426.3500			
Tablet without water (B)	2570.66	2576.16	447.9565			
Ratio of Least-Squares Means (B/A)%	102.8	103.0	105.2			
90% Confidence Intervals (B/A)%						
Lower limit:	100.18	100.24	99.76			
Upper limit:	105.64	106.06	111.04			
p-Value ANOVA						
B vs A	0.0030	0.0059	0.1407			
Period	0.58629	0.7037	0.6136			
Sequence	0.9974	0.9948	0.6111			
Intrasubject CVR	4.0	4.2	8.6			

For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
WinNonlin 5.2.1-000

Subject ID	Period	AUC 0-t (ng-h/mL)	AUCinf (ng-h/mL)	AUC%Extrap (%)	Cmax (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	2	2177	2401	97.8	428.00	1.000	2.62	0.265	8.00	16.00
2	2	2437	2672	97.8	490.00	1.000	2.73	0.254	6.00	16.00
3	1	1843	1908	98.1	336.00	1.000	2.46	0.282	6.00	16.00
4	1	2227	2274	97.9	417.00	1.000	2.52	0.275	10.00	16.00
5	1	2412	2459	98.1	442.00	1.000	2.57	0.270	8.00	16.00
6	1	2056	2115	97.2	448.00	0.750	2.79	0.253	8.00	16.00
7	2	2849	2963	96.5	485.00	1.000	2.96	0.232	8.00	16.00
8	2	2207	2285	98.3	415.00	0.667	2.84	0.244	8.00	16.00
9	1	2552	2606	96.1	434.00	1.000	3.26	0.212	6.00	16.00
10	2	2167	2218	97.7	344.00	2.000	2.63	0.263	8.00	16.00
11	2	2789	2829	98.6	549.00	2.000	2.25	0.308	10.00	16.00
12	1	4481	4539	98.2	696.00	2.000	2.29	0.303	10.00	16.00
13	1	2109	2151	98.0	380.00	0.750	2.64	0.263	6.00	16.00
14	2	2482	2595	97.1	374.00	0.750	2.83	0.245	8.00	16.00
Arithmetic Mean		2499.1	2555.2	97.75	431.429	1.1696	2.729	0.2571		
± SD		631.23	634.34	0.807	77.5056	0.47527	0.2987	0.02610		
CV%		25.3	24.8	0.8	18.0	40.6	10.9	10.2		
n		14	14	14	14	14	14	14		

Subject ID	Period	AUC 0-t (ng-h/mL)	AUCinf (ng-h/mL)	AUC%Extrap (%)	Cmax (ng/mL)	tmax (h)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	1	2691	2575	96.7	392.00	1.000	3.07	0.226	8.00	16.00
2	1	2572	2627	97.8	459.00	0.750	2.73	0.254	6.00	16.00
3	2	1963	1998	98.2	346.50	2.000	2.45	0.283	10.00	16.00
4	2	2296	2371	96.8	367.00	1.000	2.95	0.235	6.00	16.00
5	2	2428	2475	98.0	361.00	3.000	2.32	0.299	10.00	16.00
6	2	2036	2094	97.2	358.00	1.500	2.73	0.254	10.00	16.00
7	1	2694	2794	96.4	456.00	1.500	2.93	0.236	10.00	16.00
8	1	2281	2331	97.9	436.00	1.500	2.54	0.273	10.00	16.00
9	2	2521	2590	97.4	477.00	1.000	2.64	0.263	10.00	16.00
10	1	2171	2239	96.9	367.00	1.000	2.77	0.250	6.00	16.00
11	2	3189	3189	97.6	697.00	0.750	2.76	0.251	6.00	16.00
12	2	4347	4522	98.6	716.00	1.500	3.65	0.190	18.00	24.00
13	2	2196	2295	98.4	378.00	0.750	2.91	0.238	8.00	16.00
14	1	2360	2421	97.5	438.00	0.500	2.72	0.255	8.00	16.00
Arithmetic Mean		2589.0	2652.9	97.53	459.643	1.2679	2.806	0.2529		
± SD		796.97	797.17	0.775	111.8961	0.69547	0.3479	0.02868		
CV%		30.8	30.0	0.7	24.4	54.9	12.4	11.3		
n		14	14	14	14	14	14	14		

Ratio Analysis - AUC 0-t (ng-h/mL)

Subject	(A)	(B)	(B/A)%
1	2177	2401	104.8
2	2437	2672	105.5
3	1843	1951	106.4
4	2227	2296	103.1
5	2412	2426	100.6
6	2056	2036	99.0
7	2849	2694	94.5
8	2207	2291	103.8
9	2552	2521	98.8
10	2167	2171	100.2
11	2789	3109	111.5
12	4481	5147	114.9
13	2109	2190	103.8
14	2482	2360	95.1
Arithmetic Mean	2499.1	2589.0	102.95
± SD	633.23	798.97	5.696
CV%	25.3	30.8	5.5
n	14	14	14

Tablet without water (B) vs Tablet with 240 mL water (A)

Ratio Analysis - AUCinf (ng-h/mL)

Subject	(A)	(B)	(B/A)%
1	2431	2575	105.9
2	2402	2627	109.4
3	1938	1998	106.4
4	2274	2371	102.3
5	2959	2475	100.6
6	2115	2094	99.0
7	2971	2794	96.6
8	2345	2331	103.8
9	2696	2590	97.5
10	2216	2239	107.6
11	2828	3189	112.5
12	4519	5200	116.5
13	2151	2295	103.9
14	2595	2421	94.7
Arithmetic Mean	2555.2	2652.9	103.20
± SD	634.34	797.17	6.806
CV%	24.8	30.0	6.6
n	14	14	14

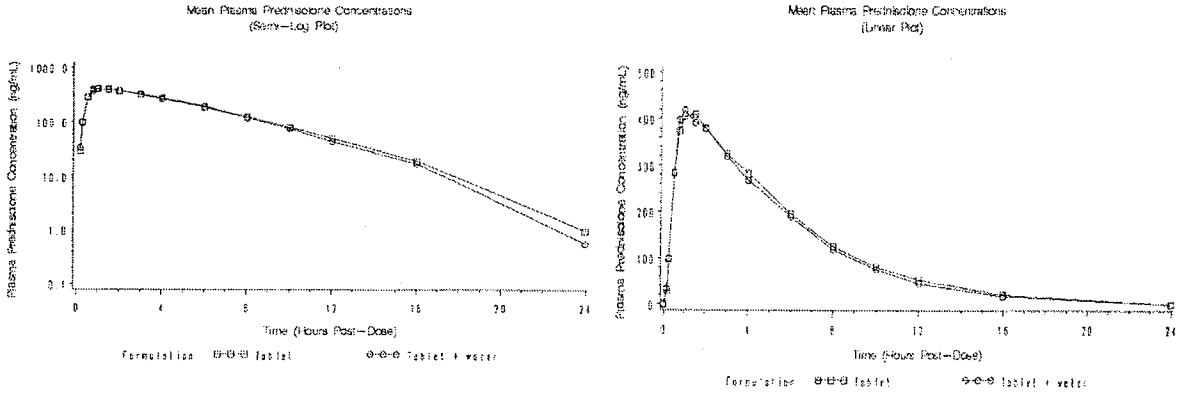
Tablet without water (B) vs Tablet with 240 mL water (A)

