CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	202020	*Submission Date*	09/26/2011
Brand Name		TBD	
Generic Name		Prednisone delayed-release tablets	
Reviewer		Ping Ji, Ph.D.	
Team Leader		Suresh Doddapaneni, Ph.D.	
OCP Division		Division of Clinical Pharmacology-II	
OND Division		Division of Pulmonary, Allergy, and Rheumatology Products	
Sponsor		HORIZON PHARMA INC	
Relevant IND(s)		072,569	
Submission Type; Code		505 (b) (2)	S
Formulation; Strength(s)		Tablet; 1, 2, and 5 mg	
Proposed Indication		Adult rheumatology arthritis	
Proposed Dosing Regimen		• Initial dose: NP01 5 mg administered once per day at bedtime. Patients currently on immediate-release prednisone, prednisolone, or methylprednisolone should be switched to NP01 at an equivalent dose. • Maintenance dose: Use lowest dosage that will maintain an adequate clinical response. • Discontinuation:Withdraw gradually if discontinuing long-term or high-dose therapy. • [redacted] (b) (4)	

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1. EXECUTIVE SUMMARY

1.1. Recommendations

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

1.2. Phase IV Commitments

None.

1.2.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Prednisone delayed-release tablet (NP01) was developed by Horizon Pharma, Inc. (Horizon) for the treatment of active rheumatoid arthritis (RA) in adult patients. A total of five relevant Phase 1 studies in healthy adult volunteers were conducted to characterize the clinical pharmacology and biopharmaceutics properties of NP01. These studies assessed the dose proportionality of 1, 2, and 5 mg tablets (Study NP01-008), demonstrated the bioequivalence (BE) of the product manufactured at two different manufacturing sites (Study 01-014), assessed the relative bioavailability of NP01 with reference IR tablet (Studies NP01-013 and NP01-005), and evaluated the food effect (Study NP01-006). Study NP01-008 demonstrated linear increases of Cmax and AUC for prednisone and prednisolone with increasing dose of 1, 2 to 5 mg. The change in the manufacturing site did not affect the BE of prednisone and prednisolone (Study 01-014). A pronounced food effect was seen after intake of a high-fat meal as compared to fasting conditions. Administration of NP01 under fasting conditions resulted in prolonged *in vivo* lag time and significantly lower and highly variable prednisone and prednisolone plasma concentrations compared to fed conditions (Study NP01-006). A pharmacokinetic summary of prednisone and prednisolone from this study is shown in Table 1.

Table 1. Pharmacokinetic summary of prednisone and prednisolone from study NP01-006.

	Prednisone		Prednisolone	
Treatment	DR Fasted	DR Fed	DR Fasted	DR Fed
Cmax (ng/mL)	6.6 (50%)	19 (17%)	43 (52%)	149 (21%)
AUC0-t (ng h/mL)	34 (44%)	101 (19%)	229 (70%)	653 (24%)
Tmax (h)	8.4 (6-10)	6.9 (3.5-10)	7.3 (3.5-9)	5.9 (4.5-8.5)

Note: DR: Prednisone delayed-release formulation
Cmax and AUC are presented as mean (SD); Tmax is presented as median (min, max).

These results show that the Cmax and AUC for both prednisone and prednisolone under fed condition are about three times of those under fasting condition. Sponsor explained

(b) (4)

Because of significant food effect of the delayed-release formulation, sponsor conducted the relative bioavailability study with the IR formulation under fed condition (NP01-005). A pharmacokinetic summary of prednisone and prednisolone from this study is shown in Table 2.

Table 2. Pharmacokinetic summary of prednisone and prednisolone from study NP01-005.

	Prednisone			Prednisolone		
Treatment	IR Fasted	DR Semi-Fasted	DR Fed	IR Fasted	DR Semi-Fasted	DR Fed
Cmax (ng/mL)	21.1 (17%)	21.4 (26%)	22.2 (16%)	137 (17%)	121 (27%)	135 (18%)
AUC(0-t) (ng h/mL)	108 (15%)	114 (27%)	124 (20%)	623 (17.3%)	600 (30%)	669 (21%)
Tmax (h)	2 (1.0-4.0)	6.0 (4.5-10)	6.5 (4.5-9)	1.13 (0-3)	5.58 (4-9)	5.81 (4.5-9)

Note: IR: Prednisone immediate-release formulation.
DR: Prednisone delayed-release formulation.
Cmax and AUC are presented as mean (SD); Tmax is presented as median (min, max).

Under either semi-fasted or fed condition, the exposures of both prednisone and prednisolone from the delayed-release formulation are comparable to those from the IR formulation. However, Tmax was 4 hours delayed for NP01 as compared to IR formulation. It is of note that in this study that the IR formulation was given under fasting condition. However, as the exposure of prednisone and prednisolone from the IR formulation was not affected by the intake of food, these study results are consistent with those if the IR was administered under fed condition (Studies NP01-013). Overall, other than the delay in release, NP01 when taken with food has superimposable pharmacokinetic profile compared to immediate release prednisone,

2. QUESTION-BASED REVIEW

2.1. General Attributes

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

Prednisone was first approved for human use in the United States in 1955 (Deltasone NDA009986 and Meticorten NDA 009766). The development of NP01 was originally initiated by Merck KGaA (Merck; Darmstadt, Germany) in 1999. In 2004, the development was transferred from Merck to Nitec Pharma AG (now Horizon Pharma, Inc. [Horizon] as of April 2010). The Marketing Authorization Application (MAA) for NP01 was recommended for approval through the EU Decentralized Procedure (DCP) with Germany as the Reference Member State (RMS) in December 2008. In March 2009, NP01 was approved in Germany and subsequently in 13 Concerned Member States (CMS; Austria, Belgium, Denmark, Finland, France, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Sweden, and the United Kingdom [UK]) for the treatment of RA in adults, especially when accompanied with morning stiffness. It is sold in the EU countries under the trade name Lodotra®.

An End-of-phase 2 meeting was held on December 13, 2007. The clinical pharmacology related aspects discussed at the meeting were the use of Decortin (marketed by Merck KG, Darmstadt, Germany) as the reference drug in the bioavailability trials and the need to conduct a multiple dose study. Agency agreed to the use of in vitro data to bridge Decortin to a US-approved prednisone IR formulation and not requiring a multiple dose study because of the short half life of the drug.

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 as they relate to clinical pharmacology and biopharmaceutics review?

The NP01 drug product is a delayed-release tablet-in-tablet dosage form, consisting of an immediate release prednisone core tablet, surrounded by an inactive outer tablet shell. Drug release is triggered by penetration of water into the tablet shell (b) (4) The composition of the tablets is shown in Table below.

Table 2.1.2. Components and composition of NP01.

Ingredient	Function	Amount per NP01 Tablet (mg)			% of NP01 Tablet (w/w)[3]		
		1 mg Tablet	2 mg Tablet	5 mg Tablet	1 mg Tablet	2 mg Tablet	5 mg Tablet

(b) (4)

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

Prednisone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. The anti-inflammatory property is thought to be used in the treatment of

rheumatoid arthritis. NP01 is indicated for the treatment of rheumatoid arthritis in adult patients.

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

The proposed dosing regimen is as follows:

- Initial dose: NP01 5 mg administered once per day at bedtime. Patients currently on immediate-release prednisone, prednisolone, or methylprednisolone should be switched to NP01 at an equivalent dose.
- Maintenance dose: Use lowest dosage that will maintain an adequate clinical response.
- Discontinuation: Withdraw gradually if discontinuing long-term or high-dose therapy.
- (b) (4)

2.2. General Clinical Pharmacology

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

The clinical development program performed with NP01 tablets comprised of nine phase 1 studies in healthy subjects and two phase 3 studies in subjects with rheumatoid arthritis. The Phase 1 studies were conducted to assess the dose proportionality of 1, 2, and 5 mg tablets (Study NP01-008), demonstrate the bioequivalence (BE) of the product manufactured at two different manufacturing sites (Study 01-014), assess the relative bioavailability of NP01 with reference IR tablet (Studies NP01-013 and NP01-005), and evaluate the food effect (Study NP01-006). Studies EMR 62215-001 and EMR62215-002 were conducted to evaluate the experimental formulations and are not included in the current review. Studies NP01-009 and NP01-010 evaluated the in vitro-in vivo correlation with various in vitro lag times and are also not included in the review.

Table 2.2.1. List of submitted 2clinical studies.

Study No.	Study Type
EMR 62215-001 and EMR62215-002	Evaluate the experimental DR formulations
EMR 62215-005	Primary comparative bioavailability study 5 mg NP01 under semi-fed and fed conditions vs. 5 mg Decortin
NP01-006	Food effect NP01 under fed vs. fasting conditions
NP01-008	Dose proportionality NP01 at doses of 1 mg, 2 mg, and 5 mg

NP01-009	*In vitro – in vivo* correlation Side batches with different *in vitro* lag times (b) (4) under fasting conditions
NP01-010	*In vitro – in vivo* correlation Side batches with different *in vitro* lag times ((b) (4) under fed conditions
NP01-013	Comparative bioavailability 5 mg NP01 after dinner vs. 5 mg Decortin after breakfast (therapeutic conditions of the label)
NP01-014	Bioequivalence of 5 mg NP01 from two different manufacturers at different manufacturing sites
EMR62215-003 (CAPRA-1)	Phase 3 study in 288 adult RA patients
NP01-07 (CAPRA-2)	Phase 3 study in 350 adult RA patients

The Phase 3 program consisted of 2 clinical efficacy and safety trials in RA. NP01-007 (n=350) was a randomized, double-blind, placebo-controlled, 12-week trial comparing the effects of NP01 versus placebo on ACR20. Duration of morning stiffness was assessed as a key secondary endpoint. The other trial (EMR 62216-003; n=288) was conducted in Europe and was a randomized, double-blind, 3-month, active-controlled trial with a 9-month open-label extension period comparing the effects of NP01 versus Decortin on patient-reported morning stiffness. ACR20 was assessed as a secondary endpoint among multiple other endpoints. See Clinical review by Dr. Rosemarie Neuner for final assessment of these studies.

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

Yes. Please refer to the analytical section for details.

2.2.3. Exposure-response

NA.

2.2.4. What are the PK characteristics of the drug?

The pharmacokinetic properties of prednisone immediate release formulations (IR) are well known. Prednisone is well absorbed following oral administration with an absolute systemic bioavailability averaging 80-100% and a Tmax of 1 to 2 h. Administration with food does not affect the extent of absorption. Prednisone is almost completely metabolized to its active metabolite prednisolone. Systemic levels of prednisolone are four to ten fold higher than those of prednisone. The elimination half lives for both prednisone and prednisolone are 2-3 hours.

2.2.4.1. What are the single dose and multiple dose PK characteristics?

Multiple dose study on NP01 was not conducted. A single dose study was conducted in healthy subjects to evaluate the PK of NP01 under fasting condition (NP01-008). The PK parameters of prednisone and its active metabolite prednisolone are shown in the following tables.

Table 2.2.4.1a. Prednisone PK parameters after single oral doses of 1, 2, and 5 mg NP01 (NP01-008).

Parameter	Mean (SD)		
	1 mg NP01 (N = 12[a])	2 mg NP01 (N = 13)	5 mg NP01 (N = 12)
C_{max} [ng/mL]	2.23 (1.72)	3.56 (2.60)	10.05 (9.03)
$AUC_{0-\infty}$ [hr·ng/mL]	12.6 (8.49)	19.8 (13.93)	56.9 (53.94)
AUC_{0-t} [hr·ng/mL]	11.4 (8.73)	19.2 (13.65)	56.3 (54.03)
t_{max} [hr]	7.7 (1.45)	8.2 (1.35)	7.8 (0.99)
t_{lag} [hr]	5.0 (0.89)	4.5 (1.51)	4.9 (0.48)
$t_{1/2}$ [hr]	2.6 (0.47)	2.7 (0.48)	2.4 (0.32)

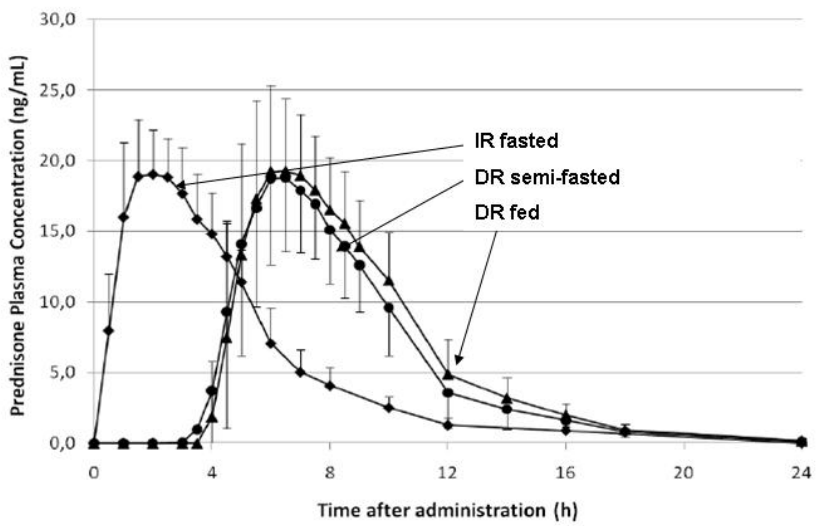
Table 2.2.4.1b. Prednisolone PK parameters after single oral doses of 1, 2, and 5 mg NP01 (NP01-008).

Parameter	Mean (SD)		
	1 mg NP01 (N = 14)	2 mg NP01 (N = 15[a])	5 mg NP01 (N = 13)
C_{max} [ng/mL]	10.96 (8.98)	19.62 (15.83)	40.12 (23.52)
$AUC_{0-\infty}$ [hr·ng/mL]	50.5 (39.37)	93.1(58.04)	197.8 (101.90)
AUC_{0-t} [hr·ng/mL]	49.0 (39.48)	91.0 (56.04)	195.6 (101.60)
t_{max} [hr]	7.4 (1.35)	7.9 (1.94)	7.4 (1.26)
t_{lag} [hr]	4.9 (0.84)	4.8 (0.90)	5.0 (0.69)
$t_{1/2}$ [hr]	2.5 (0.32)	2.5 (0.40)	2.4 (0.19)

2.2.4.2. What are the characteristics of drug absorption?

NP01 is characterized as delayed absorption as compared to immediate release formulation. Under fasting condition, the Tmax is ~7-8 hours for NP01, whereas Tmax is 2-3 hours for the immediate release formulation. In addition, Cmax and AUC were about 60% less than those for the immediate release formulation. In contrast, under fed condition, although Tmax was delayed 4 hours, Cmax and AUC were comparable to those of the immediate release formulation (Study NP01-005).

