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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name Rosemarie Neuner, MD, MPH
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Established Name Prednisone delayed release
Trade Name Rayos[®]
Therapeutic Class Corticosteroid
Applicant Horizon Pharma, Inc.

Formulation 1 mg and 5 mg Tablets
Dosing Regimen 5 mg once daily. Dose should be tapered to
the lowest effective dose after satisfactory
response has been achieved.

Indication
1) allergic conditions
2) dermatologic diseases
3) endocrine conditions
4) gastrointestinal diseases
5) hematologic diseases
6) neoplastic conditions
7) nervous system conditions
8) ophthalmic conditions
9) conditions related to organ transplantation
10) pulmonary diseases
11) renal conditions
12) rheumatologic conditions
13) specific infectious diseases

Intended Population Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval for this 505(b)(2) drug application for prednisone delayed-release tablet (NP01). The data contained in this application is sufficient to support a finding of efficacy and safety for NP01 when administered orally at doses titrated to clinical response for the following indications:

- allergic conditions: atopic dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness
- dermatologic diseases: bullous dermatitis herpetiformis, contact dermatitis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome)
- endocrine conditions: congenital adrenal hyperplasia, hypercalcemia of malignancy, nonsuppurative thyroiditis, primary or secondary adrenocortical insufficiency
- gastrointestinal conditions: Crohn's disease, ulcerative colitis
- hematologic diseases: acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, secondary thrombocytopenia in adults
- neoplastic conditions: acute leukemia, aggressive lymphoma
- nervous system conditions: acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury
- ophthalmic conditions: sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical steroids
- conditions related to organ transplantation: acute or chronic solid organ rejection
- pulmonary diseases: COPD, allergic bronchopulmonary aspergillosis, aspiration pneumonia, asthma, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy, hypersensitivity pneumonitis, idiopathic bronchiolitis obliterans with organizing pneumonia, idiopathic

eosinophilic pneumonias, idiopathic pulmonary fibrosis, pneumocystis carinii pneumonia (PCP) associated with hypoxemia, occurring in an HIV+ individual who is also under treatment with appropriate anti-PCP antibiotics, symptomatic sarcoidosis

- renal conditions: to induce diuresis or remission of proteinuria in nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
- rheumatologic conditions: acute gouty arthritis, ankylosing spondylitis, dermatomyositis/polymyositis, polymyalgia rheumatica, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis including juvenile rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, vasculitis
- specific infectious conditions: trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy

These indications are consistent with the indications approved for the reference immediate-release prednisone tablet (PredniSONE) and a related, immediate-release prednisolone product (Flo-Pred).

1.2 Risk Benefit Assessment

The risk benefit assessment for NP01 is based on the established efficacy and safety profile for prednisone, which is described in the current package insert for the reference immediate-release prednisone tablet (PredniSONE). The CMC and clinical pharmacology data included in the application link NP01 to immediate-release prednisone and provide the basis for the 505(b)(2) reference and the regulatory decision.

In addition to the key CMC and clinical pharmacology data, the application included secondary support from clinical trials. As noted in the preceding section, the reference drug is approved for a range of indications, including the treatment of rheumatoid arthritis. The efficacy of NP01 for the treatment of rheumatoid arthritis in adults was confirmed by a clinical trial, Study NP01-007, that evaluated the efficacy and safety of low dose (range 1-10 mg) NP01 administered once daily at nighttime in 294 patients with RA on concomitant DMARD therapy. A higher proportion of NP01 treated patients achieved the regulatory approved endpoint, the ACR20 response, as compared to placebo. This result was expected given the established efficacy of prednisone for the treatment of RA.

The results from the key secondary endpoint analysis of the patient reported outcome (PRO) duration of morning stiffness were also in favor of patients treated with NP01 as compared to placebo. However, the validity of these findings is uncertain since this endpoint was found to lack definitions for the resolution and recurrence of morning stiffness necessary to answer the question consistently. The regulatory acceptability of the morning stiffness endpoint is also hampered by the lack of data to support the following: documentation of its reliability and construct validity, the translation and/or cultural adaption of this endpoint, and a scientific justification for a responder definition. As a result of these deficiencies, the clinical meaningfulness of the approximate 20 minute difference over baseline in the duration of morning stiffness observed on comparison of the two treatment groups at Week 12 (Visit 4) is questionable. This application also did not contain the results from a second adequate and well-controlled study necessary for the approval of marketing claims such as morning stiffness as discussed at the EOP2 meeting held in December 2007. Data contained in this application generated from the actively-controlled, Phase 3 study EMR 62215-003, cannot be used in support of NP01's efficacy since the Applicant was unable to provide the financial disclosure information for investigators who participated in this trial as required by 21 CFR §54. There are also sufficient doubts regarding the validity of the results from EMR 62216-003 due to the high rate of major protocol violations (47%) that were incurred during its conduct.

The overall safety profile of NP01 was shown to be consistent with the historical clinical experience with low dose corticosteroid therapy. However, the lack of adequately powered studies to determine safety risk, the possible introduction of reporting and investigator bias, and an imbalance in the database submitted in support of its safety that resulted in more patients being treated with ≤ 5 mg/day of NP01 than with > 5 mg/day make this safety information less reliable and unsuitable for inclusion in the label.

The risk benefit assessment is in favor of approving NP01 for the general indications already approved for the reference immediate-release prednisone product with similar labeling. There are issues and questions raised regarding the validity of the results from the morning stiffness outcome and the adequacy of the characterization of the drug's safety profile, however, the clinical data are not needed to support the application given the adequate CMC and clinical pharmacology data. The clinical trial data, while generally supportive of efficacy and safety, do not warrant inclusion in the label.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategies (REMS) is not necessary for NP01 in view of the extensive experience associated with the use of prednisone, its well documented safety profile, and the lack of new safety signals identified during the course of this

review of data generated from clinical and pharmacokinetic studies and postmarketing adverse events associated with this new formulation.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant should not be required to conduct pediatric studies to fulfill the requirement of the Pediatric Research Equity Act (PREA) since the efficacy and safety of prednisone in children are well documented.