Ratio Analysis - Cmax (ng/mL)

Subject	(A)	(B)	(B/A)%
1	428.00	392.00	91.6
2	490.00	559.00	114.1
3	336.00	344.00	102.4
4	417.00	387.00	92.8
5	442.00	363.00	82.1
6	348.00	358.00	102.9
7	485.00	456.00	94.0
8	415.00	435.00	104.8
9	434.50	477.00	109.9
10	344.00	387.00	112.5
11	540.00	657.00	121.7
12	606.50	710.00	117.2
13	389.00	476.00	122.4
14	374.00	418.00	111.8
Arithmetic Mean	431.429	458.643	105.88
± SD	77.5090	111.8661	12.035
CV%	18.0	24.4	11.4
n	14	14	14

Tablet without water (B) vs Tablet with 240 mL water (A)

3. Figures



4. Ratios of LSM (90% Confidence Intervals)

Parameter	Prednisolone Ora red° ODT without water (B) vs Ora red° ODT with 240 mL water (A)
AUC 0-t	102.8% (100.1 – 105.6%)
AUCinf	103.0% (100.2 – 106.0%)
Cmax	105.2% (99.3 – 111.4%)

5. Safety Results:

No treatment-emergent adverse events occurred in this study, and no clinical laboratory out of range finding was clinically significant. All post-dose vital signs were normal.

Orapred° 40.3 mg tablets appeared to be equally safe and well tolerated when administered with 240 mL of water and without water in this group of healthy men and women.

Conclusion:

The 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC0-t, AUCinf and Cmax for prednisolone in plasma were within the 80-125% range.

The 40.3mg Orapred° ODT (prednisolone sodium phosphate) administered with 240 mL water displayed similar rate and extent of absorption of prednisolone as that observed when the product is administered without water under fasting conditions.

Software: The following software were used to generate the report, tables and figures for this study: Microsoft° Word 2000, Microsoft° Excel 2000, PhAST 2.3-000 and SAS° System for Windows'"releases 6.12 and 8.2 for open VMS VAX v7.2-1.

Archiving: The contents of this report was archived at [redacted] as per SOP No. SL-G-8757.

4.3 Dissolution and disintegration information

Three dissolution reports are presented: a) dissolution information on coated PSP; b) dissolution on Orapred ODT and c) dissolution method validation on Orapred ODT.

Additionally, the disintegration report is presented.

Development and Validation of ATM-644, "Dissolution Procedure for Coated Prednisolone Sodium Phosphate (PSP)"

Summary

The report describes the development and validation of ATM-644, "Dissolution Procedure for Coated Prednisolone Sodium Phosphate (PSP)". he method uses USP apparatus 2 at 100 rpm and pH 4.5 sodium acetate buffer as the medium. The amount of PSP is quantitated using a [redacted] HPLC method with UV detection at [redacted] nm. The validation parameters consisted of linearity, selectivity/specificity, accuracy/recovery, system precision, method repeatability, range, standard filter recovery, standard stability, sample stability, intermediate precision, and robustness.
The validation data reported here supports the suitability of the method for the dissolution testing of coated PSP in pH 4.5 sodium acetate dissolution medium.

Introduction

ATM-644 was developed and validated for determining the rate of release of PSP from coated PSP. The method uses USP apparatus 2 at 100 rpm and pH 4.5-sodium acetate buffer as the medium. The amount of PSP is quantitated using a [redacted] HPLC method with UV detection at [redacted] nm.

Dissolution Method Development Rationale

The purpose of the method is to show batch-to-batch consistency, to assure dissolution performance in prednisolone orally disintegrating tablets (ODTs), and to demonstrate dissolution

throughout stability studies of coated PSP. Preferably, the method will produce a dissolution profile for coated PSP similar to that of prednisolone ODTs.

Coated PSP dissolution method development was adapted from the prednisolone ODT dissolution parameters described in ATM-638, "Dissolution Procedure for 10 mg, 15 mg, and 30 mg Prednisolone [Equivalent to 13.4 mg, 20.2 mg, and 40.3 mg of Prednisolone Sodium Phosphate (PSP)] Orally Disintegrating Tablets." The dissolution method parameters found in ATM-644 are the same as ATM-638 with the exception of paddle speed.

Dissolution Parameters:

Apparatus:	USP 2, paddles
Medium:	22 mM sodium acetate buffer, pH 4.5
Medium Volume:	500 mL
Medium Temperature:	37.0 °C ± 0.5 °C
Paddle Speed:	100 rpm
Sampling Time Point (single):	30 minutes
Sampling Time Points (profile):	5, 15, 30, 45, and 60 minutes
Sampling Volume:	5 mL

A coated PSP sample size equivalent to the amount of PSP in a prednisolone ODT 30 mg dissolution sample is used (40.32 mg PSP in 500 mL medium volume). For example, for coated PSP that has a theoretical potency of 32.2%, approximately 125 mg of coated PSP is used making the target concentration 80.5 µg/mL PSP at full release (125 mg x 0.322 / 500 mL = 80.5 µg/mL).

Throughout prednisolone ODT dissolution development, various media were examined in order to obtain consistent discerning profiles. See Table 1 and Figure 1 for dissolution profile results in various media for a prednisolone ODT 30 mg development lot at 50 rpm paddle speed and 900 mL medium volume. Initially pH 6.8 medium was chosen for its discerning profile at the 5, 15, and 30 minute time points. However, coated PSP dissolution using pH 4.5 medium released more completely and was more consistent at 60 minutes than coated PSP dissolutions performed in pH 6.8 medium (See Table 2 and Figure 2). In addition, [redacted] used in part to coat the drug, dissolves slowly above pH 5. To maintain consistency with the coated and tablet dissolution methods, the medium was changed to pH 4.5 sodium acetate buffer. To ensure the medium provides discriminating profiles, dissolution profiles were obtained on 30 mg prednisolone ODTs made with different coating levels of coated PSP (25%, 30%, and 35%). A discriminating profile is observed for these tablets (See Table 3 and Figure 3). The pH 4.5 sodium acetate medium provides a discriminating profile, meets sink conditions, and is a commonly used medium.