Figure 2.2.4.2. Prednisone Plasma Concentration vs. Time Profile for NP01-005.



2.2.4.3. What are the characteristics of drug metabolites?

Prednisolone is the main active metabolite of prednisone. The Cmax and AUC of prednisolone are 4-6 fold higher than those of prednisone. The Tmax as well as Thalf of prednisolone and prednisone are comparable.

2.2.4.4. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose-proportionality for the 1, 2, and 5 mg was assessed for the log-transformed parameters C_{max}, AUC_{∞} and AUC_t for prednisone and prednisolone, using a mixed model (the so called "power model") with fixed effects for sequence and period and a random effect for subject within sequence, while log(dose) served as covariate. The results from the ANOVA for assessment of dose-proportionality are given in the Table below.

The dose levels of 1 mg, 2 mg and 5 mg showed dose-proportionality in terms of peak and systemic exposure (C_{max}, AUC_{∞} and AUC_t) for prednisone as well as for prednisolone. The 90% confidence intervals included the value "1" for all parameters for both compounds. The estimated slopes for all parameters were close to "1", indicating a well established dose-proportionality for prednisone and prednisolone C_{max} and AUCs.

Table 2.2.4.4. Analysis of Dose-proportinality for prednisone and prednisolone.

PK Parameter	Alpha	Slope 1–alpha		
		Estimate	Lower CL	Upper CL
Prednisone				
AUC_∞	0.1	1.022	0.803	1.240
AUC_t	0.1	1.048	0.805	1.291
C_{max}	0.1	1.010	0.766	1.255
Prednisolone				
AUC_∞	0.1	1.032	0.805	1.259
AUC_t	0.1	1.039	0.806	1.273
C_{max}	0.1	0.987	0.713	1.261

CL: Confidence Limit

2.2.4.5. How do the PK parameters change with time following chronic dosing?

The multiple dose study was not conducted. As the half life of both prednisone and prednisolone was within 2-3 hours, no accumulation is expected following once daily dosing regimen.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, weight, etc.) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

2.3.1.1. Age

The impact of age on the safety and pharmacokinetics of NP01 tablet was not evaluated. NP01 is not indicated in the pediatric patients. Based on the labeling from the IR prednisone (PredniSONE^{Rx}), the efficacy and safety of corticosteroids are similar in pediatric patients and adult populations. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

2.3.1.2. Gender

The impact of gender on the safety and pharmacokinetics of NP01 tablet was not evaluated.

2.3.1.3. Race

The impact of race on the safety and pharmacokinetics of NP01 tablet was not evaluated.

2.3.1.4. Hepatic impairment

The impact of hepatic function on the safety and pharmacokinetics of NP01 tablet was not evaluated.

2.3.1.5. Renal impairment

The impact of renal function on the safety and pharmacokinetics of NP01 tablet was not evaluated.

2.3.2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation?

NA.

2.4. Extrinsic Factors

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

Please see the food effect description in sections 2.5.2 and 2.5.3. The in vitro dissolution data assessing the potential interaction between alcohol and DP01 was submitted by sponsor and reviewed by ONDQA. The follow on in vivo alcohol interaction was not conducted as the in vitro data did not show a potential of drug interaction.

2.4.2. Drug-Drug Interactions

2.4.1.1. Is there any basis to suspect in vivo drug-drug interactions?

No studies have been done to evaluate the drug-drug interaction potential for NP01 tablet. Sponsor is relying on the reference label for Information related to Drug interactions with prednisone.

As stated in the RLD IR prednisone package insert, drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 (e.g., ketoconazole, itraconazole, ritonavir, indinavir, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids. Glucocorticoids are moderate inducers of CYP 3A4. Co-administration with other drugs that are

metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.

2.4.1.2. Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Label did not specify co-administration of another drug in the treatment.

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 bioequivalence was established between NP01 tablets produced by Bayer Schering Pharma AG, Leverkusen, Germany, and those produced by (b) (4) .

The development of a prednisone DR formulation was originally initiated by Merck KGaA (Darmstadt, Germany) in 1999 who acted as Sponsor of the Phase 1 studies EMR 62215-001, EMR 62215-002, and EMR 62215-005 and the Phase 3 study EMR 62215-003. In 2004, the development was transferred from Merck KGaA to Nitec Pharma, Inc., which merged with Horizon Therapeutics, Inc. on April 1, 2010 to form Horizon Pharma, Inc. (Horizon). An open-label, randomized, 2-sequence, 2-period crossover study in healthy subjects was conducted to investigate the bioequivalence of Lodotra® 5 mg tablet formulations from different manufacturers (Study NP01-14). In 51 evaluable subjects, BE was shown for prednisone and its metabolite prednisolone in all analyzed parameters of exposure for both IMPs, NP01 Bayer and NP01 (b) (4) with criteria of 90% CI of 80%–125%.

Figure 2.5.1. Mean plasma concentration-time profiles of prednisone after administration of Lodotra™ under fasting and fed conditions (NP01-014).	
Prednisone	**Prednisolone**

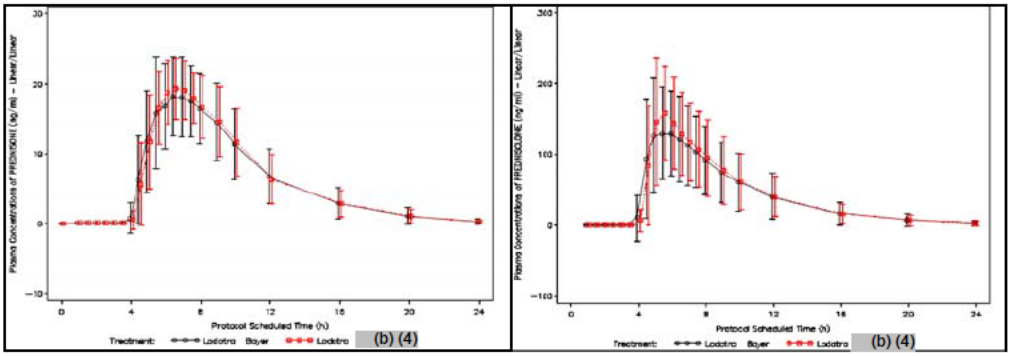


Table 2.5.1. Results of bioequivalence analysis.

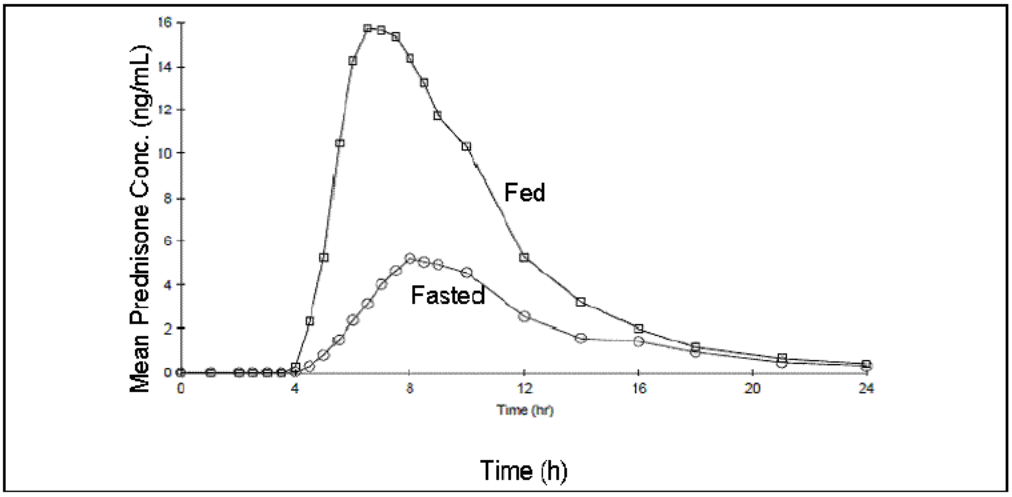
Comparison A–B		α	Estimate (%)	90% Confidence intervals	
Analyte	**Parameter**			**Lower limit (%)**	**Upper limit (%)**
Prednisolone	AUC_∞ [h•ng/mL]	0.1	97.56	94.2	101.04
	AUC_t [h•ng/mL]	0.1	97.43	94.05	100.93
	C_{max} [ng/mL]	0.1	91.86	87.02	96.98
Prednisone	AUC_∞ [h•ng/mL]	0.1	97.59	92.75	102.69
	AUC_t [h•ng/mL]	0.1	97.15	91.84	102.78
	C_{max} [ng/mL]	0.1	95.84	89.66	102.44

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?

Food significantly increased exposure of prednisone and prednisolone *for NP01.*

The effect of food on the pharmacokinetics was evaluated in study NP01-006. The bioavailability of prednision was increased and Tmax was decreased under high-fat-meal conditions as compared to the fasting conditions. The Cmax and AUC for both prednisone and prednisolone under fed conditions increased more than three-fold compared to those under fasting conditions.

Figure 2.5.2. Plasma Concentration vs. Time Profile and Summary Analysis for Food Effect (NP01-006).



Sponsor further evaluated the food effect by taking NP01 2.5 hours after a light meal (700 kcal, 22% fat) and within 0.5 hour after a normal meal (1120 kcal, 35% fat) in study EMR62215-005. In both situations, the exposure of both prednisone and prednisolone was comparable. Sponsor's explanation (b) (4) [redacted]. As type of food intake did not affect drug exposure, sponsor's recommendation that the product be taken with food appears reasonable.

Table 2.5.2. The PK parameters of prednisone in studies EM62215-005, NP01-06, and NP01-013.

	Study EM622215-005			Study NP01-06		Study NP01-013	
	IR Fasted	DR Semi-Fasted	DR Fed	DR Fasted	DR Fed	DR Fed	IR Fed
	Prednisone						
Cmax (ng/mL)	21.1 (16.7%)	21.4 (26.4%)	22.2 (16.4%)	6.55 (56%)	19.1 (16.7%)	17.8 (34%)	17.1 (16%)
AUC0-t (ng h/mL)	108 (15.4%)	114 (27%)	124 (19.5%)	34.2 (64%)	101 (18.7%)	107 (37%)	103 (20%)
AUC0-inf (ng h/mL)	110 (15.5%)	116 (26.6%)	126 (19.2%)	38.2 (57%)	103 (18.3%)	109 (36%)	105 (20%)
Tmax (h)	2 (1.0-4.0)	6.0 (4.5-10)	6.5 (4.5-9)	8 (6-18)	6.5 (5.5-10)	7 (5.5-9)	3.5 (2-7)
	Prednisolone						
Cmax	137	121	135	43.0 (62%)	149	117	132

(ng/mL)	(16.6%)	(26.8%)	(18.2%)		(20.8%)	(36%)	(14%)
AUC0-t (ng h/mL)	623 (17.3%)	600 (29.8%)	669 (21.4%)	226 (74%)	653 (24%)	656 (47%)	711 (32%)
AUC0-inf (ng h/mL)	634 (17.6%)	611 (29.2%)	680 (20.9%)	228.9 (73%)	659 (24%)	665 (45%)	719 (32%)
Tmax (h)	1.12 (0-3)	5.58 (4-9)	5.81 (4.5-9)	7.25 (5.5-9)	5.5 (4.5-8)	6 (5-8)	1.5 (0.5-4.5)

2.5.3 When would a fed BA study be appropriate and was one conducted?

Tmax was delayed for four hours, but the exposure was comparable for NP01 as compared to IR prednisone under fed conditions.

A comparative bioavailability study of NP01 (5 mg) and an immediate-release formulation (5 mg) after single oral administration was conducted in healthy subjects. This was a single-dose, open-label, randomized, 2-way crossover study to investigate the relative bioavailability of the 5 mg delayed-release tablet and a 5 mg prednisone immediate release tablet formulation in healthy subjects.

Figure 2.5.3. Plasma Concentration vs. Time Profile and Summary Analysis for Food Effect (NP01-013).

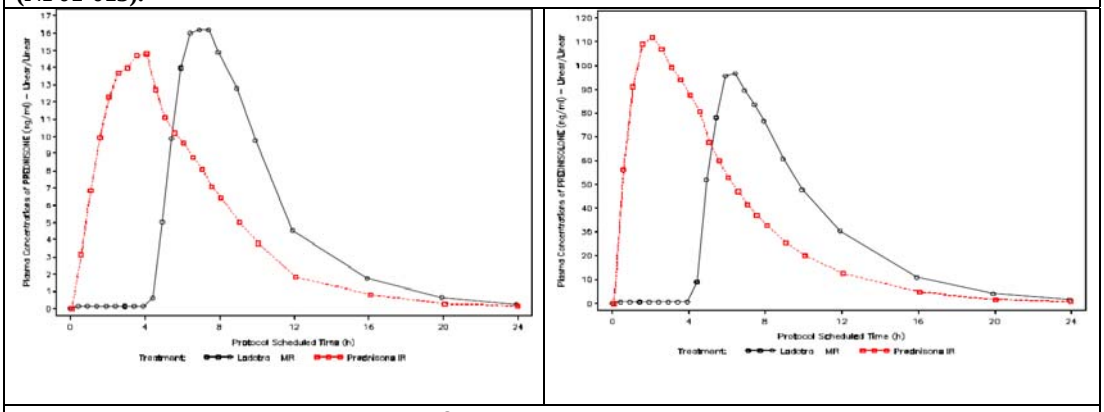


Table 2.5.3. Relative Bioavailability for Prednisone and Prednisolone.