2 Introduction and Regulatory Background

2.1 Product Information

NP01 (proposed tradename: Rayos[®]) is a new delay-release formulation of prednisone comprised of a core tablet of drug within an inactive shell developed as a treatment for adults with rheumatoid arthritis. It is designed to release prednisone during the middle of the night following bedtime dosing to shift the concentration time curve of immediate release prednisone by about 4 hours. The rationale for its novel design is based on chronotherapy for morning stiffness in rheumatoid arthritis (RA) patients. It has been postulated that autoimmune disease symptoms exhibit circadian rhythms as a result of elevated levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNF- α) resulting in worse joint pains and stiffness in the morning. Horizon Pharmaceuticals purports that the delayed release of prednisone optimizes drug effect during early morning disease exacerbations, resulting in a decrease in symptoms such as morning stiffness without compromising compliance. They are seeking marketing approval for the 1 mg and 5 mg strength tablets for the treatment of rheumatoid arthritis (RA) in adults with a proposed initial dosing regimen of 5 mg taken once a day taken at bedtime adjusted to the lowest effective dose after a satisfactory response has been achieved.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists currently available treatments for RA in the United States (U.S.), including immediate-release prednisone:

Table 1 – Currently Approved Drugs and Therapeutic Biologics for the Treatment of RA in the U.S.

Drug/Product	NDA/BLA	Sponsor	Year of Approval
Sulfasalazine	7-073	Pfizer	1950
Methotrexate sodium	8-085 (PO) 11719 (IV)	Multiple Sponsors	1953
Hydroxychloroquine	9-768	Sanofi-Aventis	1955
Prednisone	Many ANDAs	Multiple Sponsors	1955
Azathioprine	16-324	Prometheus Labs	1968
Penicillamine	19-853	Aton	1970
Auranofin	18-689	Prometheus Labs	1985
Cyclosporin	50-715 50-625	Novartis	1995 1990
Leflunomide	20-905	Sanofi-Aventis	1998
Infliximab	103772	Centocor	1999
Etanercept	103795	Immunex	1998
Anakinra	103950	Amgen	2001
Adalimumab	125057	Abbot	2002
Abatacept	125118	Bristol Myers Squibb	2005
Rituximab	103705	Genentech and Biogen Idec	2006
Certolizumab pegol	125160	UCB Inc	2008
Golimumab	125289	Centocor	2008
Tocilizumab	125276	Genentech	2010

In addition to the above listing, there are a number of nonsteroidal anti-inflammatory drugs (NSAIDs) that are approved for the reduction of the signs and symptoms of RA marketed in this country. Leflunomide and etanercept are also approved for the patient reported outcome of improvement in morning stiffness associated with RA.

2.3 Availability of Proposed Active Ingredient in the United States

Corticosteroids, such as prednisone and methylprednisolone, have been used in the U.S. since the mid-1950's to treat RA. Immediate release prednisone was first marketed in this country as Meticorten in the mid-1960's by Schering Plough Corp. It is currently widely available as a generic drug produced by a number of manufacturers such as Watson Laboratories, Roxane Laboratories, and West Ward Pharmaceuticals as a treatment for autoimmune diseases and other inflammatory conditions.

2.4 Important Safety Issues With Consideration to Related Drugs

A number of safety concerns have been associated with the use of prednisone. These are listed under the Warnings and Precautions section of the drug's label and include: hypothalamic-pituitary-adrenal suppression, Cushing's syndrome, hyperglycemia, increase risk for the exacerbation, dissemination or reactivation of latent infections,

hypertension, salt and water retention, hypokalemia, gastrointestinal perforations, behavioral and mood disturbances (e.g., euphoria, insomnia, mood swings, personality changes, severe depression and psychosis), osteoporosis, cataracts, and glaucoma.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following are highlights of the regulatory activity that occurred during the development program for NP01.

A teleconference was held on Marcy 24, 2006, to discuss PIND 72,569 with Nitec Pharma, Inc. who was originally developing NP01 for marketing. Areas of discussion included:

- Possibility of 505(b)(2) application discussed
 - Discussed possible PK-PD modeling program using dissolution data to link European Union (EU) reference licensed drug (RLD) (Decortin) to U.S. RLD (Watson Labs' prednisone 5 mg immediate release tablet)
- (b) (4)
- Applicant advised to conduct a new study using regulatory standard EP (ACR20) and evaluate morning stiffness as a secondary outcome
 - Study also needed to provide exposure data in U.S. population
- Applicant also told that they needed to provide in the IND safety qualifications for exposure level to (b) (4) in NP01

IND 72,569 was opened on July 3, 2007 with a submission by Nitec Pharma for Study NP01-006.

An End-of-Phase 2 meeting was held on December 13, 2007. The key clinical and regulatory issues that were discussed at that time are itemized below.

- Design of U.S. placebo-controlled Phase 3 study (NP01-007), statistical analysis (use of last observation carried forward for imputation of missing data) and the use of unvalidated biomarkers (IL-6, TNF- α , and osteocalcin) were discussed
- Applicant told that a labeling claim could be considered if both studies (EMR 62215-003 and NP01-007) supported efficacy for improvement in morning stiffness
- Agency agreed that the projected sized from the pooled population from studies EMR 62215-003 and NP01-007 would be adequate to support NP01's safety profile
- Agency agreed that the clinical safety information for Lodotra (EU marketed NP01) and oral prednisone were adequate to waive the 90-day bridging toxicology study

- Agency told Applicant that the safety qualification of [REDACTED] (b) (4) was acceptable
- Variety of CMC issues were also discussed including the need to provide the necessary data to support dissolution lag time, batch release and drug stability as well as a possible waiver of environmental assessment for NP01

A pre-NDA meeting was held on January 26, 2010. The following items summarize the understandings reached between the Applicant and the Division at that time.

- Morning stiffness claim issue was revisited
 - Applicant told that if reviewed efficacy data supported claim of “reduction of morning stiffness” the findings would be limited to RA and described in the clinical studies section and not in the indication section of the label
- Applicant was advised to review PRO guidance document and submit documentation of validation and justification of the instrument used to measure morning stiffness in NDA
- Applicant was also told to review Agency advice contained in August 25, 2010 statistical analysis plan (SAP) letter to sponsor regarding how to conduct primary analysis of Study NP01-007 using the treatment patients actually received instead of the treatment patients were randomized to and use baseline observation carried forward (BOCF) for patients who discontinued to treatment. Other imputation strategies could be pursued as a sensitivity analysis.
- Appropriateness of the Applicant’s pediatric drug development plan was discussed [REDACTED] (b) (4)
- Agency agreed that the projected exposure data was adequate to support the application
- The following CMC issues were also discussed: information necessary for support of the drug’s manufacturing site and the need for batch testing data, stability data, drug release data and data for impurities/degradants
- Applicant confirmed that their intended RLD is the Roxane immediate-release prednisone product and they would designate the ANDAs they intend to reference
- Applicant acknowledged that they would submit their label in PLR format

2.6 Other Relevant Background Information

According to information supplied by the Applicant, early development of NP01 was conducted by Merck KGaA in Europe. Development of the drug was subsequently transferred to Nitec Pharma AG in 2004. The latter company became Horizon Pharma, Inc. in April 2010. A Marketing Authorization Application (MAA) for NP01 was recommended for approval through the Decentralized Procedure (DCP) in the EU. Via this process, the drug was first approved in Germany in March 2009 followed by 11

other EU countries (Austria, Belgium, Denmark, Finland, Italy, Luxemburg, Netherlands, Norway, Sweden, Poland, and the United Kingdom) as well as Israel and Switzerland. At the time the original application was filed, marketing was pending approval in France and Spain. In the EU, NP01 is sold under the trade name Lodotra[®] and is indicated for the treatment of RA in adults, especially when accompanied with morning stiffness.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Horizon Pharma's submission was appropriately organized to allow information to be reviewed in an acceptable manner.