Table 1. Dissolution Profiles of Prednisolone ODT 30 mg, Development Lot LB1392-71 in Various Media

	Average % Released (n = 3)						
Time (min)	**0.1 N HCl**	**pH 4.5**	**pH 5.0**	**pH 5.5**	**pH 6.0**	**pH 6.8**	**Water**
0	0	0	0	0	0	0	0
5	69	50	50	45	53	50	50
15	97	87	84	59	75	67	58
30	99	95	100	74	85	85	62
45	99	96	101	86	88	96	65
60	100	97	102	90	90	101	68

Figure 1. Dissolution Profiles of Prednisolone ODT 30 mg, Development Lot LB1392-71 in Various Media

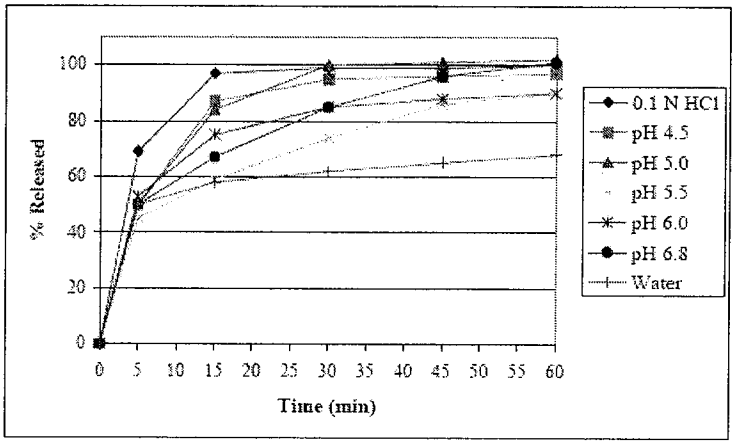


Table 2. Dissolution Profiles of Coated PSP in pH 4.5 and pH 6.8 Media, Development Lot LB1392-98 Stored for 6 Months at 30 ₀C / 60% RH

Paddle Speed	100 rpm	
Medium Volume	900 mL	
	Average % Released (n = 6)	
Time (min)	pH 4.5	pH 6.8
0	0	0
5	63	22
15	89	79
30	94	85
45	94	87
60	94	87

Figure 2. Dissolution Profiles of Coated PSP in pH 4.5 and pH 6.8 Media, Development Lot LB1392-98 Stored for 6 Months at 30 ₀C / 60% RH

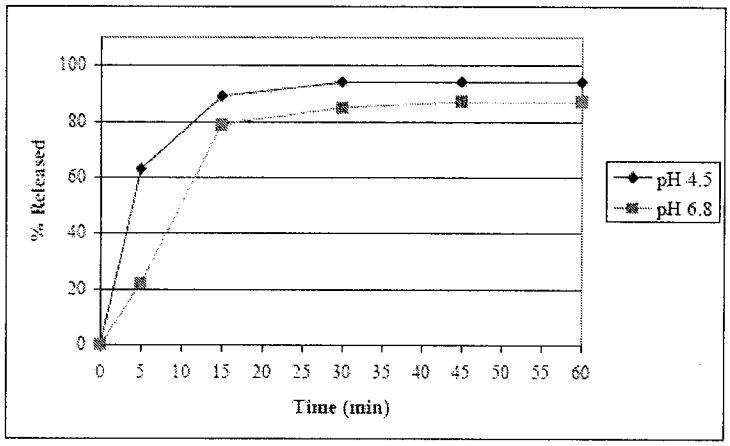
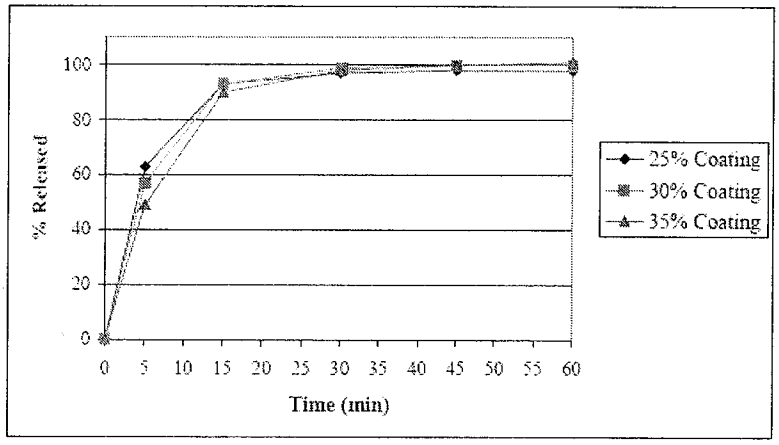


Table 3. Dissolution Profiles of Prednisolone ODT 30 mg made with Different Levels of Coated PSP

Paddle Speed	50 rpm		
Medium Volume	900 mL		
	Average % Released (n = 3)		
	Lot LB2066-63	Lot LB2066-64	Lot LB2066-65
Time (min)	25% Coating	30% Coating	35% Coating
0	0	0	0
5	63	57	49
15	93	93	90
30	97	99	98
45	98	100	100
60	98	100	101

Figure 3. Dissolution Profiles of Prednisolone ODT 30 mg made with Different Levels of Coated PSP



Variation in the paddle speed was also examined. See Table 5 and Figure 5 for dissolution profile results of coated PSP at two different paddle speeds (50 and 100 rpm) with pH 4.5 medium in a

500 mL medium volume.[7] The dissolution profiles of coated PSP, lot 740551, were studied side by side to compare both paddle speeds.

The dissolution profiles of coated PSP were similar at 50 rpm and 100 rpm, both producing a higher % released at the early time points than were seen in prednisolone ODTs (See Table 6 and Figure 6).[8] A paddle speed of 100 rpm was chosen for coated PSP dissolution, since a faster paddle speed aids in consistently wetting the sample and produces less mounding at the bottom of the dissolution vessel compared to a paddle speed of 50 rpm. In addition, less variability was seen at 100 rpm (see Table 5) compared to 50 rpm as evidenced by the %RSD values.

Table 5. Effect of Paddle Speed on Coated PSP, Lot 740551

	50 rpm		100 rpm	
Time (min)	Avg. % Released (n = 6)	% RSD	Avg. % Released (n = 6)	% RSD
0	0	0.0	0	0.0
5	73	6.5	71	8.3
15	92	4.9	93	1.9
30	93	5.2	98	1.2
45	94	5.4	99	0.5
60	94	5.3	99	0.8