Comparison T – R		α	Estimate (%)	90% Confidence limits	
Analyte	**Parameter**			**Lower (%)**	**Upper (%)**
Prednisone	$AUC_{0-\infty}$ [h•ng/mL]	0.1	89.91	69.79	115.84
	C_{max} [ng/mL]	0.1	98.73	78.8	123.68
Prednisolone	$AUC_{0-\infty}$ [h•ng/mL]	0.1	82.24	66.63	101.5
	C_{max} [ng/mL]	0.1	78.36	63.48	96.73

2.5.4. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Decortin® (marketed by Merck KG, Darmstadt, Germany), the IR prednisone product launched in Germany (in 1955), was selected as IR prednisone reference formulation for Phase 1 comparability studies and for the Phase 3 study EMR 62215-003 (titled, "A New Timed-Release Tablet Formulation of Prednisone Compared to Standard Prednisone in Patients with Rheumatoid Arthritis (RA; Prednisone TRT Study) -A Randomized Multi-Center, Double-Blind, Active Controlled Study with an Open Extension on the New Drug Only"; CAPRA-1). An agreement was reached with the Agency at the end-of Phase 2 (EOP2) meeting held on December 13, 2007 (meeting minutes dated December 12, 2007) that the conduct of an *in vivo* bioavailability and bioequivalence study comparing Decortin to the US reference IR prednisone product was not required. Please see details in the biopharmaceutics review from ONDQA for final assessment on this matter.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma and urine in the clinical pharmacology studies?

The concentrations of prednisone and prednisolone were measured by a LC-MS/MS assay. The human plasma standards were extracted by solid phase extraction and analysed using a LC-MS/MS method. Quantification was achieved using analyte to internal standard peak area ratios. Concentrations of the standards were determined by the method of ($1x^2$) weighted least squares linear regression.

2.7.2 How was the assay performed for the analytes?

The lower limit of quantification for prednisone and prednisolone was established at 0.25 ng/ml. The upper limits of quantification for prednisone and prednisolone were established at 249.86 and 250.85 ng/ml, respectively. Prednisone and prednisolone were shown to be stable in human plasma at room temperature for 4 hours and when exposed to three freeze/thaw cycles. Prednisone, prednisolone and internal standard stock solutions were shown to be stable for 85, 84 and 68 days respectively, when stored at 5ºC (± 3ºC), and at room temperature for 24 hours. Extracted prednisone and prednisolone samples were shown to be stable when left at on the autosampler for approximately 67 hours. Long-term stability of prednisone and prednisolone stored at -20°C(±10°C) will be performed at a later date, once a sufficient length of time has elapsed. Dilution analysis has shown that samples can be diluted by a factor of 1 in 2 or 1 in 5, and still produce accurate results. There was no significant ion suppression observed at the retention times of either prednisone, prednisolone or the internal standard in the chromatograms from six different extracted human plasma samples.

3. DETAILED LABELING RECOMMENDATIONS

(Reviewer suggested changes: ~~Strikeout text~~ should be removed from labeling and underlined text should be added to labeling)

12 CLINICAL PHARMACOLOGY

(b) (4)

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

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4.2. Individual Study Review

EMR 62 215-005

Study Title: Comparative bioavailability study of one new timed-release formulation of prednisone (5 mg tablet) dosed in the evening with or without food and a reference immediate-release formulation (Decortin® 5 mg tablet) dosed in the night without food, after single oral dose administration in healthy male subjects.

Objectives:
Primary Objective

To compare the bioavailability of prednisone and prednisolone of the reference formulation dosed at 02:00 in the night in the fasted state, with the test formulation, dosed at 20:00 in the evening in the semi-fasted state and in fed state.

Secondary Objective
To assess the effect of food on the pharmacokinetic profile and the bioavailability of the test formulation.

Study Design: This is an Open, randomized, 3-period crossover, single oral dose study with 7-days washout periods including 27 healthy male subjects with the aim to complete 24 evaluable subjects:

Treatment A: dosed at 02:00 in the night in the fasted state
Treatment B: dosed at 20:00 in the evening in the semi-fasted state- light meal at 17:30
Treatment C: dosed at 20:00 in the evening in the fed state normal dinner at 19:30

Blood samples for PK analysis were collected at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 6.5, 7, 8, 10, 11, 12, 16, 24, and 30 hours post-dose.

Study Population: A total of 27 subjects were enrolled and completed the study.

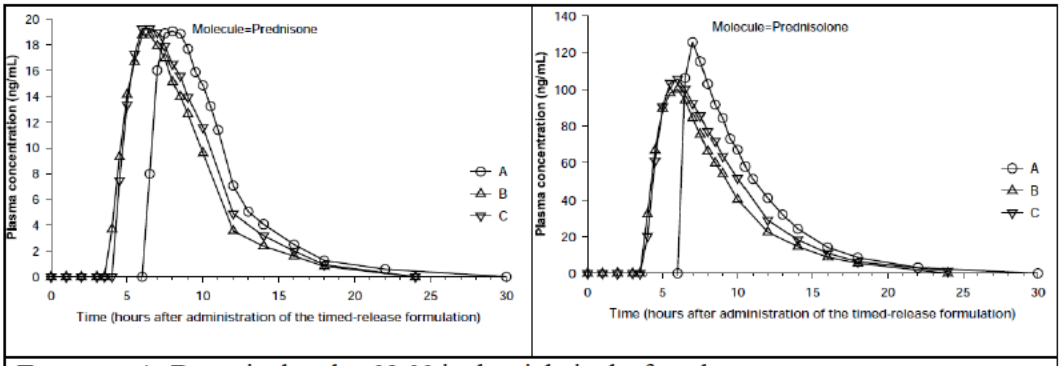
Data Analysis:

Primary target variables
Cmax, AUC0-t, AUC0-∞ for prednisone and prednisolone.

Secondary target variables
tlag, tmax, Frel(test vs .ref), MRT0-∞, kel and t1/2 for prednisone and prednisolone
Comparisons of interest:
Prednisone and prednisolone AUC0-t, AUC0-∞, Cmax, tlag and tmax for the test formulation dosed at 20:00 in the evening in the semi-fasted state versus the reference formulation dosed at 02:00 in the night in the fasted state.
Prednisone and prednisolone AUC0-t, AUC0-∞, Cmax, tlag and tmax for the test formulation dosed at 20:00 in the evening in the fed state versus the reference formulation dosed at 02:00 in the night in the fasted state.
Prednisone and prednisolone AUC0-t, AUC0-∞, Cmax, tlag and tmax for the test formulation dosed at 20:00 in the evening in the fed state versus the test formulation dosed at 20:00 in the evening in the semi-fasted state.

Pharmacokinetic Results:

Figure. Plasma Concentration vs Time Profile for prednisone and prednisolone.	
Prednisone	**Prednisolone**



Treatment A: Decortin dosed at 02:00 in the night in the fasted state
Treatment B: NP01 dosed at 20:00 in the evening in the semi-fasted state- light meal at 17:30
Treatment C: NP01 dosed at 20:00 in the evening in the fed state normal dinner at 19:30

Table 1: Summary of ANOVA results

Pharmacokinetic results:

The pharmacokinetic parameters derived for prednisone and prednisolone are summarised below:

Parameters *Prednisone*	**Treatment A: Decortin® fasted state**	**Treatment B: TR semi-fasted state**	**Treatment C: TR fed state**	*p* *
C_{max} (ng/mL)	20.7 (19.0 – 22.5)	20.2 (18.5 – 21.9)	21.8 (20.0 – 23.7)	0.54
t_{max} (h)	2.0 (1.0 – 4.0)	6.0 (4.5 – 10.0)	6.5 (4.5 – 9.0)	<0.0001
t_{lag} (h)	0.0 (0.0 – 0.5)	3.5 (2.0 – 5.5)	4.0 (3.5 – 5.0)	<0.0001
AUC_{0-t} (h.ng/mL)	107 (98.4 – 116)	108 (99.0 – 117)	121 (111 – 131)	0.16
$AUC_{0-\infty}$ (h.ng/mL)	109 (101 – 118)	110 (101 – 119)	123 (114 – 133)	0.15
C_{max}/AUC_{0-t} (h^{-1})	0.194 (0.188 – 0.200)	0.187 (0.182 – 0.193)	0.181 (0.175 – 0.186)	0.020
$MRT_{0-\infty}$ (h)	4.61 (4.47 – 4.75)	8.64 (8.38 – 8.91)	8.86 (8.59 – 9.14)	<0.0001
$t_{1/2}$ (h)	2.57 (2.52 – 2.63)	2.42 (2.36 – 2.47)	2.42 (2.36 – 2.47)	0.002

TR: timed-release formulation;
t_{max} and t_{lag} values are median (range). Other values are least-squares geometric means (90% CI) (see Table 9.4);
*: Probability associated with the hypothesis of no difference between formulations (ANOVA, except for t_{max} and t_{lag}: Friedman test).

Parameters *Prednisolone*	**Treatment A: Decortin® fasted state**	**Treatment B: TR semi-fasted state**	**Treatment C: TR fed state**	*p* *
C_{max} (ng/mL)	135 (124 – 147)	113 (104 – 123)	132 (121 – 143)	0.036
t_{max} (h)	1.0 (0.5 – 3.0)	5.0 (4.0 – 9.0)	5.5 (4.5 – 9.0)	<0.0001
t_{lag} (h)	0.0 (0.0 – 0.5)	3.5 (2.0 – 5.5)	3.5 (3.0 – 5.0)	<0.0001
AUC_{0-t} (h.ng/mL)	615 (571 – 663)	562 (521– 605)	648 (601 – 698)	0.081
$AUC_{0-\infty}$ (h.ng/mL)	626 (583 – 672)	574 (535 – 617)	659 (614 – 708)	0.076
C_{max}/AUC_{0-t} (h^{-1})	0.220 (0.209 – 0.231)	0.202 (0.192 – 0.212)	0.203 (0.193 – 0.214)	0.086
$MRT_{0-\infty}$ (h)	4.38 (4.24 – 4.51)	8.61 (8.35 – 8.88)	8.83 (8.56 – 9.10)	<0.0001
$t_{1/2}$ (h)	2.67 (2.63 – 2.70)	2.66 (2.62 – 2.69)	2.72 (2.68 – 2.76)	0.11

TR: timed-release formulation;
t_{max} and t_{lag} values are median (range). Other values are least-squares geometric means (90% CI) (see Table 9.6);
*: Probability associated with the hypothesis of no difference between formulations (ANOVA, except for t_{max} and t_{lag}: Friedman test).

Prednisone

90% CI for the ratio* of the true averages derived for prednisone pharmacokinetic parameters after the different treatments in 26 healthy male volunteers.

	Treatment B vs. Treatment A		Treatment C vs. Treatment A	
Parameters	Point estimate	90%CI**	Point estimate	90%CI**
C_{max} (ng/mL)	97%	86 – 110%	105%	93 – 119%
t_{max} (h)	4.0 h	3.5 – 4.5 h	4.5 h	4.0 – 4.8 h
t_{lag} (h)	3.5 h	3.3 – 3.8 h	3.8 h	3.8 – 4.0 h
AUC_{0-t} (h.ng/mL)	101%	90 – 113%	113%	100 – 127%
$AUC_{0-\infty}$ (h.ng/mL)	101%	90 – 113%	113%	101 – 126%
C_{max}/AUC_{0-t} (h^{-1})	97%	93 – 101%	93%	89 – 97%
$MRT_{0-\infty}$ (h)	188%	180 – 196%	192%	184 – 201%
$t_{1/2}$ (h)	94%	91 – 97%	94%	91 – 97%
	Treatment C vs. Treatment B			
Parameters	Point estimate	90%CI**		
C_{max} (ng/mL)	108%	96 – 122%		
t_{max} (h)	0.25 h	-0.25 – 0.75 h		
t_{lag} (h)	0.25h	0.00 – 0.50 h		
AUC_{0-t} (h.ng/mL)	112%	100 – 126%		
$AUC_{0-\infty}$ (h.ng/mL)	112%	100 – 125%		
C_{max}/AUC_{0-t} (h^{-1})	96%	92 – 100%		
$MRT_{0-\infty}$ (h)	103%	98 – 107%		
$t_{1/2}$ (h)	100%	97 – 103%		

Difference between Test and Reference, for t_{max} and t_{lag};
**: Standard 90% confidence interval for the expected mean Test/Reference ratio, derived from ANOVA for continuous parameters; for t_{max} and t_{lag} 90% confidence interval of the expected difference Test-Reference derived from the Wilcoxon signed rank test.

Test formulation dosed in the semi-fasted state vs. Decortin® dosed at 02:00 in the night:

The test formulation exhibited a median lag-time of (b) (4) with a range of (b) (4)

Relative to Decortin® dosed at 02:00 in the night, the rate and extent of absorption were fully bioequivalent for the test formulation, with C_{max} values of 97% and relative bioavailability of 101% for $AUC_{0-\infty}$.

Test formulation dosed in the fed state vs. Decortin® dosed at 02:00 in the night:

When the timed-release tablet was given with food, a lag time of (b) (4) on median with a range of (b) (4) was observed. The test formulation had a C_{max} of 105% relative to Decortin® dosed at 02:00 in the night and a relative bioavailability of 113% for $AUC_{0-\infty}$. The peak plasma concentration occurred on median 4.5 h later than with the reference.

Test formulation dosed in the fed state vs. Test formulation dosed in the semi-fasted state:

Compared to the experimental timed-release tablet dosed in the semi-fasted state, the experimental tablet dosed in the presence of food yielded up to 12% higher rate and extent of absorption (AUCs). In the fed state, C_{max} of 108% relative to the experimental tablet dosed in the semi-fasted state and a relative bioavailability of 112% for $AUC_{0-\infty}$ were observed.

Prednisolone:

90%CI for the ratio* of the true averages derived for prednisolone pharmacokinetic parameters after the different treatments in 26 healthy male volunteers.