3.2 Compliance with Good Clinical Practices

According to a statement included in the reports for studies NP01-007 and EMR62215-003, the Applicant certified that these trials were conducted in compliance with the following: Good Clinical Practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

As this was a 505(b)(2) application, no inspections of clinical sites that had participated in the pivotal Phase 3 study NP01-007 were deemed necessary.

3.3 Financial Disclosures

This application contains financial disclosure information for the placebo-controlled study, NP01-007. According to the Applicant, financial disclosure information for Study EMR 66215-003 was not provided for the following reasons:

- Study EMR 66215-003 is not a covered clinical study as defined in the March 2001 FDA Guidance for Industry –Financial Disclosure by Clinical Investigators since only safety data generated from this trial was included in support of the safety profile of NP01.
- The highest enrollment at a participating site for EMR 66215-003 was approximately 5% of the total safety database. Therefore, no single investigator made a significant contribution to the demonstration of the drug's safety.
- Efforts by the Applicant to obtain financial disclosure information for this study were reportedly unsuccessful since it was conducted from 2004 to 2006 by another sponsor, Merck KgaA (Darmstadt, Germany).

The financial disclosure form signed by the Applicant certified that only the principal investigator for Study NP01-007, (b) (6) had a financial arrangement where outcomes affected compensation as defined in 21 CFR 54.2(a) (b) (6) had a consulting agreement with Nitec Pharma GmbH prior to the latter's merger with Horizon Therapeutics, Inc. to form Horizon Pharma, Inc., for which he received between 7,500 to 15,000 € in compensation from the Applicant. Since (b) (6) site enrolled (b) (4) patient into Study NP01-007 which evaluated a total of 350 patients with RA, it's unlikely that this financial arrangement impacted on the study's results.

Additionally, none of the clinical investigators or subinvestigators for NP01-007 reportedly had a proprietary interest as described in 21 CFR 54.2(b) in NP01 or a significant equity in Horizon Pharmaceuticals, who is commercially developing this drug for marketing in the United States.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Xiaobin Shen is the Chemistry, Manufacturing and Controls (CMC) reviewer of this application. At the time this review was written, the CMC review was pending the completion of the EES for one of the two drug product packaging and labeling sites in Germany. Dr. Shen will be recommending approval of this application based on an acceptable resolution of this outstanding item.

4.2 Clinical Microbiology

Since NP01 is not a therapeutic antimicrobial, clinical microbiology data were not required or submitted in support of this application.

4.3 Preclinical Pharmacology/Toxicology

The clinical pharmacology/toxicology data included in this application was reviewed by Dr. Asoke Mukherjee, who recommends approval of this application based on the following:

- Non-clinical information referenced by the Applicant from the RLD prednisone (PredniSONE Tablets) (NDA 17109) sponsored by Roxane Laboratories

- NP01 should be classified as Pregnancy Category D to be consistent with the June 2007 recommendations made by Pediatric and Maternal Health Staff for prednisolone labeling

4.4 Clinical Pharmacology

Dr. Ping Ji reviewed the clinical pharmacology data contained in this application. Dr. Ji recommends approval of this application with the following caveats that should be described in the label:

- NP01 has a substantial food effect as demonstrated by a 60% decrease in its bioavailability in fasting subjects
- Its bioavailability under fed conditions is similar to that of immediate release prednisolone tablets
- With exception of a 4-hour delay in NP01's T_{max} , its PK profile is superimposable with that of immediate release prednisolone tablet
- In view of these findings, NP01 needs to be taken with food

4.4.1 Mechanism of Action

Prednisone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. In addition to metabolic effects, glucocorticoids exert both anti-inflammatory and immunodulatory effects via a variety of mechanisms¹:

- the classic genomic mechanism which involves activation of the cytosolic glucocorticoid receptor (cGCR) that results in alterations in the synthesis of regulatory proteins
- the cGCR-mediated nongenomic mechanism which produces a release of proteins from intracellular protein complexes including glucocorticoid-specific receptors
- the membrane-bound glucocorticoid (mGCR) nongenomic mechanism that is responsible for inducing apoptosis
- the nonspecific, nongenomic mechanism that produces alterations in the biological properties of membranes.

Clinically, these multiple mechanisms of action result in the inhibition of leukocyte trafficking to inflamed tissues, interference in inflammatory cell function, and the suppression of both the production and activity of humoral factors involved in the inflammatory process².

Reference:

^{1,2}Buttgereit F and Burmester G-R: Chapt. 42 – Glucocorticoids; Primer on the Rheumatic Diseases. 13th Ed. 2008; p. 644-650.

4.4.2 Pharmacodynamics

The Applicant referenced the current product labeling for the RLD prednisone (PredniSONE Tablets) (NDA 17109) sponsored by Roxane Laboratories for background information on the pharmacodynamics of corticosteroids.

4.4.3 Pharmacokinetics

NP01 is comprised of an immediate release core tablet surrounded by an inactive tablet shell. As a result of its unique design, (b) (4). The Applicant conducted a number of pharmacokinetic studies in healthy adult volunteers that assessed food effect (NP01-006) and relative bioavailability (EMR 62215-005) in support of the biopharmaceutics of NP01 (refer to Table 3). Study NP01-006, which was an open-label, single oral dose, 2-way crossover food effect study, demonstrated that NP01 has a substantial food effect that resulted in approximately a 60% decrease in its AUC and C_{max} under fasting conditions. Table 2 and Figure 1 below summarize the pharmacokinetic profiles of prednisone IR and NP01 under fed and fasted conditions from data generated by the second study (EMR 62215-005) which was an open label, single oral dose, 3-way cross over, relative bioavailability study:

Table 2 – Pharmacokinetic Summary of NP01 and IR Prednisone

	Prednisone IR fasted	NP01 semi-fasted	NP01 fed
C_{max} (ng/ml)	21.1 (17%)	21.4 (26%)	22.2 (16%)
AUC_{0-t} (ng h/ml)	108 (15%)	114 (27%)	124 (20%)
T_{max} (h)	2 (1.0-4.0)	6.0 (4.5-10)	6.5 (4.5-9)

IR: prednisone immediate-release

C_{max} and AUC are presented as mean (SD); T_{max} is presented as median (min-max)

Table Courtesy of Dr. Ping Ji

Figure 1 – Mean Plasma Profiles for Prednisone IR versus NP01

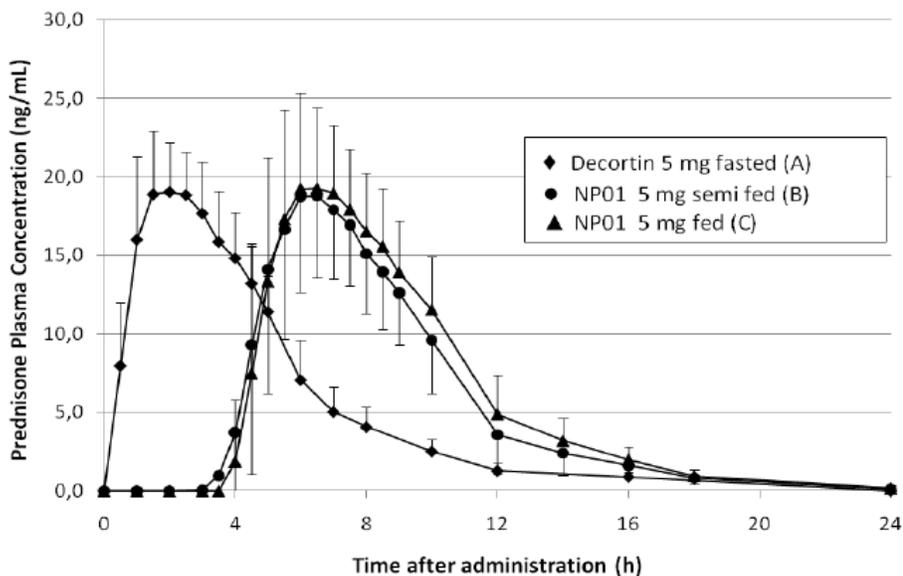


Figure courtesy of Dr. Ping Ji

Review of these data shows that NP01 administered under fed conditions has a similar bioavailability profile as compared to prednisone IR, however, it has a delayed T_{max} of approximately 4 hours as compared to prednisone IR. In view of these findings, the clinical pharmacology reviewer has recommended that NP01 should be taken with food.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for NP01 includes 9 Phase I studies, 1 Phase 2a study, 2 Phase 3 studies and 1 Phase 4 (foreign post marketing) study which are summarized in Table 3. All trials were conducted in adults 18 years and older; therefore, a separate table of pediatric enrollment is not presented here. Also, the application did not include any studies or other information to support the validation of the morning stiffness PRO instrument as had been previously requested during the 2010 pre-NDA meeting.

Table 3 – Key Design Features of NP01 Trials

Study/Objectives	Study Design; Duration; No. Study Sites	Dosage Regimen; Route of Adm.	No. of Subjects	Diagnosis and Entry Criteria	Endpoints
Phase 1					
EMR 62215-001 Objective: Compare the oral bioavailability of 4 experimental DR prednisone tablets and a reference IR prednisone tablet	Single-center, OL, R, 3-period X-over study	Single oral dose of 5 mg DR prednisone tablet (A, B, C, or D) at 8 PM or 5 mg of reference IR prednisone (Decortin)	N=12	Healthy male subjects	PK and safety
EMR 62215-002 Objectives: 1. Compare bioavailability of DR prednisone vs. reference IR prednisone tablet; 2. Determine food effect on PK profile and bioavailability of DR prednisone; 3. Assess effect of time of administration (2 AM vs. 8 AM) for IR prednisone tablet	Single-center, OL, R, 4-period X-over study	Single oral dose of 5 mg DR prednisone tablet at 8 PM in semi-fasted or fed state vs. 5 mg of IR prednisone (Decortin) at 2 AM or 8 AM in fasted state	N=28	Healthy male subjects	PK and safety
EMR 62215-005 Objectives: 1. Compare bioavailability of DR prednisone vs. reference IR prednisone tablet; 2. Determine food effect on PK profile and bioavailability of DR prednisone	Single-center, OL, R, 3-period X-over study with 7-day washout periods	Single oral dose of 5 mg DR prednisone tablet 8 PM in semi-fasted or fed state vs. 5 mg of IR prednisone (Decortin) at 2 AM in fasted state	N=27	Healthy male subjects	PK and safety
NP01-006 Objectives: 1. Assess food effect; 2. Determine the single-dose PK profile of NP01; 3. Assess safety and tolerability of NP01	Single-center, OL, R, 2-way X-over, bioavailability, safety and tolerance study	Single oral dose of 5 mg NP01 at 8 AM post fast vs. after high fat meal	N=24	Healthy male and female subjects	PK and safety
NP01-008 Objectives: 1. Assess dose proportionality of single multiple doses of NP01; 2. Determine PK profile of single multiple doses of NP01; 3. Assess safety and tolerability of single multiple doses of NP01	Single-center, OL, R, balanced, 3-way crossover study	Single oral dose of 1 mg, 2 mg, and 5 mg NP01 at 8 AM after overnight fast	N=18	Healthy male and female subjects	PK and safety
NP01-009 Objectives: 1. Assess bioavailability of 4 batches of NP01 tablets with different in vitro dissolution times under fasting conditions; 2. Determine t_{lag} and t_{max} for batches of NP01 with different dissolution times; 3. Assess safety and tolerability	Single-center, OL, R, 4-way X-over study	Single oral doses of NP01 with in vitro dissolution times of 3.2, 3.9, 4.4, and 4.9 hrs at 8 AM after overnight fast	N=28	Healthy male subjects	PK and safety

Adapted from Sponsor's 5.2 tabular Listing of All Clinical Studies located in Module 5. Study NP01-015 is ongoing. Abbreviated report submitted in 120-day safety update.

Table 4 – Key Design Features of NP01 Trials (cont.)