Figure 5. Effect of Paddle Speed on Coated PSP, Lot 740551

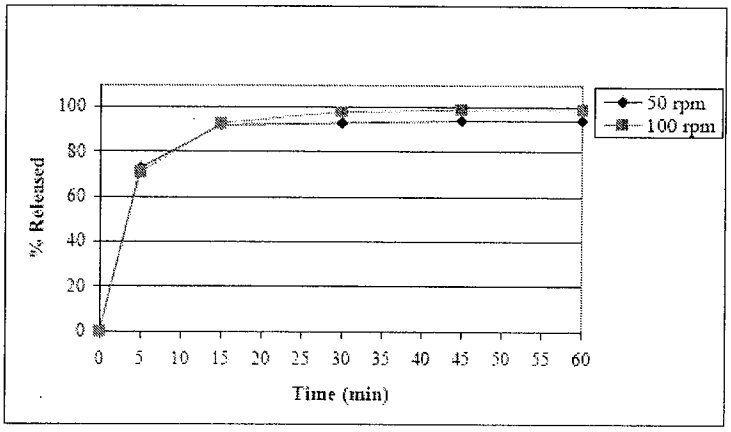
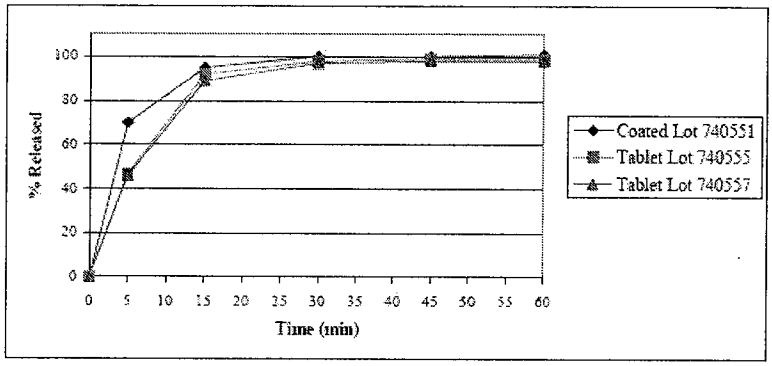


Table 6. Dissolution Profiles of 15 mg and 30 mg Prednisolone ODTs and Corresponding Coated PSP Lot (pH 4.5 Medium, 500 mL Medium Volume)

	Average % Released		
Paddle Speed	100 rpm	50 rpm	50 rpm
	Coated PSP	15 mg ODT	30 mg ODT
Time (min)	Lot 740551	Lot 740555	Lot 740557
0	0	0	0
5	70	47	46
15	95	92	89
30	100	98	97
45	100	99	98
60	101	99	98

Figure 6. Dissolution Profiles of 15 mg and 30 mg Prednisolone ODTs and Corresponding Coated PSP Lot (pH 4.5 Medium, 500 mL Medium Volume)



Report # RA-20050-032 Dissolution Comparison of 10 mg, 15 mg, and 30 mg Prednisolone Orally Disintegrating Tablets in Three Different Media pH

Summary of *In vitro* Dissolution Studies

Study Number	Lot No.	Dosage Form and Strength	Dissolution Apparatus	Media/ Temperature	Speed of Rotation/ Flow	Sample Times (min)	No. of Dosage Units Tested	% Dissolved		Study Report Location
								Mean	Range	
RA-2005-032	740556	Orapred ODT™ 30 mg	USP 2, Paddles	0.1 N HCl 37.0 °C ± 0.5 °C	50 rpm	5	12	68	59-83	Attach. 1 Section 2.7.1
						10	12	87	82-97	
						15	12	91	87-97	
						30	12	94	90-99	
						45	12	94	90-100	
						60	12	95	90-100	
RA-2005-032	740556	Orapred ODT™ 30 mg	USP 2, Paddles	22 mM sodium acetate, pH 4.5 37.0 °C ± 0.5 °C	50 rpm	5	12	45	38-54	Attach. 1 Section 2.7.1
						10	12	79	74-87	
						15	12	87	84-90	
						30	12	91	87-94	
						45	12	92	88-95	
						60	12	92	89-96	
RA-2005-032	740556	Orapred ODT™ 30 mg	USP 2, Paddles	50 mM potassium phosphate, pH 6.8 37.0 °C ±0.5 °C	50 rpm	5	12	44	41-51	Attach. 1 Section 2.7.1
						10	12	66	63-72	
						15	12	77	73-81	
						30	12	89	83-94	
						45	12	91	86-97	
						60	12	92	86-99	

TITLE Dissolution Comparison of 10 mg, 15 mg, and 30 mg Prednisolone Orally Disintegrating Tablets in Three Different Media pH

Summary

The dissolution profiles of 10 mg, 15 mg, and 30 mg prednisolone [equivalent to 13.4 mg, 20.2 mg, and 40.3 mg of prednisolone sodium phosphate (PSP)] orally disintegrating tablets (ODTs) are compared using USP Apparatus 2 (paddles) at 50 rpm in 0.1 N HCl, pH 4.5 acetate, and pH 6.8 phosphate media. Dissolution similarity factors, f_2, of the 10 mg and 15 mg prednisolone ODTs were calculated against the 30 mg prednisolone ODT used in the bioequivalence study in pH 4.5 medium. The f_2 values were 71 and 73 for the 10 mg and 15 mg prednisolone ODTs respectively. Since the similarity factors, f_2, are

between 50 and 100, the dissolution profiles of the 10 mg and 15 mg prednisolone ODTs may be considered similar to the 30 mg prednisolone ODT in pH 4.5 medium.

Introduction

Dissolution profiles in 0.1 N HCl, pH 4.5 acetate, and pH 6.8 phosphate media were generated for three prednisolone ODT strengths. The 10 mg, 15 mg, and 30 mg prednisolone ODTs are made from a common blend and are representative of the to be marketed formulation ($1/10_{th}$ scale batch size). The prednisolone ODTs were manufactured at the commercial manufacturing site, CIMA LABS Inc., Eden Prairie. The profiles of the 10 mg and 15 mg prednisolone ODTs were compared to the 30 mg prednisolone ODT used in the bioequivalence study in pH 4.5 medium. The study supports the bioequivalence of the 10 mg and 15 mg prednisolone strength ODTs. The dissolution results and the similarity factors are included in this report.

Experimental

Procedure:	**ATM-638**, "Dissolution Procedure for 10 mg, 15 mg, and 30 mg Prednisolone [Equivalent to 13.4 mg, 20.2 mg, and 40.3 mg of Prednisolone Sodium Phosphate (PSP)] Orally Disintegrating Tablets"
Apparatus:	USP 2 (paddles)
Medium Volume:	500 mL
Paddle Speed:	50 rpm
Media:	0.1 N HCl 22 mM sodium acetate buffer, pH 4.5 50 mM potassium phosphate buffer, pH 6.8
Sampling Intervals:	5, 10, 15, 30, 45, and 60 minutes
Sample Size:	n = 12

Samples:	Product	Lot Number
	Prednisolone ODT 10 mg	740552
	Prednisolone ODT 15 mg	740554
	Prednisolone ODT 30 mg	740556* (bio-lot)

*The time zero assay value for lot 740556 was 97.8% label claim and dropped to 95.8% label claim after three months storage at 25 ^{o}C / 60% RH.[1]

Results

The individual dissolution results for each prednisolone ODT strength in each medium are listed in Tables 1 – 9. Figures 1 through 3 show dissolution profiles of each prednisolone ODT strength in each medium. The mean results (n = 12) for each lot in pH 4.5 medium and the similarity factors, f_2, are given in Table 10. The similarity factors are calculated by comparing the 10 mg and 15 mg prednisolone ODTs to the 30 mg prednisolone ODT in pH 4.5 medium. For dissolution profiles to be considered similar,

f_2 values are generally greater than 50 (50 - 100), which provide assurance of the sameness or equivalence of the two profiles. The f_2 values were 71 and 73 for the 10 mg and 15 mg prednisolone ODTs, respectively, in pH 4.5 medium indicating that the profiles are similar.