	Treatment B vs. Treatment A		Treatment C vs. Treatment A	
Parameters	Point estimate	90%CI**	Point estimate	90%CI**
C_{max} (ng/mL)	84%	74 – 94%	97%	86 – 110%
t_{max} (h)	4.3 h	4.0 – 4.8 h	4.7 h	4.3 – 5.0 h
t_{lag} (h)	3.5 h	3.3 – 3.8 h	3.8 h	3.5 – 3.8 h
AUC_{0-t} (h.ng/mL)	91%	82 – 101%	105%	95 – 117%
$AUC_{0-\infty}$ (h.ng/mL)	92%	83 – 101%	105%	95 – 117%
C_{max}/AUC_{0-t} (h^{-1})	92%	86 – 98%	93%	86 – 99%
$MRT_{0-\infty}$ (h)	197%	188 – 206%	202%	193 – 211%
$t_{1/2}$ (h)	100%	98 – 102%	102%	100 – 104%
	Treatment C vs. Treatment B			
Parameters	Point estimate	90%CI**		
C_{max} (ng/mL)	116%	103 – 131%		
t_{max} (h)	0.50 h	-0.25 – 1.00 h		
t_{lag} (h)	0.25h	0.00 – 0.50 h		
AUC_{0-t} (h.ng/mL)	115%	104 – 128%		
$AUC_{0-\infty}$ (h.ng/mL)	115%	104 – 127%		
C_{max}/AUC_{0-t} (h^{-1})	101%	94 – 108%		
$MRT_{0-\infty}$ (h)	102%	98 – 107%		
$t_{1/2}$ (h)	102%	100 – 104%		

*: Difference between Test and Reference, for t_{max} and t_{lag};
**: Standard 90% confidence interval for the expected mean Test/Reference ratio, derived from ANOVA for continuous parameters; for t_{max} and t_{lag} 90% confidence interval of the expected difference Test-Reference derived from the Wilcoxon signed rank test.

Test formulation dosed in the semi-fasted state vs. Decortin® dosed at 02:00 in the night:

The test formulation exhibited a median lag-time of [redacted] (b) (4) with a range of [redacted] (b) (4)

Comparing the test formulation to Decortin®, the peak exposure to prednisolone was 16% lower but the extent of exposure was fully bioequivalent, with a relative exposure of 92% for $AUC_{0-\infty}$.

Test formulation dosed in the fed state vs. Decortin® dosed at 02:00 in the night:

When the timed-release tablet was given with food, a lag time of [redacted] (b) (4) on median with a range of [redacted] (b) (4) was observed. The rate and extent of exposure were fully bioequivalent to Decortin®, with C_{max} values of 97% and relative bioavailability of 105% for $AUC_{0-\infty}$.

Test formulation dosed in the fed state vs. Test formulation dosed in the semi-fasted state:

Compared to the experimental timed-release tablet dosed in the semi-fasted state, the experimental tablet dosed in the presence of food yielded a higher rate and extent of exposure. In the fed state, C_{max} of 116% relative to the experimental tablet dosed in the semi-fasted state and a relative bioavailability of 115% for $AUC_{0-\infty}$ were observed.

All the pharmacokinetic parameters of interest (C_{max} and AUC) showed intra-subject variability ranging between 22 to 26% (CV%) for both prednisone and prednisolone.

EMR 62 215-006

Study Title: A Phase 1, Open-label, Randomized, Balanced, Two-treatment (Fasted Versus Fed) Crossover Trial to Investigate the Food Effect of Lodotra™, Administered as Single Oral Dose to Healthy Volunteers.

Objectives:

The primary objective of this study was:
• To investigate the effect of food on Lodotra™ when given as single oral dose (1 tablet, containing 5-mg prednisone) to healthy male and female subjects who were either in fasted condition (for at least 10 hours) or after intake of a high-fat meal

The secondary objectives of this study were:
• To determine the pharmacokinetic (PK) parameters of prednisone and prednisolone
• To assess the safety and tolerability of Lodotra™

Study Design: This study was a single center, Phase 1, open-label, randomized, balanced, 2-period crossover trial in healthy male and female volunteers to investigate the effect of food on Lodotra™, a modified-release tablet containing 5-mg prednisone, which was administered at approximately 8:00 AM in fasted condition or after intake of a high-fat meal.

Study Population: A total of 24 subjects were enrolled and completed the study.

Data Analysis:

All PK parameters for both prednisone and prednisolone were listed and summarized using appropriate descriptive statistics. An absence of food effect on bioavailability (BA) was indicated if the log-transformed 90% CI of the GMR for AUC0-last, AUC0-∞, and Cmax of prednisone and prednisolone between fed and fasted treatments were entirely contained within the equivalence limits of 80 to 125%. If any of the 90% CI of the GMR for AUC0-last, AUC0-∞, and Cmax of prednisone and prednisolone between fed and fasted treatments were not contained within the equivalence limits of 80 to 125%, this indicated there was a food effect on BA.

Pharmacokinetic Results:

Figure. Mean plasma concentration-time profiles of prednisone after administration of Lodotra™ under fasted and fed conditions.	
Prednisone	**Prednisolone**

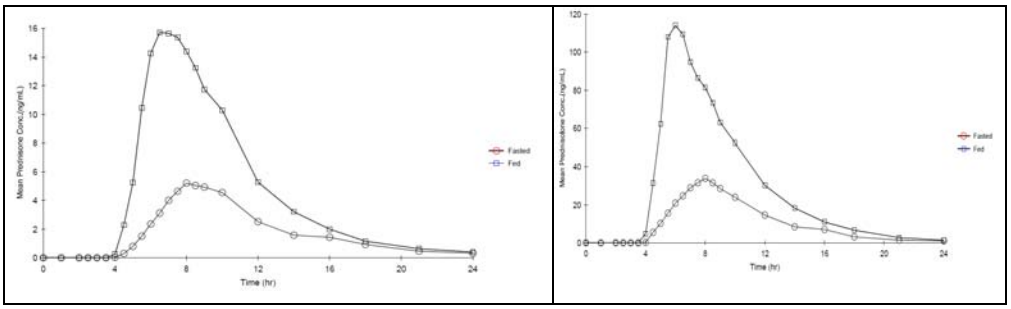


Table 1: Summary of PK results

Parameter (unit)	Statistics	N	Treatment A (Fasted)	N	Treatment B (Fed)
			Prednisone		
t_{lag} (hr)	Median (Min-Max)	24	5.50 (3.50-7.50)	24	4.50 (3.50-6.00)
C_{max} (ng/mL)	Mean (SD)	24	6.551 (3.6696)	24	19.086 (3.2022)
t_{max} (hr)	Median (Min-Max)	24	8.00 (6.00-18.00)	24	6.50 (5.50-10.00)
$AUC_{0\text{-last}}$ (ng hr/mL)	Mean (SD)	24	34.166 (21.8873)	24	100.771 (18.7397)
$AUC_{0\text{-}\infty}$ (ng hr/mL)	Mean (SD)	20	38.245 (21.8376)	24	102.960 (18.8975)
λ_z (1/hr)	Mean (SD)	20	0.286682 (0.0663769)	24	0.285214 (0.0762738)
$t_{1/2}$ (hr)	Mean (SD)	20	2.631 (1.0959)	24	2.537 (0.4460)

Prednisone

Parameter (unit)	Statistics	N	Treatment A (Fasted)	N	Treatment B (Fed)
			Prednisolone		
t_{lag} (hr)	Median (Min-Max)	24	5.00 (1.00-7.00)	24	4.00 (3.50-5.00)
C_{max} (ng/mL)	Mean (SD)	24	43.041 (27.2966)	24	149.333 (31.0725)
t_{max} (hr)	Median (Min-Max)	24	7.25 (5.50-9.00)	24	5.50 (4.50-8.50)
$AUC_{0\text{-last}}$ (ng hr/mL)	Mean (SD)	24	225.601 (167.7087)	24	653.358 (156.3472)
$AUC_{0\text{-}\infty}$ (ng hr/mL)	Mean (SD)	24	228.900 (169.3509)	24	658.959 (160.2506)
λ_z (1/hr)	Mean (SD)	24	0.280321 (0.0268302)	24	0.267400 (0.0282487)
$t_{1/2}$ (hr)	Mean (SD)	24	2.495 (0.2438)	24	2.620 (0.2720)

Conclusions: For both prednisone and prednisolone analytes and for Cmax, AUC0-last, and AUC0-∞ PK parameters, the lower bound of 90% CI was significantly higher than the 125% acceptable BE upper limit. The ratios of the geometric least squares mean ratios ranged from 319% to 420%, representing a 3- to 4-fold reduction in BA under fasted relative to fed conditions. Under fed conditions, the plasma concentrations of prednisone and prednisolone and the derived PK parameters of both were comparable to an earlier study conducted under comparable dietary conditions.

EMR 62 215-008

Study Title: A Phase I, Open-Label, Randomized, Balanced, Three-Way Crossover Trial: A Bridging Pharmacokinetic Study to Investigate Dose Proportionality of Lodotra® Administered as Single Oral Dose to Healthy Volunteers

Objectives:

Primary:
• To investigate the dose proportionality of Lodotra® following single oral doses of 1, 2 and 5 mg to healthy male subjects
Secondary:
• To evaluate the pharmacokinetic profile of prednisone and prednisolone following single oral doses of Lodotra® 1, 2 and 5 mg tablets
• To evaluate the safety and tolerability following single oral doses of Lodotra® 1, 2 and 5 mg tablets

Study Design: This study was a single centre, Phase I, open-label, randomized, balanced, three-way crossover study in healthy male subjects to investigate pharmacokinetics after single oral doses of Lodotra® modified-release tablets containing 1, 2 or 5 mg prednisone.

The 24-hours pharmacokinetic profile of prednisone and prednisolone was determined. Blood samples were collected at pre-dose and 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 20 and 24 hours post-dose for determination of prednisone and prednisolone plasma concentrations. Safety assessments were performed at screening and follow-up visit.

Study Population: A total of 15 subjects were enrolled and completed the study.

Data Analysis:

Pharmacokinetic:
Primary:
• Cmax and AUC∞ of prednisone plasma concentration
Secondary:
• Cmax and AUC∞ of prednisolone plasma concentration

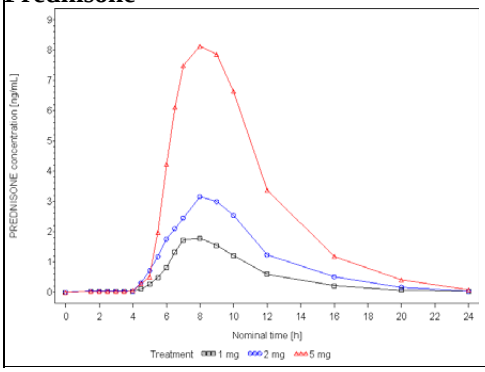
• tmax, tlag, AUCt, λz, t1/2, CL/F, Vz/F and MRT of prednisone and prednisolone plasma concentration

Safety variables:
Adverse events, concomitant medication, changes in physical examination, routine safety laboratory, vital signs and 12-lead ECGs

Pharmacokinetic Results:

Figure. Mean plasma concentration-time profiles of prednisone after administration of Lodotra™ under fasted and fed conditions.

Prednisone



Prednisolone

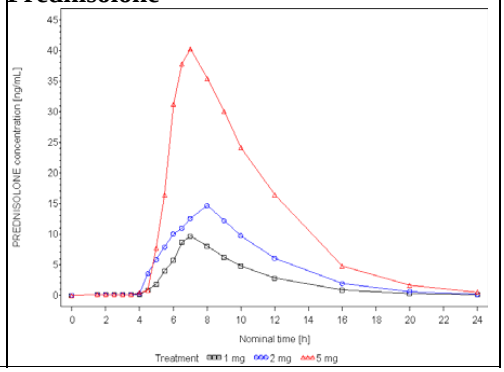


Table 11-2 Plasma Pharmacokinetic Parameters of Prednisone

Parameter	Units	Statistics	Dose of Lodotra®		
			1 mg N = 17	2 mg N = 18	5 mg N = 17
C_{max}	[ng/mL]	Mean	2.0996	3.8723	9.6104
		SD	1.6284	2.7941	8.0892
		Min	0.243	1.249	2.748
		Median	1.5910	2.7935	7.9290
		Max	5.101	9.860	36.581
		gCV%	120.7	74.9	76.1
		G mean	1.4705	3.1120	7.5975
AUC_{∞}	[ng•h/mL]	Mean	11.18	21.44	55.00
		SD	8.13	14.24	46.32
		Min	2.0	6.0	14.0
		Median	9.00	17.00	43.00
		Max	30.0	52.0	215.0
		gCV%	99.4	74.9	72.2
		G mean	8.40	17.48	44.14
AUC_t	[ng•h/mL]	Mean	11.00	21.39	54.76
		SD	8.25	14.30	46.15
		Min	1.0	6.0	13.0
		Median	9.00	17.00	43.00
		Max	30.0	52.0	214.0
		gCV%	114.6	76.8	73.1
		G mean	7.95	17.33	43.84
t_{max}	[h]	Mean	7.76	7.92	8.15
		SD	1.34	1.29	1.32
		CV%	17.2	16.2	16.2
		Min	5.0	6.0	6.0
		Median	8.0	8.0	8.0
		Max	10.0	10.0	10.0
		G mean	7.65	7.82	8.05

gCV%: Coefficient of Variation percentage for geometric mean; G mean: geometric mean; Max: Maximum; Min: Minimum; SD: Standard Deviation

Table 11-3 Plasma Pharmacokinetic Parameters of Prednisolone

Parameter	Units	Statistics	Dose of Lodotra® 1 mg N = 17	2 mg N = 18	5 mg N = 17
C_{max}	[ng/mL]	Mean	11.8470	21.9629	52.8698
		SD	9.4378	18.6989	47.3900
		Min	1.452	5.407	11.822
		Median	8.7650	14.1020	39.1030
		Max	28.590	69.097	200.173
		gCV%	134.8	81.0	88.1
		G mean	7.9350	16.8659	39.6747
AUC_∞	[ng•h/mL]	Mean	53.29	99.67	257.12
		SD	39.45	61.45	201.47
		Min	7.0	24.0	56.0
		Median	43.00	81.00	182.00
		Max	137.0	231.0	926.0
		gCV%	109.5	69.4	72.3
		G mean	38.78	83.39	208.42
AUC_t	[ng•h/mL]	Mean	52.82	99.17	255.24
		SD	39.48	61.22	201.01
		Min	6.0	24.0	55.0
		Median	42.00	81.00	180.00
		Max	136.0	230.0	923.0
		gCV%	114.5	69.1	72.6
		G mean	37.91	83.01	206.54
t_{max}	[h]	Mean	7.26	7.58	7.62
		SD	1.29	1.90	1.78
		CV%	17.7	25.0	23.4
		Min	5.0	4.5	5.5
		Median	7.0	7.0	7.0
		Max	9.0	12.0	12.0
		G mean	7.15	7.36	7.44