Study/Objectives	Study Design; Duration; No. Study Sites	Dosage Regimen; Route of Adm.	No. of Subjects	Diagnosis and Entry Criteria	Endpoints
NP01-010 Objectives: 1. Assess bioavailability of 4 batches of NP01 tablets with different in vitro dissolution times under fasting conditions; 2. Determine t_{lag} and t_{max} for batches of NP01 with different dissolution times; 3. Assess safety and tolerability	Single-center, OL, R, 4-way X-over study	Single oral doses of NP01 with in vitro dissolution times of 3.2, 3.9, 4.4, and 4.9 hrs at 10 PM 30 minutes after overnight fast	N=28	Healthy male subjects	PK and safety
NP01-013 Objectives: Compare bioavailability of DR prednisone vs. reference IR prednisone tablet in fed state	Single-center, OL, R, 2-way X-over study with 3-day washout period	Single oral dose of 5 mg NP01 at 10 PM after dinner or 5 mg of IR prednisone (Decortin) after breakfast	N=24	Healthy male and female subjects	PK and safety
NP01-014 Objectives: 1. Assess bioequivalence of two different formulations of NP01 2. Determine t_{lag} and t_{max} of both formulations of NP01; 3. Assess safety and tolerability of both formulations of NP01	Single-center, OL R, 2-sequence, 2-way X-over study	Single oral dose of 5 mg NP01 by Bayer Schering Pharma after breakfast or 5 mg NP01 by (b) (4) after breakfast	N=52	Healthy male and female subjects	PK and safety
NP01-015^a Objectives: 1. Assess bioequivalence of two different formulations of NP01 2. Determine t_{lag} and t_{max} of both formulations of NP01; 3. Assess safety and tolerability of both formulations of NP01	Single-center, OL R, 3-sequence, 3-way X-over study	Single oral dose of 1, 2 and 5 mg NP01 after breakfast	N=54	Healthy male and female subjects	PK and safety
Phase 2a					
NP01-201 Objective: Assess the efficacy and safety of NP01 on nocturnal symptoms (awakenings) in steroid dependent asthma compared to IR prednisone	Single-center, OL, 8-week, exploratory study	4 wks of repeat oral dosing with 1 mg and 5 mg NP01 at 10 PM vs 4 wks of repeat oral dosing with 1 mg and 5 mg Cortancyl tablets at 8 AM	N=14	Male and female subjects with nocturnal asthma on stable doses of oral glucocorticoids for 4 wks	¹ EP: variation in total number of nocturnal awakenings between the last 2 wks of both treatments; ² EP; PFTs, QoL and safety

Adapted from Sponsor's 5.2 tabular Listing of All Clinical Studies located in Module 5. Study NP01-015 is ongoing. Abbreviated report submitted in 120-day safety update.

Table 5 – Key Design Features of NP01 Trials (cont.)

Study/Objectives	Study Design; Duration; No. Study Sites	Dosage Regimen; Route of Adm.	No. of Subjects	Diagnosis and Entry Criteria	Endpoints
Phase 3					
NP01-007 Objectives: 1. Demonstrate superiority of NP01 in ACR20 response rate vs. placebo; 2. Demonstrate superiority of NP01 in reducing AM stiffness, other clinical efficacy parameters, Quality of Life, inflammatory markers and safety	12 wk, MC, R (2:1), DB, PC, parallel group study	5 mg NP01 administered orally at 10 PM daily vs. oral placebo	N=350 n=231 NP01 subjects n=119 placebo subjects	Adults ages 18-80 yrs with RA on DMARD therapy ≥ 6 months stable for ≥ 6 wks prior to screening with AM stiffness ≥ 45 minutes and not on glucocorticoids or biologic agents	¹ EP: ACR20 response rate at Wk 12 Key ² EP: relative Δ in duration of AM stiffness between baseline and Wk 12; Other ² EP: ACR50/70; DAS28; time to ACR20; EULAR response; HAQ-DI; FACIT-F and SF-36
EMR 62215-003 Objectives: 1. Demonstrate superiority of NP01 vs. placebo in reducing AM stiffness; 2. Compare standard RA parameters in DB phase; 3. Demonstrate maintained efficacy and safety in OL phase	12 wks, MC, R (1:1), DB, active controlled, double –dummy, parallel-group study with 9-month OLE and 12-month adrenocortical substudy	3-10 mg/day NP01 administered orally at 10 PM vs. 3-10 mg/day Decortin administered orally at 6-8 AM	N=288 n=144 NP01 subjects n=144 Decortin subjects OLE: N=249 Substudy: N=28	Adults ages 18-80 yrs with RA on DMARD therapy ≥ 3 months stable for ≥ 4 wks prior to screening with AM stiffness ≥ 45 minutes, ≥ 3 TJ and ≥ 1 SJ, on glucocorticoids ≥ 3 months stable doses ≥ 2.5 and ≤ 10 mg/d for 1 month on no biologic agents	¹ EP: Relative Δ in duration of AM stiffness between baseline and Wk 12; ² EP: mean durat. daily AM stiffness wk; recurrence of stiffness during day; DAS28; pain intensity, physician's global assessment HAQ-DI, acute phase reactants
LOD9577 Objectives: 1. Assess improvement in activity status and QoL from reduction in AM stiffness; 2. Determine the safety and tolerability of NP01; 3. Conduct socio-economic evaluations	3-9 months, MC, OL, explorative study	1, 2, 5 mg NP01 administered daily	N=2730 Enrollment stopped early to meet PMC	Adults with RA age ≥ 18 yrs with AM stiffness taking or starting low dose glucocorticoid therapy	Efficacy (HAQ-DI, performance capability via VAS and QAS) and safety assessments

5.2 Review Strategy

The Applicant conducted two randomized controlled trials, Studies NP01-007 and EMR 62215-003, in support of efficacy for this application. As discussed in Section 3.3, the Applicant was unable to collect the necessary financial disclosure information as required by 21 CFR §54 for the investigators involved in EMR 62215-003, and therefore considers this trial not to be a covered clinical study in support of efficacy but only supportive of safety. Study LOD9577, which was an uncontrolled, open label postmarketing trial, was also reviewed in support of the safety of chronic administration of NP01. The other trials listed in Table 3 were not reviewed in support of NP01's efficacy as a treatment for RA in adults for the following reasons: they were single dose studies in healthy volunteers or uncontrolled, open-label studies conducted in a different population (e.g., asthmatics Study NP01-201).

The safety database included all subjects who participated in the three Phase 3 trials, as well as the safety data collected from the Phase 1 and 2 studies. These data will be discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

NP01's efficacy as a treatment for RA was evaluated by the Applicant in two Phase 3 clinical efficacy trials, NP01-007 and EMR 62215-003. Additional safety information was generated from the open label postmarketing trial LOD9577. Although EMR 62215-003 does not qualify as a covered clinical study under 21 CFR §54, the design of this protocol along with that of NP01-007 are discussed below for completeness. A study report of the postmarketing safety study LOD9577 may be found in Section 10.