FDA/CDER industry guidance[2] on dissolution testing of immediate release solid oral dosage forms indicates that a statistically meaningful similarity factor, f_2, can be obtained when three or more useful dissolution time points are available for both reference and test formulations. The guidance further indicates that useful dissolution time points are those below 85% released, plus only one of the time points above 85% should be used. Using these criteria, the pH 4.5 media dissolution results provide three useful data points for the f_2 comparison (5, 10, and 15 minute time points - see Table 10). The f_2 results for these tablets are therefore considered meaningful.

Conclusion

The f_2 values indicate that the dissolution profiles of 10 mg, 15 mg, and 30 mg prednisolone ODTs may be considered similar in pH 4.5 medium.

Table 1. Prednisolone ODT 10 mg Dissolution Data in 0.1 N HCl[3]

Lot# 740552	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	92	97	99	99	100	100
%RSD	16.8	5.1	3.8	3.4	2.8	3.4

Table 2. Prednisolone ODT 15 mg Dissolution Data in 0.1 N HCl[4]

Lot# 740554	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	79	95	98	98	99	100
%RSD	15.0	2.5	2.8	2.9	2.8	2.8

Table 3. Prednisolone ODT 30 mg Dissolution Data in 0.1 N HCl[5]

Lot# 740556	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	68	87	91	94	94	95
%RSD	12.8	4.2	3.1	2.7	2.8	2.8

Table 4. Prednisolone ODT 10 mg Dissolution Data in pH 4.5 Medium[6]

Lot# 740552	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	51	78	89	94	95	96
%RSD	14.3	5.8	4.0	4.3	4.3	4.9

Table 5. Prednisolone ODT 15 mg Dissolution Data in pH 4.5 Medium[7]

Lot# 740554	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	43	74	87	94	95	96
%RSD	10.5	5.8	5.1	3.2	3.0	3.1

Table 6. Prednisolone ODT 30 mg Dissolution Data in pH 4.5 Medium[8]

Lot# 740556	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	45	79	87	91	92	92
%RSD	9.4	4.6	2.0	2.1	2.2	2.2

Table 7. Prednisolone ODT 10 mg Dissolution Data in pH 6.8 Medium[9]

Lot# 740552	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	47	65	76	92	95	97
%RSD	6.4	5.4	3.5	3.4	3.5	3.5

Table 8. Prednisolone ODT 15 mg Dissolution Data in pH 6.8 Medium[10]

Lot# 740554	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	38	62	75	90	95	96
%RSD	13.0	4.1	5.1	2.8	2.5	2.3

Table 9. Prednisolone ODT 30 mg Dissolution Data in pH 6.8 Medium[11]

Lot# 740556	% Released					
Tablet No.	5 min.	10 min.	15 min.	30 min.	45 min.	60 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	44	66	77	89	91	92
%RSD	7.5	3.7	2.9	3.0	3.0	3.4

Table 10. Prednisolone ODT Dissolution Results in pH 4.5 Medium[12]

	Mean % Released		
Time Point (min.)	Prednisolone ODT 10 mg Lot# 740552	Prednisolone ODT 15 mg Lot# 740554	Prednisolone ODT 30 mg Lot# 740556
5	51	42	45
10	78	74	79
15	89	87	87
30	94	94	91
45	95	95	92
60	96	96	92
f2 (compared to Prednisolone ODT 30 mg)	71	73	Not Applicable

Figure 1. Prednisolone ODT Dissolution Results in pH 4.5 Medium

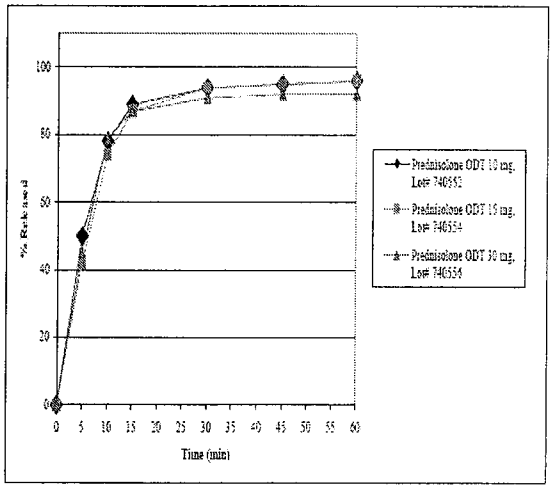


Figure 2. Prednisolone ODT Dissolution Results in 0.1 N HCl

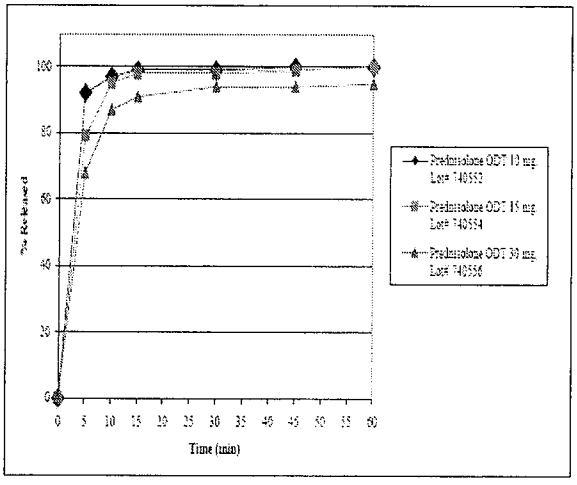
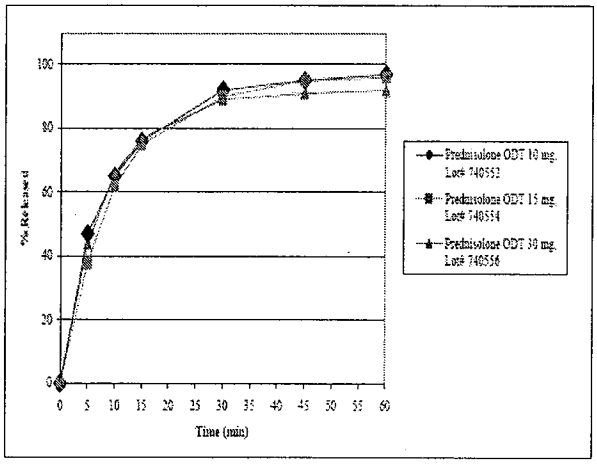