Table 1: Summary of PK results

PK Parameter	Alpha	Slope 1–alpha Estimate	Lower CL	Upper CL
Prednisone				
AUC_∞	0.1	1.022	0.803	1.240
AUC_t	0.1	1.048	0.805	1.291
C_{max}	0.1	1.010	0.766	1.255
Prednisolone				
AUC_∞	0.1	1.032	0.805	1.259
AUC_t	0.1	1.039	0.806	1.273
C_{max}	0.1	0.987	0.713	1.261

CL: Confidence Limit

Conclusions:

- Oral administration of Lodotra® as 1 mg, 2 mg and 5 mg tablets with modified release properties in fasted state resulted in linear dose-proportional pharmacokinetic profiles.
- Cmax values for prednisone were 1.47, 3.11 and 7.60 ng/mL and AUC∞ values 8.40, 17.48 and 44.14 ng•h/mL for the three dose levels. Cmax and AUC∞ values of the present study were about 50% smaller than those in the earlier clinical study EMR 62 215-005, conducted under fed and semi-fed conditions.
- The active metabolite prednisolone showed 4.5- to 5-fold higher peak (Cmax: 7.94, 16.87 and 39.67 ng/mL) and systemic (AUC∞: 38.78, 83.39 and 208.41 ng•h/mL) exposures compared with prednisone.
- The pharmacokinetic data showed high inter-subject variability (CV%) of 70% to 120%, a significantly increased in vivo lag time and time until maximum plasma concentration (tmax) compared to a previous study (EMR 62 215-005) conducted under fed and semi fed conditions. Further, Cmax and AUC∞ of the present study were about 50% lower than in the previous study EMR 62 215-005 when comparing the 5 mg dose groups. These differing results are attributed to the 10 hours fasting conditions which were selected to comply with the guidance for bioequivalence studies, intended to minimize experimental bias.
- Absorption and elimination were similar for prednisone and prednisolone which appeared simultaneously in plasma after a median lag time of approximately 5 hours and tmax of 7 to8 hours. Both, prednisone and prednisolone, were rapidly eliminated from plasma with a MRT of around 10 hours and an average terminal elimination half-life (t1/2) of 2.17 to 2.75 hours, for both prednisone and prednisolone, and across all three Lodotra® doses.

EMR 62 215-013

Study Title: Comparative bioavailability study of Lodotra® (5 mg MR-tablet) and an immediate-release formulation (prednisone IR, 5 mg tablet) after single oral administration in healthy subjects

Objectives:

The objective of the study was to compare the bioavailability of prednisone from an IR-reference
formulation dosed at 08:00 in fed state after breakfast, with the Lodotra®-test formulation, administered at 22:00 after a light evening meal.

Study Design: This was a single-dose, open-label, randomized, 2-way crossover study to investigate the relative bioavailability of the 5 mg modified-release (MR) Lodotra® tablet and a 5 mg prednisone immediaterelease (IR) tablet formulation in healthy subjects.
The 24-hour pharmacokinetic (PK) profile of prednisone and prednisolone was obtained. Blood samples after single doses of Lodotra® or prednisone IR for determination of

prednisone and prednisolone were taken at pre-dose and 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 20 and 24 hours post-dose.
Safety assessments were performed at Screening and at the End-of-study Visit.

Study Population: A total of 28 subjects were enrolled and completed the study.

Data Analysis:
The primary and secondary PK parameters (except tmax and tlag) were log-transformed and analyzed by analysis of variance (ANOVA) with subject, sequence, period and treatment as factors according to "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98). The mean square error of the ANOVA derived from Cmax, AUC0–t and AUC0–∞ were used to calculate the 90% CIs for the difference between Lodotra® (Test) and the Prednisone IR (Reference) on the log scale. Estimates of the ratio Lodotra® versus prednisone IR and 90% CIs were obtained by back-transformation. Tmax and Tlag were analyzed using non-parametric methods.

Pharmacokinetic Results:

Figure. Mean plasma concentration-time profiles of prednisone after administration of Lodotra™ under fasted and fed conditions.

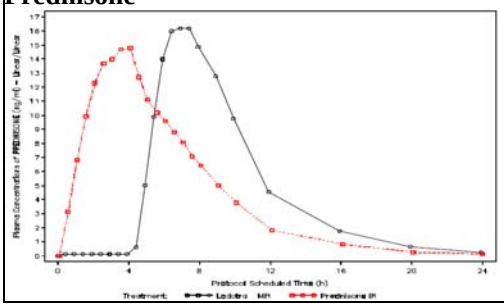
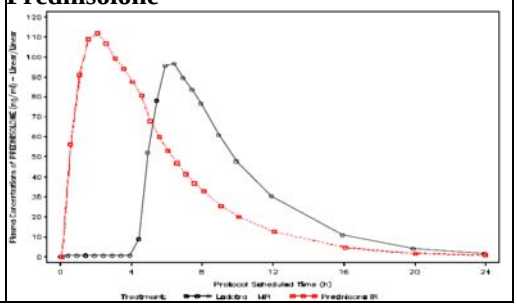
Prednisone	**Prednisolone**
	

Table 1: Summary of PK results

Parameter	Statistics	Prednisone		Prednisolone	
		Lodotra®	Prednisone IR	Lodotra®	Prednisone IR
		N=27	N=27	N=27	N=27
$AUC_{0-\infty}$ [ng•h/mL]	Mean	109	105	665	719
	SD	39.43	20.57	312.4	231.2
	SEM	7.588	3.958	60.13	44.49
	CV(%)	36.29	19.64	46.98	32.15
	Min	3.8	78	57	530
	Median	118	101	637	687
	Max	180	170	1800	1700
	g-Mean	92.0	103	569	695
	gCV(%)	94.90	18.44	77.69	25.13
C_{max} [ng/mL]	Mean	17.8	16.1	117	132
	SD	6.090	2.578	42.42	17.98
	SEM	1.172	0.4962	8.164	3.460
	CV(%)	34.17	15.99	36.35	13.58
	Min	1.1	12	8.0	100
	Median	18.5	15.6	120	131
	Max	27	23	220	190
	g-Mean	15.6	15.9	102	131
	gCV(%)	75.78	15.42	74.59	13.12
t_{max} [h]	Mean	7.00	3.54	6.24	1.78
	SD	0.9410	1.188	0.9013	0.9871
	SEM	0.1811	0.2286	0.1735	0.1900
	CV(%)	13.44	33.58	14.45	55.36
	Min	5.5	2.0	5.0	0.50
	Median	7.00	3.50	6.00	1.55
	Max	9.0	7.0	8.0	4.5
	g-Mean	6.94	3.37	6.18	1.53
	gCV(%)	13.34	32.68	14.16	64.15

Conclusions:

Pharmacokinetics

The pharmacokinetic profile of Lodotra® compared favorably to prednisone IR. The values for tlag and tmax were in accordance with the expectation of a delayed-release formulation. The estimate difference was 4.5 hours for tlag and 3.51 hours for tmax when Lodotra® was compared to prednisone IR.

Safety

Single doses of 5 mg Lodotra® and 5 mg prednisone IR were safe and well tolerated.

EMR 62 215-014

Study Title: Open-label, randomized, 2-sequence, 2-period crossover study in healthy subjects to investigate the bioequivalence of Lodotra® 5 mg tablet formulations from different manufacturers

Objectives:

Primary objective

To evaluate the bioequivalence (BE) of prednisone from single oral doses of NP01 manufactured by Bayer Schering Pharma AG, Leverkusen, Germany, compared to that of NP01 manufactured by (b) (4)

Secondary objective

To evaluate the lag time (tlag) and time to reach maximal concentration (tmax) of prednisone and prednisolone of single oral doses of NP01 manufactured by Bayer Schering Pharma AG, Leverkusen, Germany, and (b) (4) To evaluate the safety and tolerability of single oral doses of the two NP01 batches

Study Design: This was an open-label, randomized, balanced, 2-sequence, 2-period, single-dose, crossover clinical study with an optional second stage conducted in healthy subjects to investigate the BE of two batches of NP01 5 mg tablets produced by two different manufacturers

The 24-hour pharmacokinetic profile of prednisone and prednisolone was obtained. Blood samples after single doses of NP01 for determination of prednisone and prednisolone were taken at pre-dose and 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 20 and 24 hours post-dose. Safety assessments were performed at the Screening Visit and on Days 1 and 2 of the experimental periods and at the End-of-study Visit.

Study Population: A total of 52 subjects were enrolled and completed the study.

Data Analysis:

Pharmacokinetics

The following pharmacokinetic parameters were derived from plasma concentrations of prednisone and prednisolone:

- Primary:
  Cmax, AUCt , AUC∞ of prednisone/prednisolone plasma concentration
- Secondary:
  tmax, tlag, λZ, t1/2 and MRT of prednisone and prednisolone plasma concentration.

Pharmacokinetic Results:

Figure. Mean plasma concentration-time profiles of prednisone after administration of Lodotra™ under fasted and fed conditions.	
Prednisone	**Prednisolone**

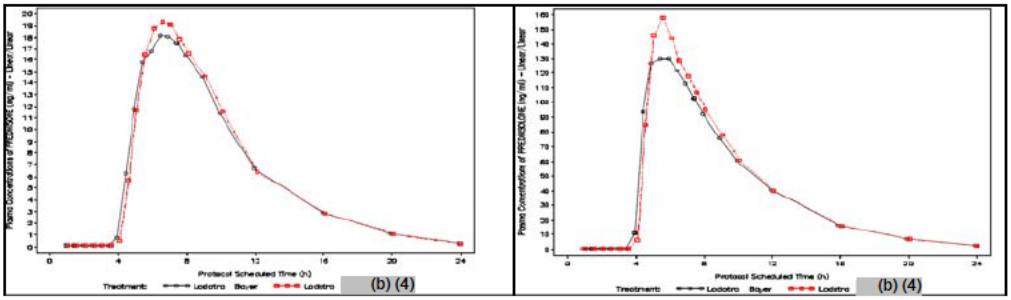


Table 1: Summary of PK results

		Prednisone			Prednisolone		
		NP01 Bayer	NP01	(b) (4)	NP01 Bayer	NP01	(b) (4)
Parameter	**Statistics**	**N=52**	**N=51**		**N=52**	**N=51**	
C_{max}	Mean	21.4	21.4		178	195	
[ng/mL]	SD	6.19	4.39		60.25	65.35	
	SEM	0.858	0.6148		8.356	9.151	
	CV (%)	28.88	20.50		33.87	33.54	
	Min	4	14		58	95	
	Median	20.8	21.0		165.0	179.0	
	Max	45	32		325	372	
	g-Mean	20.5	21.0		168.0	185.0	
	gCV (%)	34.14	20.33		36.44	33.37	
AUC_{∞}	Mean	136	136		886	917	
[ng•h/mL]	SD	44.29	39.37		452.30	475.40	
	SEM	6.142	5.513		62.73	66.56	
	CV (%)	32.69	28.86		51.08	51.86	
	Min	36	86		318	433	
	Median	122.0	124.0		686.0	708.0	
	Max	235	234		1967	2072	
	g-Mean	128.0	131.0		792.0	819.0	
	gCV (%)	36.35	27.26		49.04	48.7	
AUC_t	Mean	132	133		870	902	
[ng•h/mL]	SD	43.91	38.66		438.30	462.10	
	SEM	6.089	5.414		60.78	64.7	
	CV (%)	33.16	28.97		50.35	51.22	
	Min	31	85		315	429	
	Median	121.0	120.0		678.0	703.0	
	Max	232	232		1910	2022	
	g-Mean	125.0	129.0		780.0	808.0	
	gCV (%)	38.22	27.33		48.58	48.2	

t_{max} [h]	Mean	6.77	6.51	5.49	5.18
	SD	1.39	0.87	1.38	0.69
	SEM	0.1912	0.1222	0.1914	0.09595
	CV(%)	20.38	13.4	25.16	13.22
	Min	5	5	5	5
	Median	6.5	6.5	5.0	5.0
	Max	12	10	12	8
	g-Mean	6.7	6.5	5.4	5.1
	gCV(%)	18.69	12.52	20.55	12.14

Table 11-5: Results of bioequivalence analysis

Comparison A–B		α	Estimate (%)	90% Confidence intervals	
Analyte	**Parameter**			**Lower limit (%)**	**Upper limit (%)**
Prednisolone	AUC_∞ [h•ng/mL]	0.1	97.56	94.2	101.04
	AUC_t [h•ng/mL]	0.1	97.43	94.05	100.93
	C_{max} [ng/mL]	0.1	91.86	87.02	96.98
Prednisone	AUC_∞ [h•ng/mL]	0.1	97.59	92.75	102.69
	AUC_t [h•ng/mL]	0.1	97.15	91.84	102.78
	C_{max} [ng/mL]	0.1	95.84	89.66	102.44

A=NP01 Bayer; B=NP01 (b) (4) AUC_∞=Area under the curve extrapolated to infinity; AUC_t= Area under the curve to last concentration measured; C_{max}=Maximal concentration

Conclusions:

NP01 Bayer and NP01 (b) (4) were bioequivalent with respect to AUCt, AUC∞ and Cmax.