5.3.1 NP01-007

Title: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of a New Modified-Release Tablet Formulation of Prednisone (NP01) in Patients with Rheumatoid Arthritis

Dates Conducted: This trial was started on March 31, 2008 and completed on May 20, 2009.

Objectives:

Primary Objective:

- To evaluate the superiority of 5 mg NP01 administered in the evening to placebo as assessed by the American College of Rheumatology (ACR)20 responder rate

Secondary Objectives:

Major secondary objective:

- To evaluate the superiority of 5 mg NP01 administered in the evening to placebo in terms of relative reduction of morning stiffness

Other secondary objectives:

- Time to response as assessed by ACR20 criteria
- ACR50
- ACR70
- DAS28 score at each visit
- European League Against Rheumatism (EULAR) response criteria
- Morning stiffness at each visit:
 - Relative (to baseline) reduction of duration of morning stiffness
 - Absolute reduction of duration of morning stiffness
 - Severity of morning stiffness
 - Reoccurrence of stiffness during day
- Individual ACR20 and DAS20 criteria (ACR core set):
 - Tender joint count
 - Swollen joint count
 - Patient's assessment of pain (ACR20) via a 100 mm visual analogue scale (VAS)
 - Patient's global assessment of disease activity via a 100 mm VAS
 - Physician's global assessment of disease activity (ACR20) via a 100 mm VAS
 - Functional Disability Index of the Health Assessment Questionnaire (HAQ-DI; ACR20)
 - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Requirements for additional analgesics
- Occurrence of pain in morning and evening
- Inflammatory cytokines (IL-6 and TNF α)
- Urine CTXI
- Quality of Life (QoL)
 - HAQ-DI (as part of the ACR20)
 - Short Form (SF)-36 (QoL)
 - Fatigue (fatigue subset of the Functional Assessment of Chronic Illness Therapy Fatigue [FACIT-F] questionnaire)

Safety:

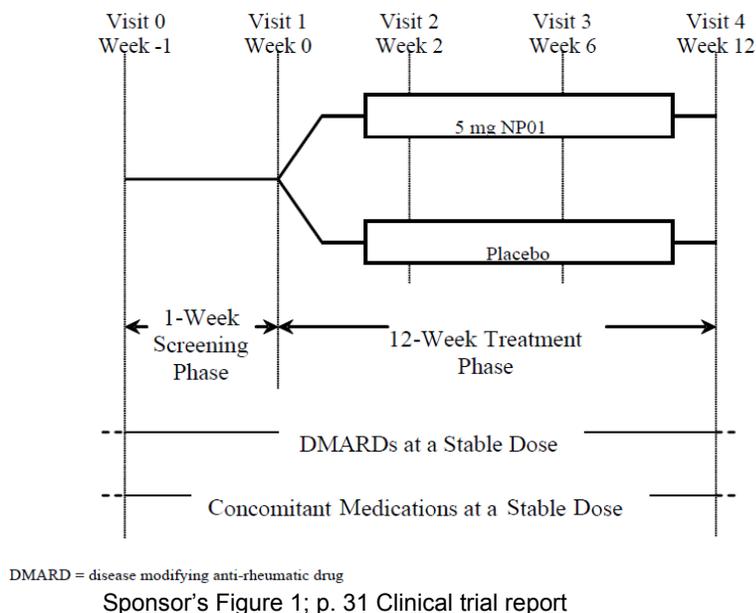
- Adverse events (AEs)
- Standard lab parameters
- Physical exam findings
- Vital signs (blood pressure, heart rate, body weight)

Overall Design:

This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study to evaluate the efficacy and safety of a 5 mg dose of NP01 when administered in the evening to approximately 294 patients with RA on concomitant DMARD therapy. The overall duration of the trial was to have been 1.5 years. The duration of participation for each patient was to have been 13 weeks (including the 1-

week screening phase). The trial was comprised of two parts: a 1-week, single-blind screening phase followed by a 12-week, randomized, controlled treatment phase (Figure 2).

Figure 2 – Schemata for NP01-007



Study candidates who met all of the trial's inclusion and exclusion criteria at Visit 0 of the 1-week screening phase were to have been administered placebo in addition to their standard RA medications and instructed to record daily in their diary cards the following information: morning stiffness, pain intensity, intake of study medication and use of analgesics. This recorded information was to have used to determine patients' eligibility for participation in the second part of the trial based on fulfillment of the following randomization criteria:

- Morning stiffness of 45 minutes or more (on at least 4 days within the last 7 days)
- Swollen joint count ≥ 4 out of 28 joints
- Tender joint count ≥ 4 out of 28 joints
- Adequate compliance in completing study diaries during screening phase
- Medication compliance (± 1 tablet of the calculated dose range)
- Negative Hemocult/guaiac test

Upon completion of the 1-week, single-blind, screening phase (Visit 1), eligible patients were randomized via a 2:1 ratio to receive NP01 5 mg/day or matching placebo administered orally in the evening for the next 12 weeks (double-blind treatment phase). All subjects were to have also recorded in their study diaries daily information concerning their morning stiffness, pain intensity, intake of study medication, and use of

analgesics. The protocol mandated that all study visits were to take place between 8 AM and 10 AM. Upon completion of the double-blind treatment phase of the trial, patients were to have been switched to 5 mg/day of immediate release prednisone and tapered down according to local practice if permitted.

Major Inclusion Criteria:

Subjects were to have met the following criteria:

1. Diagnosis of RA
2. Documented history of RA (sero-negative or sero-positive) in agreement with the ACR criteria, including the symptoms morning stiffness, joint pain, tender and swollen joints, inflammatory state with elevated ESR or CRP
3. On DMARD treatment for at least 6 months, with a stable dose for at least 6 weeks prior to the screening visit (Visit 0)
4. Morning stiffness of at least 45 minutes
5. Swollen joint count ≥ 4 out of 28 joints
6. Tender joint count ≥ 4 out of 28 joints
7. Aged 18 to 80 years
8. Women of childbearing potential had to be using a medically accepted contraceptive regimen

Exclusion Criteria:

Potential trial candidates were to have been prohibited from participating in this trial if any of the following criteria applied:

1. Suffered from another disease, which required glucocorticoid treatment during the study period, e.g., asthma, neurodermatitis
2. Synovectomy within 4 months prior to study start
3. Use of glucocorticoids (by any route) within 6 weeks prior to screening visit (Visit 0)
4. Use of biologicals such as TNF α inhibitors and other compounds within 3 months prior to the screening visit (Visit 0) or other compounds within 1 year prior to screening Visit 0
5. Clinically relevant abnormal lab values suggesting an unknown disease and requiring further clinical evaluation
6. Pregnancy or nursing
7. Participated in another clinical study (use of an investigational product) within 30 days preceding Visit 0
8. Re-entry of patients previously enrolled in this study
9. Alcohol or drug abuse
10. Requirement of non-permitted concomitant medication
11. Known hypersensitivity to prednisone or prednisolone
12. Any contraindication for low-dose prednisone treatment
13. Significant renal impairment (serum creatinine >150 $\mu\text{mol/L}$)
14. Significant hepatic impairment based on investigator's opinion