Figure 3. Prednisolone ODT Dissolution Results in pH 6.8 Medium



Development and Validation of ATM-638: "Dissolution Procedure for 10 mg, 15 mg, and 30 mg Prednisolone [Equivalent to 13.4 mg, 20.2 mg and 40.3 mg of Prednisolone Sodium Phosphate (PSP)] Orally Disintegrating Tablets"

Summary

The report describes the development and validation of ATM-638, "Dissolution Procedure for 10 mg, 15 mg, and 30 mg Prednisolone [Equivalent to 13.4 mg, 20.2 mg, and 40.3 mg of Prednisolone Sodium Phosphate (PSP)] Orally Disintegrating Tablets". The method uses USP apparatus 2 at 50 rpm and pH 4.5 sodium acetate buffer as the medium. The amount of PSP is quantitated using a [redacted] HPLC method with UV detection at [redacted] nm. The validation parameters consisted of linearity, selectivity/specificity, accuracy/recovery, system precision, method repeatability, range, standard filter recovery, standard stability, sample stability, intermediate precision, and robustness.

The validation data reported here supports the suitability of the method for the dissolution testing of 10 mg, 15 mg, and 30 mg prednisolone (equivalent to 13.4 mg, 20.2 mg, and 40.3 mg of PSP) orally disintegrating tablets (ODTs) in pH 4.5 sodium acetate dissolution medium.

Introduction

ATM-638 was developed and validated for determining the rate of release of PSP from 10 mg, 15 mg, and 30 mg prednisolone (equivalent to 13.4 mg, 20.2 mg, and 40.3 mg of PSP) orally disintegrating tablets (ODTs). The method uses USP apparatus 2 at 50 rpm and pH 4.5 sodium acetate buffer as the medium. The amount of PSP is quantitated using a [redacted] HPLC method with UV detection at [redacted] nm.

Dissolution Method Development Rationale

The objective of the dissolution method is to produce a discerning dissolution profile for all prednisolone ODT potencies using the same test parameters. The method is used to show batch-to-batch consistency and dissolution throughout stability studies.

Dissolution method parameters do not currently exist in the United States Pharmacopeia (USP)

for prednisolone sodium phosphate tablets. See below for ATM-638 dissolution method parameters.

Dissolution Parameters:

Apparatus:	USP 2, paddles
Medium:	22 mM sodium acetate buffer, pH 4.5
Medium Volume:	500 mL
Medium Temperature:	37.0 °C ± 0.5 °C
Paddle Speed:	50 rpm
Sampling Time Point (single):	30 minutes
Sampling Time Points (profile):	5, 15, 30, 45, and 60 minutes
Sampling Volume:	5 mL

Throughout development, various media were examined in order to obtain consistent discerning profiles. See Table 1 and Figure 1 for dissolution profile results in various media for a prednisolone ODT 30 mg development lot at 50 rpm paddle speed and 900 mL medium volume.[1]

Initially pH 6.8 medium was chosen for its discerning profile at the 5, 15, and 30 minute time points. However, dissolution of coated PSP using pH 4.5 medium showed more complete and consistent release at 60 minutes than when performed in pH 6.8 medium (See Table 2 and Figure 2).[2]

In addition, [redacted], used in part to coat the drug, dissolves slowly above pH 5. To maintain consistency with the coated and tablet dissolution methods, the medium was changed to pH 4.5 sodium acetate.

To demonstrate that pH 4.5 the medium provides discriminating profiles, dissolution profiles were obtained on 30 mg prednisolone ODTs made with different coating levels of coated PSP (25%, 30%, and 35% w/w). A discriminating profile is observed for these tablets (See Table 3 and Figure 3).[3] The pH 4.5 sodium acetate medium provides a discriminating profile, meets sink conditions[4], and is a commonly used medium.

Table 1. Dissolution Profiles of Prednisolone ODT 30 mg, Development Lot LB1392-71 in Various Media

	Average % Released (n = 3)						
Time (min)	**0.1 N HCl**	**pH 4.5**	**pH 5.0**	**pH 5.5**	**pH 6.0**	**pH 6.8**	**Water**
0	0	0	0	0	0	0	0
5	69	50	50	45	53	50	50
15	97	87	84	59	75	67	58
30	99	95	100	74	85	85	62
45	99	96	101	86	88	96	65
60	100	97	102	90	90	101	68

Figure 1. Dissolution Profiles of Prednisolone ODT 30 mg, Development Lot LB1392-71 in Various Media

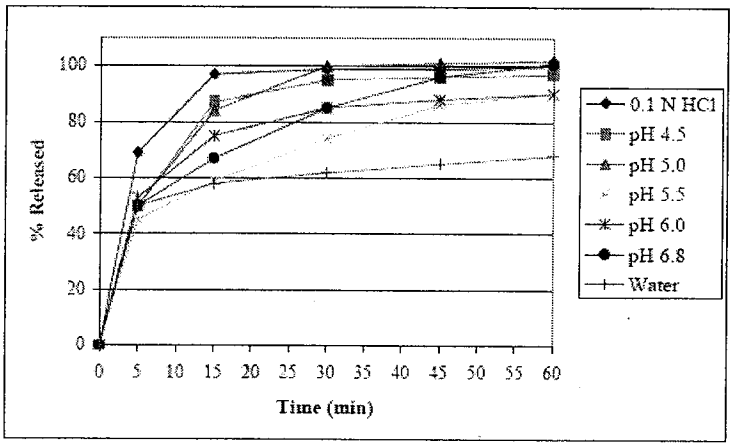


Table 2. Dissolution Profiles of Coated PSP in pH 4.5 and pH 6.8 Media, Development Lot LB1392-98 Stored for 6 Months at 30 ₀C / 60% RH

Paddle Speed	100 rpm	
Medium Volume	900 mL	
	Average % Released (n = 6)	
Time (min)	pH 4.5	pH 6.8
0	0	0
5	63	22
15	89	79
30	94	85
45	94	87
60	94	87

Figure 2. Dissolution Profiles of Coated PSP in pH 4.5 and pH 6.8 Media, Development Lot LB1392-98 Stored for 6 Months at 30 ₀C / 60% RH