4.3. Clinical Pharmacology and Biopharmaceutics filing form/checklist for NDA 202020

Clinical Pharmacology and Biopharmaceutics filing form/checklist for NDA20-2020

Office of Clinical Pharmacology ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	202020	**Brand Name**	NP01 (Proposed)
OCP Division (I, II, III, IV, V)	II	**Generic Name**	Prednisone, modified release
Medical Division	DPARP	**Drug Class**	
OCP Reviewer	Ping Ji	**Indication(s)**	Relieve signs and symptoms of adult RA
OCP Team Leader	Suresh Doddapaneni	**Dosage Form**	Modified release formulation
Pharmacometrics Reviewer	NA	**Dosing Regimen**	NP01 5 mg administered once per day (b) (4).
Date of Submission	Sep 26, 2011	**Route of Administration**	Oral
Estimated Due Date of OCP Review	Mar 19, 2011	**Sponsor**	Horizon Pharma Inc
Medical Division Due Date	Mar 19, 2011	**Priority Classification**	S
PDUFA Due Date	July 26, 2012		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE	x			
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	2	2	
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:	x	1	1	
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:	x	1	1	
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 -	x	7	3	
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x	1	1	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	x	1		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	1	1	
Total Number of Studies		14	9	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _y_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

no

Ping Ji, PhD
Reviewing Clinical Pharmacologist Date:

Suresh Doddapaneni, PhD
Team Lead Date:

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

/s/

PING JI
06/21/2012

SURESH DODDAPANENI
06/21/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-020	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Dates:	9/26/2011; 12/22/2011; 1/20/2012; 1/31/2012; 3/21/2012; 5/4/2012		
Division:	DPARP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Horizon Pharma, Inc.	**Secondary Signature:** Sandra Suarez-Sharp, Ph.D.	
Trade Name:	Rayos MR	**Date Assigned:**	11/11/2011
Generic Name:	Prednisone modified release tablets	**Date of Review:**	6/20/2012
Indication:	Treatment of rheumatoid arthritis in adult patients	**Type of Submission:** 505(b)(2) New Drug Application	
Formulation/strengths:	MR Tablets/ 1 mg, 2 mg, 5 mg		
Route of Administration:	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

This submission is a 505(b)(2) New Drug Application for prednisone delayed release tablets (NP01) containing 1 mg, 2 mg, and 5 mg of prednisone. The indication is for the treatment of rheumatoid arthritis in adult patients. The applicant is relying on PredniSONE Tablets (NDA 017109) by Roxane Laboratories, Inc. and Decortin® (a European IR prednisione drug product) as the reference drugs.

Prednisone, a synthetic, non-fluorinated, glucocorticoid, is a disease-modifying anti-rheumatic drug. The NP01 tablet consists of an immediate release prednisone core tablet, surrounded by an inactive tablet shell (b) (4) (b) (4)

This submission includes a drug product development section, a dissolution development report with a proposed dissolution method specification and acceptance criteria, BA/BE data comparing NP01 to Decortin® (the European listed drug), *in vitro* dissolution profile comparisons supporting the approval to use the EU RLD as a reference rather than the US RLD, as well as PK and dissolution data used in the development of an *in vitro in vivo* relationship (IVIVR) for lag time.

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criteria, acceptability of the waiver request for the 1 mg and 2 mg strength based on dissolution profile comparisons, acceptability of the *in vitro* dissolution data supporting the use of the EU RLD as a reference rather than the US RLD, acceptability of the in vitro alcohol dose-dumping information requested during the review cycle, as well as the acceptability of the IVIVR.

A. Dissolution Method

The proposed dissolution method is:

Apparatus	Paddle (USP Apparatus 2)
Medium	Purified water, 500 mL
Bath temperature:	37°C ± 0.5°C
Agitation	100 rpm
Units per vessel	1
Sampling times	3.0 and 7.0 hours
Sinker:	Present

During the review cycle, the ONDQA Biopharmaceutics Team requested the Applicant to justify the use of 100 rpm rotation speed. Subsequently, the Applicant provided data showing that a rotation speed of (b) (4) or 100 rpm did not affect the rate and extent of dissolution. In an IR letter sent to the Applicant on June 14, 2012, the ONDQA Biopharmaceutics Team accepted the Applicant's proposal of 100 rpm rotation speed.

B. Dissolution Acceptance Criteria

The proposed acceptance criteria are NMT (b) (4) release at 3 hours and Q = (b) (4) at 7 hours. In an IR letter to the Applicant dated April 27, 2012, the ONDQA Biopharmaceutics Team recommended the dissolution acceptance criteria of **NMT (b) (4) at 3 hours, Lag Time (b) (4) hours for any individual tablet, and Q = (b) (4) at 7 hours**. This recommendation is based on the mean in-vitro dissolution profiles for all strengths at release and under long term (12 months) stability studies. The Applicant accepted **NMT (b) (4) at 3 hours and Q = (b) (4) at 7 hours** but proposed **Lag Time (b) (4) hours for any individual tablet,** (refer to submission dated May 4, 2012). In an IR letter sent to the Applicant on June 14, 2012, the following lag time acceptance criterion was recommended: **Mean Lag Time (b) (4) hours. No individual tablet Lag Time should exceed (b) (4) hours**. In an email dated June 15, 2012, the Applicant accepted the Agency's recommendation.

C. Waiver Request for a BA/BE Study Comparing the Proposed Product to the US Reference Drug

The pivotal BE study supporting the approval of the proposed dug product was conducted using the European RLD (Decortin®). The Applicant requested a waiver for BA/BE data comparing NP01 with the US reference listed drug. Instead, *in vitro* dissolution profiles comparisons were provided comparing the EU RLD IR prednisone product and the US RLD IR prednisone product.

An agreement was reached with the Agency at the EOP2 meeting scheduled for December 13, 2007 (Question 7; meeting minutes dated December 12, 2007) that there is sufficient information to show that the dissolution profiles of Decortin (the reference product used in pivotal BE Study EMR 62215-005) and US-approved IR prednisone drug products, including the US RLD PredniSONE Tablets USP, are similar, and that an additional BE study between the US RLD and the proposed product was not needed. Instead, the FDA agreed on the use of dissolution profiles comparisons to support the link. The data provided showed that the dissolution profiles of the EU and the US-approved drug products are similar in pH 1.2, 4.5, and 6.8 buffers (greater than (b) (4) of prednisone is dissolved in 15 minutes for the drug products in the media tested).

It is unknown, however, whether the European RLD and the US RLD for prednisone have the same formulation composition. Despite the fact that the IR prednisone formulation meets the criteria for a BCS Class 1 drug, the Biopharmaceutics team asserts that, from a regulatory perspective, the waiver should not have been granted due to lack of information supporting that the two references meet the requirement of "similar composition". Since in the present submission the Applicant included results from a clinical efficacy and safety trial conducted with the proposed product for exclusivity purposes, these data may be used internally to support the approvability of the proposed product and to justify that additional BA/BE data is unnecessary.

D. Data Supporting the Approval of Lower Strengths

(b) (4) However, these data are superseded by the dose proportionality data for the of 1 mg, 2 mg, and 5 mg strength tablets obtained as part of the Phase 1 study NP01-008. Dr. Ping Ji, the Clinical Pharmacology reviewer, confirmed that all strengths are dose-proportional (refer to the Clinical Pharmacology review for the complete evaluation of Study NP01-008). Thus, a biowaiver is not needed for the approval of the 1 mg and 2 mg strengths.

E. *In Vitro* Alcohol Dose-Dumping

The Applicant provided adequate data demonstrating that there is no *in vitro* alcohol dose-dumping. However, the *in vitro* data shows that alcohol does further delay the release of the drug.

F. The *In Vitro/In Vivo* Relationship (IVIVR)

The Applicant submitted PK and dissolution data for NP01 tablets manufactured with (b) (4) in order to demonstrate the existence of an IVIVR for lag time and thereby set dissolution acceptance criteria for the

drug product. The PK study, however, was performed under fed conditions and therefore, the PK results are confounded by a food effect. Also, the formulations representing the extremes in dissolution profiles tested in this PK study were determined to be not bioequivalent. Thus, there is no *in vitro/ in vivo* relationship, and these data can not be used to set the dissolution acceptance criteria.

RECOMMENDATION:

1. A biowaiver is granted for the BA/BE requirement to provide data comparing NP01 with the US reference listed drug.

2. NP01 1 mg, 2 mg, and 5 mg strength MR tablets are recommended for approval from a Biopharmaceutics standpoint.
    - The following dissolution method and acceptance criteria for the 1mg, 2 mg, and 5 mg strength MR tablets are recommended and have been agreed upon with the Applicant (via email communication to Mr. Youbang Liu on June 15, 2012):
        i. Dissolution method: Apparatus II, 100 rpm agitation rate, 500 mL media volume, 37 °C, water as medium.
        ii. Dissolution acceptance criteria: NMT (b) (4) release at 3 hours, Mean Lag Time (b) (4) hours. No individual tablet Lag Time should exceed (b) (4) hours, and Q = (b) (4) at 7 hours.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: Dr, Angelica Dorantes, Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The chemical structure of prednisone is shown in Figure 1.

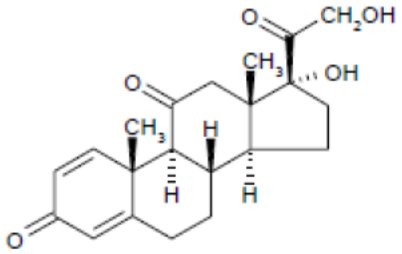


Figure 1. Chemical structure of prednisone.

Prednisone does not exhibit any acid or basic characteristics in solution. Prednisone's solubility is constant over the physiologically-relevant pH range. The solubility of prednisone in water and standard buffer solutions (pH 1.2, 4.5, 6.8, and 7.5) was tested and shown to range from 0.15 to 0.17 mg/mL at 37°C (see Table 1).

Table 1. Solubility of Prednisone at Different pH Values

	Concentration [µg/mL]				
Substance	pH 1.2	pH 4.5	pH 6.8	pH 7.5	Water
Prednisone (mean ± SD)	168.2±2.2	159.5±0.4	154.8±0.2	152.7±1.4	168.0±0.4

Reviewer's Assessment:
The Applicant has provided adequate solubility data.

Drug Product

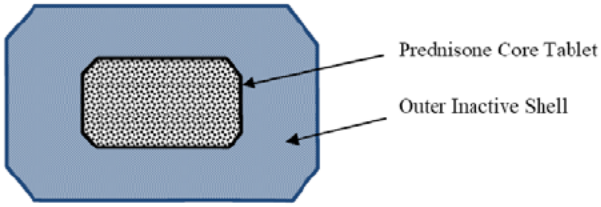
The development of an NP01 modified-release prednisone formulation was originally initiated by Merck KGaA in 1999. In 2004, the development was transferred from Merck to Nitec Pharma AG (now Horizon Pharma, Inc.).

The NP01 drug product is a MR tablet-in-tablet dosage form, consisting of an immediate release prednisone core tablet surrounded by an inactive tablet shell. NP01 is available as 1-mg, 2-mg, and 5-mg strength tablets to allow patients individualized low-dose regimens by combining the different strengths of prednisone as needed. The prescribed number of tablets of NP01 to achieve the desired dose of prednisone is administered once a day (QD) at bed time under semi-fed or fed conditions.

(b) (4)

Drug release for the proposed drug product is triggered by penetration of water into the outer tablet shell (b) (4) The outer shell delays the release of prednisone approximately 4 hours after dosing. The total tablet weight is 410 mg, (b) (4) The round tablet is 9 mm in diameter, with a thickness of 5 mm. A cross-section diagram of the NP01 modified release tablet is presented in Figure 2.

Figure 2. Cross-sectional Diagram of the NP-01 Drug Product



The composition of the proposed drug product for all strengths is displayed in Table 2.

Table 2. Components and Composition of NP01 Drug Product

Ingredient	Function	Amount per NP01 Tablet (mg)			% of NP01 Tablet (w/w)[3]		
		1 mg Tablet	2 mg Tablet	5 mg Tablet	1 mg Tablet	2 mg Tablet	5 mg Tablet
[redacted] (b) (4)							
Total tablet		410	410	410	100	100	100

According to the Applicant, [redacted] (b) (4) .

[redacted] (b) (4)

Reviewer's Assessment:

The different strength tablets meet the definition of proportionally similar as defined in the BA/BE Guidance. Namely, the strengths meet the following condition:

- ***For high potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within + 10 % of the total weight of the strength on which a biostudy was performed), the same inactive ingredients***

are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-MR guidances up to and including Level II.

The proposed product is being manufactured at two sites, (b) (4) and Bayer Schering Pharma AG (Bayer) in Germany. There is BE data (study NP01-014) supporting these two manufacturing sites (see Table 3).

Table 3. Bioequivalence of Prednisone after a Single Oral Dose of 5 mg Prednisone Manufactureed by (b) (4) and Bayer (Study NP01-014).

Parameter	Comparison T – R		
	Alpha	Estimate [%]	1-alpha CI
C_{max} [ng/mL]	0.10	95.8	89.7; 102.4
$AUC_{0-\infty}$ [hr·ng/mL]	0.10	97.6	92.7; 102.7
AUC_{0-t} [hr·ng/mL]	0.10	97.2	91.8; 102.8

Source: Table 14.4.5.2 in the Study NP01-014 clinical study report

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = area under the concentration-time curve from time zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum concentration; R = (b) (4) T = Bayer Schering Pharma AG (Bayer)

Reviewer's Assessment:
The in vivo data demonstrate that the proposed product manufactured from both sites is bioequivalent (refer to Clinical Pharmacology review for a complete assessment of this data).

2. Dissolution Method

The Applicant's proposed dissolution method is:

Apparatus	Paddle (USP Apparatus 2)
Medium	Purified water, 500 mL
Bath temperature:	37°C ± 0.5°C
Agitation	100 rpm
Units per vessel	1
Sampling times	3.0 and 7.0 hours
Sinker:____	Present ____

According to the Applicant, disintegration testing is not applicable for NP01 as the shell is designed to prevent drug release for a number of hours. They state that dissolution behavior is the key parameter that characterizes NP01.

Selection of Apparatus and Paddle Speed

A summary of the dissolution results for various rotation speeds and apparatuses are provided in Table 4.

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(b) (4)

3. Acceptance Criteria

The proposed acceptance criteria are NMT (b) (4) release at 3 hours and Q = (b) (4) at 7 hours. The Applicant states that all dissolution profiles of the batches used in all of the clinical trials for the proposed NP01 product conform to the proposed specification.