15. Any uncontrolled concomitant disease requiring further clinical evaluation (e.g., uncontrolled diabetes, uncontrolled hypertension)

Treatment:

During the 1-week screening phase, patients were administered 1 placebo tablet daily with their concomitant DMARD therapy. Following randomization, subjects received NP01 oral tablets containing 5 mg prednisone or matching placebo which were to have been taken daily with or after the evening meal (around 10 pm \pm 30 minutes) and swallowed unchewed with sufficient liquid. In the event that more than 2-3 hours had passed since the evening meal, patients were instructed to take the study tablets with a light meal or snack. No changes in study medication dose were permitted during the 12-week double-blind portion of the trial. The protocol mandated that subjects who either completed or withdrew prematurely from the trial were to have been switched to 5 mg of immediate release prednisone a day which was to have tapered down according to local practice if permitted.

Rescue Medications:

In the event of an acute exacerbation of pain, the protocol permitted patients to use a non-anti-inflammatory analgesic such as acetaminophen/paracetamol as rescue medication. Subjects were required to record the use of all rescue medication in their study diaries.

Concomitant Medications:

The protocol permitted the concomitant use of DMARD therapy that had been administered at stable doses for at least 6 weeks prior to the screening visit over the course of the study. In addition to continuing their stable doses of DMARDs therapy, patients were also allowed to continue taking stable doses of NSAIDs and participate in physical therapy provided that either of these treatment modalities had been started prior to entering the trial. The use of all other medications as treatment for concomitant diseases was permitted as long as their dosages remained stable throughout the study.

Use of the following concomitant treatments by patients was prohibited while participating in the trial:

- Glucocorticoids other than the study medication
- Intra-articular injections and synoviorthesis
- Biologicals
- Initiation of DMARD therapy
- Initiation of NSAID therapy

Removal of Patients from Treatment or Assessment:

Patients were to have been withdrawn from the study if they requested to be discontinued from the trial for any reason, continuation in the trial was detrimental to the patient's well being, failed to respond to study treatment and required urgent additional medication, experienced a serious AE, became pregnant, required the use of a non-

permitted concomitant drug, incurred unblinding of study drug, or demonstrated repeatedly unreliability to keep study appointments (i.e., > 3 days) during the double-blind treatment phase of the trial.

Study Procedures:

The following Table 6 is a tabular flow chart of the scheduled study visits which were to have taken place between 8-10 AM as well as protocol specified procedures and evaluations:

Table 6 – Schedule of Procedures and Evaluations for Study NP01-007

	Randomization ↓				
	Screening	Double-blind phase			
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
	Week -1	Week 0	Week 2	Week 6	Week 12
Informed consent	✓				
Inclusion and exclusion criteria	✓				
Demographic and baseline characteristics	✓				
Medical history	✓				
Previous medication ^a	✓				
Concomitant medication	✓	✓	✓	✓	✓
Physical examination	✓				✓
Vital signs	✓	✓	✓	✓	✓
Rheumatoid Disease Status ^b	✓	✓	✓	✓	✓
Safety laboratory ^c	✓				✓
Inflammatory cytokines (IL-6 and TNF α)	✓				✓
Urinalysis ^c	✓				✓
Dispense Hemocult/guaiaec Test ^d	✓	✓		✓	
Collect and develop Hemocult/guaiaec Test		✓			✓
Dispense study medication	✓	✓	✓	✓	
Fix appointment for next visit	✓	✓	✓	✓	
Dispense, collect and review study diaries ^e	✓	✓	✓	✓	✓
AEs ^f		✓	✓	✓	✓
Assess compliance		✓	✓	✓	✓
QoL questionnaire (SF-36)		✓			✓
Fatigue questionnaire (FACIT-F)		✓			✓
Randomization criteria		✓			
Randomization and fax confirmation		✓			
Collect unused medication		✓	✓	✓	✓
Switch to immediate-release predniso(lo)ne					✓

ACR = American College of Rheumatology; AE = adverse event; CPR = C-reactive protein; DAS = disease activity score; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy - Fatigue; HAQ-DI = Functional Disability Index of The Health Assessment Questionnaire; IL = interleukin; SF-36 = Short Form 36; TNF = tumor necrosis factor

^a All medication taken within the last 30 days before Visit 0 was documented. In addition, previous medication for treatment of RA taken within the last 6 months before Visit 0 was documented.

^b The following factors contributing to ACR20 and/or DAS28 were determined: tender and swollen joint counts, patient's assessment of pain, patient's and physician's global assessments of disease activity, HAQ-DI, ESR and CRP.

^c Safety laboratory included biochemistry, hematology and differential cell count; urinalysis included a pregnancy test for women of childbearing potential.

^d If patient experienced any gastrointestinal AE during course of study additional hemocult/guaiaec tests were performed.

^e At Visit 0, the study diary was dispensed. There was no previous diary (from the last visit) to collect and review. At Visit 4, a new diary was not dispensed; however the current diary (used since the last visit) was collected and reviewed. Patients completed the diaries every day during the study (each diary contained an additional 7 days in case a visit was postponed).

^f For ongoing AEs at final visit, the clinical course of the AE was followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation was found or the Investigator considered it medically justifiable to terminate follow-up (as per Protocol Amendment 1).

Outcome Measures:

The following efficacy assessments were to have been performed:

Primary efficacy endpoint:

The primary efficacy variable was to have been the ACR20 response rate at Week 12 (Visit 4). The ACR 20 response rate is a validated, regulatory standard endpoint used in clinical trials evaluating treatments for RA. Responders are defined as patients whose improvement from baseline to Visit 4 (Week 12) fulfilled all of the following criteria:

- $\geq 20\%$ reduction in the tender joint count (0-28)
- $\geq 20\%$ reduction in the swollen joint count (0-28)
- $\geq 20\%$ reduction in three of the five following additional measures:
 - Patient's assessment of pain (100 mm visual assessment scale [VAS])
 - Patient's global assessment of disease activity (100 mm VAS)
 - Physician's global assessment of disease activity (100 mm VAS)
 - HAQ-DI
 - CRP or ESR as acute phase reactant

At each visit, study investigators were to have performed a standardized joint examination assessing the following 28 joints bilaterally for swelling and tenderness (based on applied pressure and range of motion): shoulder, elbow, wrist (radiocarpal, carpal, and carpometacarpal were collectively designated wrist), metacarpophalangeal I-V, thumb interphalangeal, proximal interphalangeal II-V, and knee. The swollen joint count represented the number of joints in which there was synovial fluid and/or soft tissue swelling, but not if bony overgrowth was found. The tender joint count represented the number of joints in which pain was reported after a maneuver.