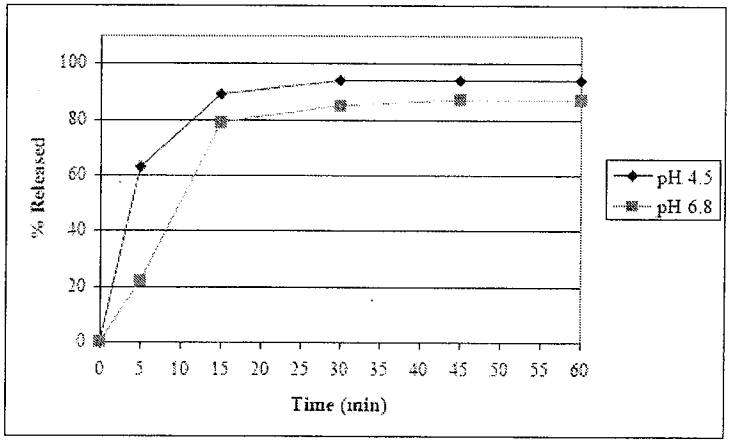
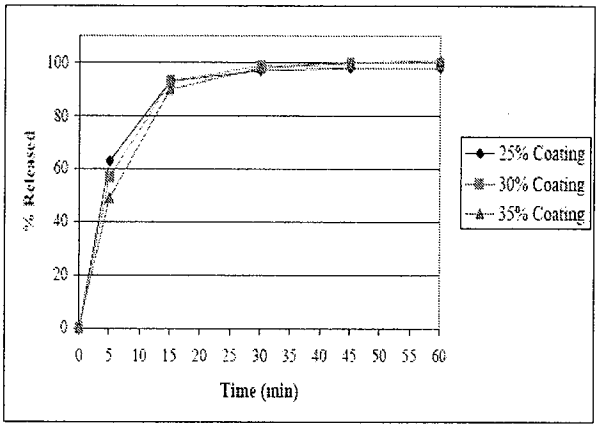


Table 3. Dissolution Profiles of Prednisolone ODT 30 mg made with Different Levels of Coated PSP

Paddle Speed	50 rpm		
Medium Volume	900 mL		
	Average % Released (n = 3)		
	Lot LB2066-63	Lot LB2066-64	Lot LB2066-65
Time (min)	25% Coating	30% Coating	35% Coating
0	0	0	0
5	63	57	49
15	93	93	90
30	97	99	98
45	98	100	100
60	98	100	101

Figure 3. Dissolution Profiles of Prednisolone ODT 30 mg made with Different Levels of Coated PSP

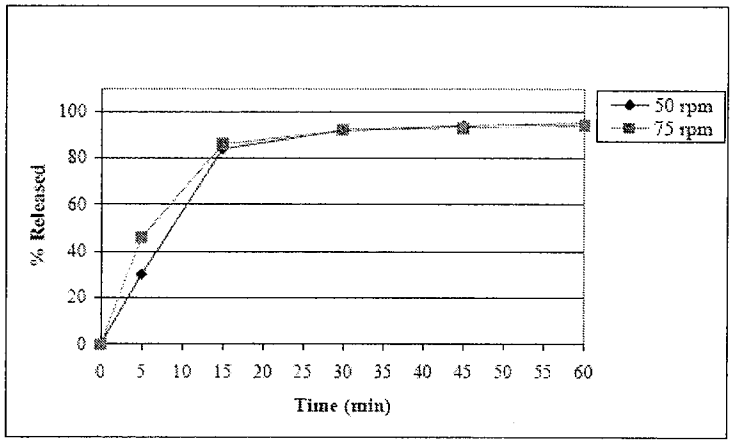


USP 2 paddle apparatus is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used.[5] The variation in paddle speed was examined. See Table 4 and Figure 4 for dissolution profile results for a prednisolone ODT 30 mg development lot at two different paddle speeds (50 and 75 rpm) in pH 4.5 medium in a 900 mL medium volume.[6] The profiles of both paddle speeds were similar with the 50 rpm paddle speed providing slightly more discrimination at the 5 minute time point. For the reasons stated above, a paddle speed of 50 rpm was chosen.

Table 4. Effect of Paddle Speed on Prednisolone ODT 30 mg, Development Lot LB1392-74

	Average % Released (n = 6)	
Time (min)	50 rpm	75 rpm
0	0	0
5	30	46
15	84	86
30	92	92
45	94	93
60	95	94

Figure 4. Effect of Paddle Speed on Prednisolone ODT 30 mg, Development Lot LB1392-74



Finished Product Specifications Rationale for Prednisolone Orally Disintegrating 10 mg, 15 mg, and 30 mg Tablets

Summary

The report provides rationale for setting of finished product specifications for Prednisolone orally disintegrating 10 mg, 15 mg, and 30 mg [equivalent to 13.4 mg, 20.2 mg, and 40.3 mg prednisolone sodium phosphate (PSP)] tablets.

Introduction

Finished product release and stability specifications for prednisolone 10 mg, 15 mg, and 30 mg orally disintegrating tablets (equivalent to 13.4 mg, 20.2 mg, and 40.3 mg PSP tablets) are defined and referenced herein. Pertinent release and stability data from PSP prototype and registration tablets are summarized and included in this report to support rationale for the relevant PSP tablets specifications.

Specification Rationale

All PSP tablet specifications defined herein are met for all prototype and registration batches, through all release and shelf life testing, conducted to date. Registration batches here refer to 1/10th scale lots.

The PSP data summarized below are from registration and prototype pilot scale batches. Stability data refer to registration batches tested through 6M at 25 °C/60% RH, and at 40 °C/75% RH and to prototype batches tested through 6M at 40 °C/75% RH and 18M at 25 °C/60% RH. Identity and content uniformity are not reconfirmed during the stability program.

Table 1. Tablet Batch information

Lot#	Tablet Strength	Batch Type - Usage
LB2066-02	10 mg	Prototype - Stability
740552	10 mg	Registration - Stability
740553	10 mg	Registration - Stability
740554	15 mg	Registration - Stability
740555	15 mg	Registration - Stability
LB2066-05	30 mg	Prototype - Stability
740556	30 mg	Registration – Bioequivalency Studies ODP-001-01 and ODP-001-02 and Stability
740557	30 mg	Registration - Stability

Description

Specification for 10 mg tablets:	White, flat faced, beveled edge tablets debossed with "ORA" on one side and "10" on the other.
Specification for 15 mg tablets:	White, flat faced, beveled edge tablets debossed with "ORA" on one side and "15" on the other.
. Specification for 30 mg tablets:	White, flat faced, beveled edge tablets debossed with "ORA" on one side and "30" on the other.
Method:	Visual, ATM-123

Dissolution:

Specification:		NLT –% (Q) in 30 minutes
	Stage 1)	NMT 0 Tablets less than _ % (n=6)
	Stage 2)	Average NLT_ %; NMT 0 Tablets <_ % (n=12)
	Stage 3)	Average NLT _ %; NMT 2 Tablets <_ %, and NMT 0 Tablets < –% (n=24)
Method:		USP 2 at 50 rpm in pH 4.5 buffer, ATM-638

At regulatory release, the mean dissolution for registration batches was 95% with a mean range of 91%-98%. On stability, under accelerated conditions, the mean was 90% with a mean range of 88%-93%. Values for ranges are shown in Table 4 at release and 6M. The lowest value observed for any lot on stability was –% for lot 740557 under 3M stored at 40 °C/75%RH, showing a release of –% with individuals ranging ——→ %.