The Applicant used data from PK study NP01-010 to justify setting their proposed acceptance criteria. In this study, the Applicant tested formulations with various lag times. The formulation with the slowest lag time had the first dissolution time point at which all individual tablets had NLT (b) (4) release at (b) (4) (refer to Table 8). The

Applicant claims that the extended *in vitro* lag times did not impact the maximum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞) observed *in vivo*.

Table 8. Summary of *in vitro* and PK results (Study NP01-010) for NP01 5-mg tablets with various lag times

(b) (4)

[redacted]

Table 9 presents the relative BA data for the formulations various formulations mentioned above. The three test formulations (T1, T2, and T3) were not bioequivalent to the reference formulation (R: Lot N945.22) when applying formal bioequivalence criteria (the 90% CI of the ratio test/reference fall within a range of 80%-125%). The Applicant states that the high rate of outliers in the reference group R caused a higher inter-subject variability and a slightly lower Cmax and AUC for this treatment group.

Table 9. Relative BA of Prednisone after Single Oral Administration of Four Different 5 mg NP01 Bathes with Different Dissolution Profiles under Fed Conditions (Study NP01-010)

Parameter	Estimate (90% CI)		
	T1 vs. R	T2 vs. R	T3 vs. R
C_{max} [ng/mL]	[redacted]		
$AUC_{0-\infty}$ [hr·ng/mL]			
AUC_{0-t} [hr·ng/mL]			

(b) (4)

Source: Table 14.4.5.a in the Study NP01-010 amended clinical study report

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = area under the concentration-time curve to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum concentration; [redacted]

(b) (4)

(b) (4)

Reviewer's Assessment:

Note that this PK study was done under fed conditions; therefore, the results are likely confounded by a food effect. In addition, although there is a rank order relationship between the in vitro and in vivo lag times, there is not a rank order correlation between lag time and the main PK parameters (Cmax and AUC). Furthermore, the formulations tested in this study were determined to be not bioequivalent. Thus, this PK data can not be used to set the dissolution specifications (e.g. lag time, Q) for the proposed product.

Dissolution results at release and after 24 months for lots used in Phase 3 studies EMR 62215–003 and NP01-007 are provided in Tables 10 and 11.

Table 10. Mean Dissolution Profiles at Release and after Storage at 25°C/60% RH for 24 Months For NP01 used in Phase 3 Study EMR 662215-003

Time (hr)	Lot G964				Lot J334			
	Release (n=12)		24 Months (n=6)		Release (n=12)		24 Months (n=6)	
	Mean (%Rel)	SD (%)	Mean (%Rel)	SD (%)	Mean (%Rel)	SD (%)	Mean (%Rel)	SD (%)
2.0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0
3.0	0	0	0	0	0	0	0	0
3.5	0	0	0	0	12	133	4	174
4.0	15	156	0	0	78	48	75	49
4.5	54	67	0	0	97	4	85	33
5.0	80	29	23	81	98	2	95	4
5.5	89	16	66	40	98	2	97	1
6.0	93	7	88	10	98	2	97	1
6.5	--[1]	--[1]	93	3	98	2	98	2
7.0	94	6	94	2	98	2	98	2
7.5	--[1]	--[1]	94	2	98	2	98	2
8.0	95	5	94	2	98	2	98	2
10.0	95	4	94	2	98	2	98	1
Time (hr)	Lot G 969				Lot J335			
	Release (n=12)		24 Months (n=6)		Release (n=12)		24 Months (n=6)	
	Mean (%Rel)	SD (%)	Mean (%Rel)	SD (%)	Mean (%Rel)	SD (%)	Mean (%Rel)	SD (%)
2.0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0
3.0	0	0	0	0	0	0	0	0
3.5	0	0	0	0	0	0	0	0
4.0	1	258	0	0	42	72	0	346
4.5	18	149	0	0	94	6	47	71
5.0	55	55	8	155	96	4	84	17
5.5	81	22	23	112	96	4	96	9
6.0	91	7	60	41	96	3	97	8
6.5	--[1]	--[1]	90	8	96	3	97	8
7.0	94	5	94	5	97	3	97	8
7.5	--[1]	--[1]	94	5	97	2	97	8
8.0	95	4	94	4	97	2	97	8
10.0	95	4	95	3	97	2	98	8

Source: Dissolution Profiles for Clinical Lots

%Rel = %release; RH = relative humidity; SD = standard deviation

[1] Dissolution points were not specified of the method at the time of testing.

Table 11. Mean Dissolution Results for Lot P574.12 in Phase 3 Study NP01-007

Time (hr)	% Release (%LC)			
	Release		Storage at 25°C/60% RH for 24 Months in 75-mL Bottle	
	Mean (n=6)	%RSD	Mean (n=12)	%RSD
2.5	0	0	0	0
3.0	0	0	0	0
3.5	0	0	0	0
4.0	5	164	1	346
4.5	44	54	15	136
5.0	89	11	51	61
5.5	94	4	83	19
6.0	96	3	91	11
6.5	96	3	93	9
7.0	96	2	93	9
7.5	97	2	94	8
8.0	97	2	95	8

Source: Dissolution Profiles for Clinical Lots

LC = label claim; RH = relative humidity; %RSD = relative standard deviation

The data in Tables 10 and 11 demonstrate that the mean *in vitro* lag time for batches used in Phase 3 studies ranged from (b) (4) (lot J334) to (b) (4) (lots G969 and P574.12). Of the NP01 tablet lots used in the Phase 3 trials, the lowest percent dissolved individual value observed at 7 hours after storage on stability at 25°C/60% RH was (b) (4)

For NP01 tablet lots stored in the US commercial stability configuration, the lowest individual value observed at 7 hours through 12 months of stability at 25°C/60% RH is (b) (4) (Lot BXA4GAK, 2 mg, 3 months, US commercial 100-count). This lot met stage 2 dissolution requirements.

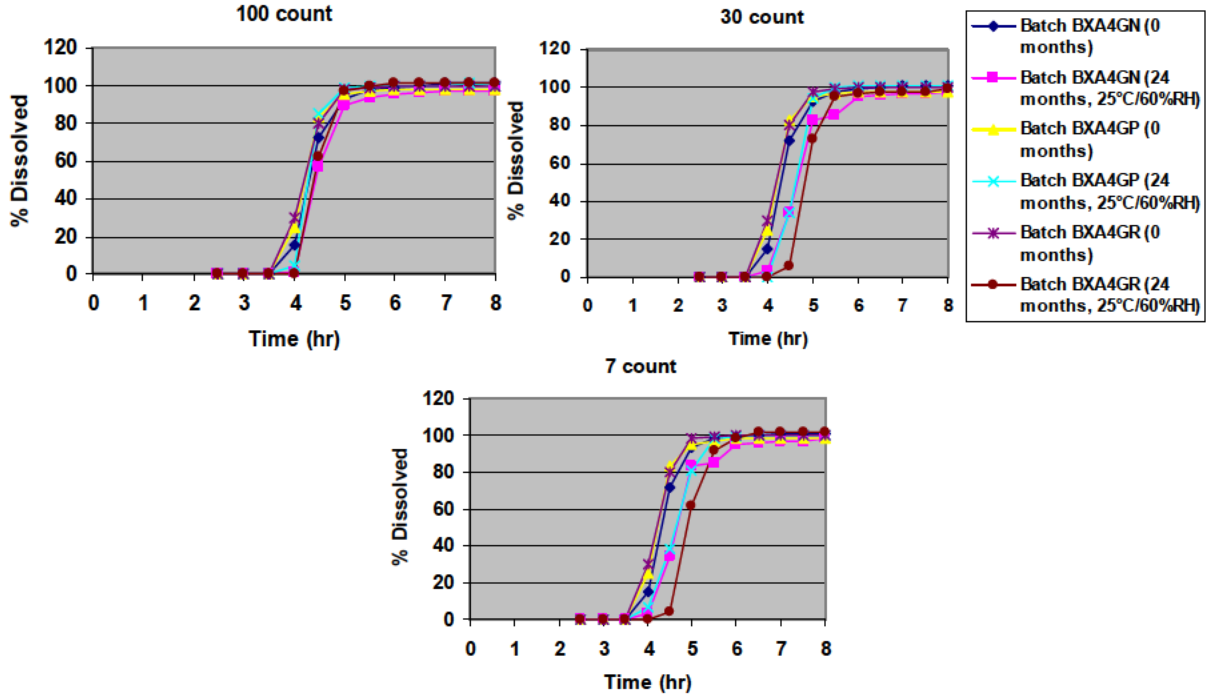
Reviewer's Assessment:

More data is needed to support the selection of the dissolution acceptance criteria. Therefore, the following Biopharmaceutics comment was included in the 74 day letter dated December 9, 2011.

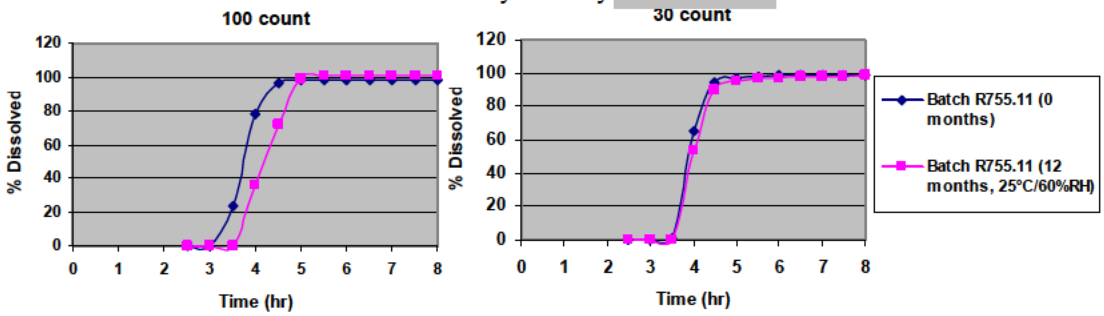
> **FDA Request**
> Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.

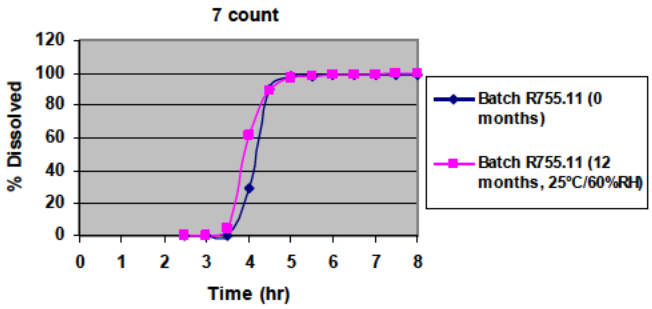
The Applicant provided the requested data which is summarized in Reviewer's Figures 2 and 3.

Reviewer's Figure 2 a, b, c. Summary of 5 mg NP01 Tablet Mean Dissolution Data for Primary Stability (Bayer)



Reviewer's Figure 3 a, b, c. Summary of 5 mg NP01 Tablet Mean Dissolution Data for Primary Stability (b) (4)





The data above show that the Q= (b) (4) at 7 hours aspect of the dissolution acceptance criteria could be tightened to Q= (b) (4) at 7 hours. To ensure consistent lag time and overall performance of the drug product, a lag time acceptance criterion should be added. Dissolution profile data from the clinical stability batches support lag times ranging from (b) (4) (refer to January 20, 2012 submission). The following Biopharmaceutics comment was sent to the Applicant in IR letter dated April 27, 2012.

FDA Comment

The following dissolution acceptance criteria are recommended for your product: **NMT (b) (4) at 3 hours, Lag Time (b) (4) hours for any individual tablet, and Q = (b) (4) at 7 hours**. This recommendation is based on the mean in-vitro dissolution profiles for all strengths of your proposed product from pivotal clinical batches and primary stability batches at release and under long term (12 months) stability studies. Revise the dissolution acceptance criteria accordingly and submit an updated sheet of specifications for the drug product.

Applicant's Response (excerpt)

Horizon agrees with the Agency's limits of not more than (b) (4) at 3 hours, and Q = (b) (4) at 7 hours for individual tablets. Horizon also agrees with the Agency's proposal for the addition of a lag time acceptance criterion; however, in evaluating updated individual tablet stability data sets that were recently provided to the Agency as Sequence 0011, Horizon proposes an intermediate lag time of (b) (4) hours. Individual tablet stability results for RAYOS support a lag time of (b) (4) hours, using a paddle speed of 100 rpm, based on trends over time and varying temperature. For example, 2-mg Bayer stability lot BXA4GAK, stored at long-term conditions (25°C/60% RH) in the 7-count bottle showed a lag time (e.g. (b) (4) dissolved) of (b) (4) hours at the 9 and 18 month time points. The tablets with these lag times reached the Q = (b) (4) after 7 hours. Therefore, Horizon is proposing a lag time acceptance criterion of (b) (4) hours for individual tablets.

Proposed Revised Dissolution Acceptance Criteria for Rayos 1 mg, 2mg, 5 mg

Sample Point	Stage 1	Stage 2	Stage 3
3 hours	(b) (4)		
5.5 hours			
7 hours			

The Applicant accepted NMT (b) (4) at 3 hours and Q = (b) (4) at 7 hours but proposed Lag Time (b) (4) hours for any individual tablet. The ONDQA Biopharmaceutics team found the Applicant's proposal and justification acceptable. In an IR letter sent to the Applicant on June 14, 2012, the ONDQA Biopharmaceutics Team recommended the following lag time acceptance criteria: Mean Lag Time (b) (4) hours. No individual tablet Lag

Time should exceed (b) (4) hours. In an email dated June 15, 2012, the Applicant accepted the Agency's recommendation.

Note that the lag time criterion of (b) (4) would not reject batches manufactured with (b) (4) that can also produce lag times of (b) (4) However, the (b) (4) is adjusted to meet the requirements for in-process controls such as weight, hardness, and thickness. Therefore, there is low risk that the (b) (4) will be outside the target range.

4. Data to Support Approval of 1 mg and 2 mg Strength Tablets

(b) (4)

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(b) (4)

5. Information supporting BE of European RLD to the US RLD

The Applicant evaluated the BE of the proposed product to Decortin®, a EU reference listed drug (RLD), instead of the US RLD. Note that NP01 differs from the reference IR prednisone preparations, Decortin® and PredniSONE Tablets by its pharmaceutical form (MR vs. IR). Since the Applicant has to bridge their proposed product to a US approved product, they requested a biowaiver and provided data to support the bioequivalency of the EU RLD and US RLD.