All lots meet specification at release and through 6M for registration batches and through 18M for prototype batches at all storage conditions. Note: For prototype tablets, the method used a pH 6.8 buffer as the dissolution medium.

Table 4. Dissolution Data

	Range, % at 30 minutes		
Lot#	At Release	6M at 40 °C/75%RH	6M at 25 °C/60%RH
LB2066-02	100-106	91-103	101-106
740552	87-101	87-95	87-99
740553	91-101	86-90	90-101
740554	90-100	89-96	92-100
740555	96-103	90-92	88-97
LB2066-05	96-102	91-95	96-99
740556	89-93	85-91	86-96
740557	94-100	87-94	89-96

References: ARNs: 7892, 7893, 9283-9286, 9246, 9247, 8555, 8556, and 9928-9933

Dissolution Data for the Orapred ODT (Registration batches)

Lot #	% Released based on Label claim (% RSD) n = 12				
	5 Min	15 Min	30 Min	45 Min	60 Min
740552 (10 mg)	39 (12.4)	84 (6.5)	94 (4.7)	96 (4.1)	98 (6.8)
740553 (10 mg)	45 (9.9)	87 (3.4)	95 (3.2)	97 (2.8)	98 (2.8)
740554 (15 mg)	40 (10.5)	88 (3.0)	96 (3.1)	97 (3.5)	97 (3.2)
740555 (15 mg)	47 (5.4)	92 (2.3)	98 (2.4)	99 (2.4)	99 (2.2)
740556a (30 mg)	45 (25.4)	85 (1.7)	91 (1.5)	92 (1.5)	92 1.5)
740557 (30 mg)	46 (10.2)	89 (1.5)	97 (2.0)	98 (2.2)	98 (1.9)

a: Biobatch

Disintegration Time:

Specification: NMT ⎯ seconds per USP <701>
1) n = 6, NMT 0 tablets > ⎯ seconds. If one or two tablets > ⎯ seconds, proceed to stage 2 and test an additional 12 tablets.
2) n=18, NMT 2 tablets > ⎯ seconds

Method: ATM-679

All lots meet specification at release and through 6M for registration lots and through 18M for prototype lots at all storage conditions.

Table 9. Disintegration Data

	Average Disintegration Time, sec.			
Lot#	At Release	6M at 40 °C/75%RH	6M at 25 °C/60%RH	18M at 25 °C/60%RH
LB2066-02	24 range 23-25	21 range 20-22	21 range 18-26	21 range 19-27
740552	14 range 11-17	7 range 2-10	10 range 7-11	NT
740553	11 range 10-12	11 range 10-12	9 range 2-12	NT
740554	16 range 13-17	12 range 11-15	15 range 14-17	NT
740555	16 range 13-18	12 range 8-14	15 range 13-18	NT
LB2066-05	29 range 26-33	21 range 20-22	24 range 23-25	30 range 25-32
740556	17 range 7-22	16 range 14-18	18 range 16-20	NT
740557	22 range 20-25	15 range 14-20	19 range 16-22	NT

NT: Not tested, pull date: May 2006.

Tablets made with three different hardness levels from Full-scale coated PSP lot 950125 produced average disintegration times of 29-30 seconds with individuals ranging between 26 to 34 seconds (Ref. LB2799-06).

Further disintegration data is presented for the registration stability batches:

Table 11: Analytical data for the Orapred ODT. (Registration batches)

Lot #	ARN #	Assay %LC	Content Uniformity[a] (%) n = 30	Mean Hardness[a] (N) n = 30	Mean Disintegration time USP[a] (s) n = 6	
740552 (10 mg)	9283	98.7	89.5–105.6 (3.0)	10 (15)	14 (16)	
740553 (10 mg)	9284	98.2	92.3–105.8 (2.9)	10 (15)	11 (9)	
740554 (15 mg)	9285	99.3	95.1–104.9 (2.6)	11 (12)	16 (10)	
740555 (15 mg)	9286	99.7	90.7–106.9 (2.9)	12 (11)	16 (11)	
740556[b] (30 mg)	9246	97.8	89.5–101.1 (2.6)	14 (18)	17 (31)	
740557 (30 mg)	9247	97.6	95.3–104.5 (2.8)	15 (11)	22 (8)	

a (% RSD)
b Biobatch tablet lot

Specifications (Orapred ODT., Tablets)

The regulatory specifications for 30 mg Orapred ODT tablet is located below; for 10 and 15 mg, the specifications are the same as that of the 30 mg tablet.

Table 3: Orapred ODT, 30 mg, 1/2", Grape Flavor, White color

Test	Regulatory Specification	Test Method

4.4 Consult Review (including Pharmacometric Reivews)

None

4.5 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-959	Brand Name	Orapred ODTTM
OCPB Division (I, II, III)	DPE II	Generic Name	Prednisolone Sodium
Medical Division	Division of Analgesics Anesthetics and Rheumatology Products	Drug Class	Glucocorticoid Anti-inflamatory agent
OCPB Reviewer	David J. Lee, Ph.D.	Indication(s)	
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Orally Disintegrating Tablets
		Dosing Regimen	
Date of Submission	8/1/2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/9/2006	Sponsor	Medicis Pediatrics, Inc.,
PDUFA Due Date	5/28/2006	Priority Classification	Standard
Division Due Date	5/15/2006		

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			Reports were submitted as part of the PK studies
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		Relative bioavailability of Orapred ODT vs Orapred oral solution (study OPD-001-01)
alternate formulation as reference:	X	1		Relative bioavailability of Orapred ODT with and without water consumption (study OPD-002-01)
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		Single dose 3-way cross over Orapred ODT, Pediapred (RLD), Orapred oral solution
replicate design; single / multi dose:				
Food-drug interaction studies:				Matter resolved at a Pre-NDA meeting
Dissolution:		1		
(IVIVC):				
Bio-wavier request based on BCS				see QBR questions
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		More than one aspect is covered by single study.

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 ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is the test product (Orapred) bioequivalent with the reference listed drug product? Is there any difference in PK of prednisolone when Orapred is consumed with or without water? Is the food effect appropriately addressed? Are lower strengths eligible for a biowaiver? Is the analytical method adequately validated? Is the dissolution method and specifications appropriate for this product?			
Other comments or information not included above	The pivotal BE study OPD-001-01 needs to be inspected by DSI and a DSI consult will be initiated			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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

/s/

David Lee
5/22/2006 11:16:36 AM
BIOPHARMACEUTICS
2 BE studies: Orapred ODT vs Pediapred Solution (RLD) vs Orapred Solution - ODT was BE to Pediapred; Orapred ODT with and without water - Both are BE; no problems; Labeling recommendation of removing all references to [redacted] from the proposed PI

Suresh Doddapaneni
5/22/2006 01:15:43 PM
BIOPHARMACEUTICS