The Applicant compared the *in vitro* dissolution profiles of Decortin® and US-marketed prednisone IR drug products (Table 15) under the following conditions in Table 16:

Table 15. Prednisone IR Drug Products Examined

Brand Name*	Pharmaceutical Manufacturer	Country	Lot number	Expiry date
Prednisone	Watson Labs	US	P03A0042	Feb. 2005
Prednisone	Mutual Pharm	US	49474	March 2006
Prednisone	Roxane	US	257751A	Oct. 2004
Decortin	Merck KGaA	Germany	29996 01	June 2006

* Trademarks are not mentioned in this document

Adapted from *Comparison of In Vitro Dissolution Behavior of US-Immediate Release Solid Oral Dosage Forms Containing 5 mg Prednisone* (May 16, 2006)

Table 16. Description of Dissolution Conditions Used to Test the Prednisone IR Drug Products

Parameter of the method	Method 1
Apparatus	paddle
Dissolution medium	1. SGFsp pH 1.2 2. 0.1 M phosphate buffer solution pH 4.5 3. SIFsp pH 6.8
Volume	900 mL
Degassing	yes
Agitation	50 rpm
Temperature	37°C
Number of samples	12
Sampling time	5, 10, 15, 30, and 60 min

Adapted from *Comparison of In Vitro Dissolution Behavior of US-Immediate Release Solid Oral Dosage Forms Containing 5 mg Prednisone* (May 16, 2006)

The dissolution profile comparisons are shown in Figure 18.

Figure 18 a, b, c. *in vitro* Dissolution Behavior of the Different IR Prednisone Products in Various Media

(b) (4)

Reviewer's Assessment:

The following information is needed to support the use of the EU product as the reference in the biowaiver request:

1. ***The EU and US RLD IR products should have the same dosage form;***
2. ***The EU and US RLD IR products should be proportionally similar in their active and inactive ingredients; and***
3. ***The EU and US RLD IR products should have similar dissolution profiles in three media (pH 1.2, 4.5, and 6.8).***

The EU and the US-approved drugs are IR tablets; therefore, they have the same dosage form. The dissolution profiles of the EU and the US-approved drug products are similar in the three media tested (greater than (b) (4) of prednisone is dissolved in 15 minutes for the drug products in the media tested). Since only two out of three requirements are met; therefore a biowaiver may not be granted.

However, at a meeting held with the Applicant on December 13, 2007, the FDA agreed that the information provided above was sufficient to waive the need for a bioequivalence study comparing the US and EU reference prednisone products. It is unknown if the European RLD and the US RLD for prednisone have the same formulation composition. Despite the fact that the IR prednisone formulation meets the criteria for a BCS Class 1 drug, the Biopharmaceutics team asserts that, from a regulatory perspective, the waiver should not have been granted due to lack of information supporting that the two references meet the requirement of "similar composition". Since in the present submission the applicant included the results from a clinical efficacy and safety trial conducted with the proposed product for exclusivity purposes, this data may be used internally to support the approvability of the proposed product.

6. *In vitro* Assessment of Alcohol Effect on NP01 Drug Release

The original submission did not include *in-vitro* alcohol testing of the drug product. Therefore, the following Biopharmaceutics comment was in the 74 day letter dated December 9, 2011.

FDA Request

We are concerned that your delayed release (DR) product may release its entire contents ("dose dumping") in the stomach when co-administered with alcohol defeating the purpose of the formulation. Therefore, we recommend that you evaluate the potential for a drug-alcohol interaction with your DR product in *in vitro* settings.

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
- The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
- The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA within six weeks of the expedition date of this letter.

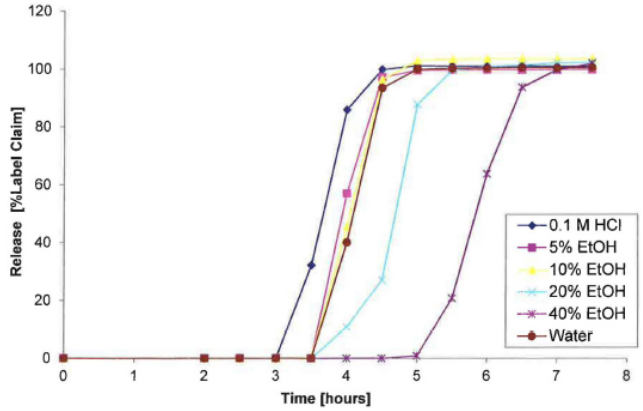
Applicant's Response (excerpt)

The *in vitro* release profiles of NPOI tablets were assessed in the presence of various amounts of ethanol. The objective of this *in vitro* study was to determine if the presence of alcohol impacts the delayed-release character of the drug product. The dissolution profiles of 12 tablets of one lot of NP01 5-mg tablets were collected with a paddle apparatus at 100 rpm in the following six media:

- 0.1 N HCl;
- 5% ethanol in 0.1 N HCl;

- 10% ethanol in 0.1 N HCl;
- 20% ethanol in 0.1 N HCl;
- 40% ethanol in 0.1 N HCl;
- Water

Mean Dissolution Profiles for NP01 5 mg Tablet in Various Concentrations of Ethanol



The results of the study show that the presence of alcohol does not result in dose dumping of the product. The f2 similarity factors were calculated and are provided. The product is designed for delayed release and not controlled release over time and therefore, the *in vitro* product release profile is not compatible with this calculation.

The Applicant determined that f2 similarity factor calculation was not suitable to evaluate similarity of drug release profiles without time corrections. Therefore, they corrected the individual drug release profiles for lag time and evaluated the immediate release parts of the release profiles for similarity by f2 calculation with reference to 0.1 M HCl (refer to Figure 19 and Table 17).

Figure 19. Lag Time Corrected Drug Release Profiles for NP01 5 mg Tablet in Various Concentrations of Ethanol

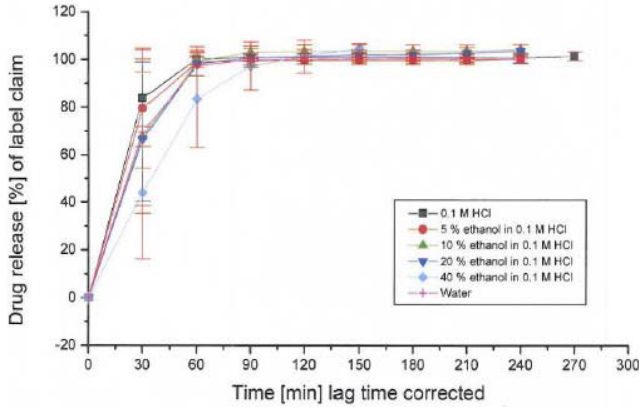


Table 17. f2 Similarity Factors for Drug Release in Different Media vs. 0.1 M HCl (reference)

Medium	f2 without lag time correction	[2]f2 with lag time correction
5 % ethanol	25.7	74.2
10 % ethanol	21.9	47.2
20 % ethanol	11.9	45.6
40 % ethanol	9.4	25.8
water	20.1	49.4

Reviewer's Assessment:
The dissolution profiles are not similar even after correcting for lag time. Increasing the alcohol concentration (10-40%) leads to prolonged lag time. Therefore, there is no in vitro alcohol dose dumping. Rather, the presence of alcohol leads to further delay in the onset of drug release.

7. Evaluation of IVIVR

The Applicant attempted to establish a relationship between drug release *in vivo* and the dissolution profile collected *in vitro*. (b) (4) Dissolution testing was conducted on these tablets with the current *in vitro* dissolution method. The PK of these tablets in study NP01-010 was also characterized. The dissolution and PK data for the batches used in this study are presented in Figures 13 and 14 and Tables 8 and 9 above. The Applicant found (b) (4)

Reviewer's Assessment:
PK study NP01-010 was performed under fed conditions; therefore, the results of this study are confounded by a food effect.. As previously mentioned, although there is a rank order relationship between the in vitro and in vivo lag times, there is not a rank order correlation between the lag time and the main PK parameters (Cmax and AUC). In addition, the data from Table 9 demonstrate that the formulations tested in this study were not bioequivalent. Thus, there is not an in vitro/ in vivo relationship between the in vitro and in vivo lag times.

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/s/

KAREEN RIVIERE
06/20/2012

SANDRA SUAREZ
06/20/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-020	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	September 26, 2011		
Division:	DPARP	**Biopharmaceutics Lead:** Angelica Dorantes, Ph.D.	
Sponsor:	Horizon Pharma, Inc.	**Secondary Signature:** Sandra Suarez-Sharp, Ph.D.	
Trade Name:	Rayos MR	**Date Assigned:**	November 11, 2011
Generic Name:	NP01 (prednisone, modified release)	**Date of Review:**	November 30, 2011
Indication:	Treatment of rheumatoid arthritis in adult patients	**Type of Submission:** 505(b)(2) New Drug Application	
Formulation/strengths:	Tablets/ 1 mg, 2 mg, 5 mg		
Route of Administration:	Oral		

SUBMISSION:

This is a 505(b)(2) New Drug Application for delayed release tablets containing 1 mg, 2 mg, and 5 mg of prednisone. The indication is for the treatment of rheumatoid arthritis in adult patients. The applicant is relying on PredniSONE Tablets (NDA 017109) by Roxane Laboratories, Inc. and Decortin® (a European IR prednisione drug product) as the reference drugs.

BIOPHARMACEUTIC INFORMATION:

Rayos MR (NP01) is a modified (delayed)-release tablet of prednisone, a synthetic, (b) (4) glucocorticoid, disease-modifying anti-rheumatic drug. The NP01 tablet consists of an immediate release prednisone core tablet, surrounded by an inactive tablet shell ((b) (4) (b) (4)

This submission includes a drug product development section, a dissolution development report with a proposed dissolution specification and acceptance criteria, BA/BE data comparing NP01 with Decortin® (the European listed drug), *in vitro* dissolution data supporting the bioequivalence of the EU RLD and the US RLD, as well as PK and dissolution data supporting the development of the IVIVR for lag time.

Note that the pivotal BE study included in the present submission compared the proposed product Rayos MR to the European reference listed drug for prednisone. During a meeting held with the sponsor on December 13, 2007, the FDA agreed that the information provided was sufficient to waive the need for a bioequivalence study comparing the US and EU reference prednisone products. It is unknown if the European RLD and the US RLD for prednisone have the same formulation composition. Despite the fact that the IR prednisone formulation meets the criteria for a BCS Class 1 drug, the Biopharmaceutics team asserts that, from a regulatory perspective, the waiver should not have been granted due to lack of information supporting that the two references meet the requirement of "similar composition". Since in the present submission the applicant included the results from a clinical efficacy and safety trial conducted with the proposed product for exclusivity purposes, this data may be used internally to support the approvability of the proposed product.

The proposed dissolution method:

Apparatus	Paddle (USP Apparatus 2)
Medium	Purified water, 500 mL
Bath temperature:	37°C ± 0.5°C
Agitation	100 rpm
Units per vessel	1
Sampling times	3.0 and 7.0 hours
Sinker:	Present

The proposed acceptance criteria: (NMT) (b) (4) release at 3 hours and Q = (b) (4) at 7 hours.

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion, acceptability of the waiver request for the 1 mg and 2 mg strength based on dissolution profile comparisons, acceptability of the *in vitro* dissolution data supporting the bioequivalence of the EU RLD and the US RLD, acceptability of the in vitro alcohol dose-dumping information being requested, as well as the acceptability of the *in vitro in vivo* relationship (IVIVR).

To aid in the review of the Applicant's submission, the following will be requested:

1. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.

2. To support a biowaiver for the 1 mg and 2 mg strengths, provide *in vitro* comparative dissolution data and f2 similarity values (n=12) in three media: 0.1 N HCl and phosphate buffers pH 4.5 and 6.8, using the same dissolution testing conditions and the 5 mg strength as the reference.

3. We are concerned that your delayed release (DR) product may release its entire contents ("dose dumping") in the stomach when co-administered with alcohol defeating the purpose of the formulation. Therefore, we recommend that you evaluate the potential for a drug-alcohol interaction with your DR product in *in vitro* settings.
   - Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
   - The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
   - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
   - The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
   - The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA within six weeks of the expedition date of this letter.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 202-020 for filing purposes. We found this NDA **filable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission. The above comments should be conveyed to the sponsor as part of the 74-day letter.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Ph.D.

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

/s/

KAREEN RIVIERE
11/30/2011

SANDRA SUAREZ
12/01/2011

Clinical Pharmacology and Biopharmaceutics filing form/checklist for NDA20-2020

Office of Clinical Pharmacology ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	202020	**Brand Name**	NP01 (Proposed)
OCP Division (I, II, III, IV, V)	II	**Generic Name**	Prednisone, modified release
Medical Division	DPARP	**Drug Class**	
OCP Reviewer	Ping Ji	**Indication(s)**	Relieve signs and symptoms of adult RA
OCP Team Leader	Suresh Doddapaneni	**Dosage Form**	Modified release formulation
Pharmacometrics Reviewer	NA	**Dosing Regimen**	NP01 5 mg administered once per day (b) (4)
Date of Submission	Sep 26, 2011	**Route of Administration**	Oral
Estimated Due Date of OCP Review	Mar 19, 2011	**Sponsor**	Horizon Pharma Inc
Medical Division Due Date	Mar 19, 2011	**Priority Classification**	S
PDUFA Due Date	July 26, 2012		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE	**x**			
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**	**2**		
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:	**x**	**1**		
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:	**x**	**1**		
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 -	**x**	**7**		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**x**	**1**		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**x**	**1**		
Total Number of Studies		**14**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data			x	

	comparing to-be-marketed product(s) and those used in the pivotal clinical trials?				
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _y_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Ping Ji, PhD
Reviewing Clinical Pharmacologist Date:

Suresh Doddapaneni, PhD
Team Lead Date:

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

/s/

Ping Ji
11/18/2011

SURESH DODDAPANENI
11/18/2011