Secondary efficacy endpoints:

This study had a number of secondary endpoints defined as follows:

Key secondary efficacy variable:

- Relative change (%) in the duration of morning stiffness between baseline and Visit 4 (Week 12): Data for this nonvalidated endpoint was to have been obtained from patients' diary cards. Subjects were to have recorded the start and stop time of morning stiffness in their patient diary every day during the 12-week treatment phase. Duration of morning stiffness was the difference between the time of resolution of morning stiffness and the time of wake-up. As per a SEALD consult obtained on December 4, 2007, this endpoint was found to lack definitions for resolution of morning stiffness and recurrence of stiffness to be used by patients to answer the question consistently in addition to lacking information necessary to support its reliability and construct validity. The Applicant also did not provide any scientific justification for a responder definition or a clinically meaningful reduction of morning stiffness in the protocol or discussion regarding translation or cultural adaption of this endpoint.

Other secondary efficacy variables:

- ACR20 response rate at Weeks 2 and 6 (Visits 2 and 3)
- ACR50 response rate at Weeks 2, 6, and 12 (Visits 2, 3 and 4)
- ACR70 response rate at Weeks 2, 6, and 12 (Visits 2, 3 and 4)

(Note: Determination of the ACR50 and 70 response rates is based on $\geq 50\%$ and 70% improvement from baseline to Visit 4, respectively, of the same criteria listed above used to determine the ACR20 response rate.)

- Time to response based on ACR20 criteria: This endpoint was defined as the date when all assessments leading to the ACR20 response were first collected relative to patient baseline.
- Change from baseline in DAS28 at each visit: The DAS28 score is another validated, regulatory standard endpoint commonly used by foreign regulatory authorities to assess efficacy of treatments in RA trials. It is a composite index score comprised of the number of tender and swollen joints based on a 28 joint count, an acute phase reactant (e.g., ESR or CRP), and the patient's global disease assessment. Its score is calculated via a standardized formula and ranges from 0-10 with higher scores consistent with higher disease activity.
- EULAR response criteria: This validated endpoint is based on the DAS28 score and is used to characterize patients' RA disease status. Patients were classified as patients with good, moderate, or no response based on their change in DAS28 score as shown in the following Table 7:

Table 7- Characterization of RA Disease Status by DAS28 Score

Baseline DAS28	Improvement >1.2	Improvement >0.6 to ≤ 1.2	Improvement ≤ 0.6
≤ 3.2	Good response	Moderate response	No response
>3.2 to ≤ 5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Sponsor's table 4; p. 49 Clinical Study Report

- Relative (%) and absolute reduction of duration of morning stiffness between baseline and each study visit: Determined from data recorded in patients' diary card in the same manner as the key secondary endpoint.
- Change from baseline in severity of morning stiffness at each visit: Patients were required to assess the severity of morning stiffness via a 100 mm VAS every morning and record this information in their diary cards. Severity of morning stiffness was calculated as the average of the morning stiffness severity over the last 7 days prior to the visit (including the day of the visit). If more than 4 assessments were missing, then the severity was set to missing.
- Change from baseline in terms of reoccurrence of stiffness during day (while performing routine activities): Every evening during the treatment phase, patients were to record in their diaries if they had reoccurrence of stiffness (yes/no). Reoccurrence of stiffness during the day was assessed as the percentage of

days with reoccurrence of stiffness over the last 7 days prior to each visit (if 4 or more responses were missing, the percentage was set to missing)

- Change from baseline in tender and swollen joint counts at post-baseline study visits: The analysis of tender joint count and swollen joint count was based on a standardized 28-joint assessment as described above. For each patient, only those joints that were evaluable at baseline and endpoint were included in the statistical analysis of joint counts.
- Change from baseline in patient assessment of the pain intensity at each visit: In addition to performing a daily pain assessment, subjects were also required to assess their pain via a 100 mm VAS (0=no pain and 100 mm = very intense pain) at each study visit.
- Change from baseline in physician's and patient's global assessments of disease activity at each visit: At each study visit, both the investigator and patient were required to separately assess the patient's overall disease activity via a 100 mm VAS (0=no disease activity and 100 mm = high disease activity).
- Change in baseline in occurrence of pain in the morning and evening (100 mm VAS): Patients were to have assessed their pain level via a 100 mm VAS (0=no pain and 100 mm = very intense pain) twice daily in the morning and evening. This information was to have been recorded in their patient diary card. This assessment was to have been computed as the change in percentage of occurrence of pain in morning/evening over the last 7 days prior to each visit (if 4 or more responses were missing, the percentage was set to missing). For purposes of this study, the minimal clinically important difference was prespecified to be a score of -11.9 mm.
- Change from baseline in the use of additional analgesics: Patients were to have recorded in their diary cards the use of analgesics over the last 24 hours (yes/no). Positive responses also required recording the type, dose and time the analgesic was taken by subjects in their diaries. This endpoint was computed as the change from baseline in percentage of days with the event over the last 7 days prior to each visit (if 4 or more responses were missing, the percentage was set to missing).
- Use of additional analgesics: This endpoint was assessed as the number of days with additional analgesics during the double-blind treatment phase based on data captured in patients' diary cards.
- Inflammatory parameters - Five inflammatory parameters were to have been assessed at each visit and were to have been compared to baseline levels:
 - CRP, ESR, TNF α , IL-6 and urine CTX I: ESR was to have been measured within the first hour following blood draw at each visit by the local lab. CRP, IL-6, and TNF α levels were to have been analyzed from patients' blood and serum samples by the central lab. Urine CTX I was to have assessed by the central lab via a competitive binding enzyme immunoassay.

- Patient Reported Outcomes (PRO) - Three patient reported health-related quality of life assessment tools were to have been evaluated:
 - Change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) at each visit: This is a validated, self-reported functional status instrument that was used to measure disability over the 12-weeks of the treatment phase as assessed by 8 domains of functionality. The highest scores from the 8 domains (range: 0-24) are summed and divided by 8 to yield a Functional Disability Index (range: 0-3 with higher scores indicative of increased functional disability). Subject's global well being and pain severity were to have also been evaluated via a 100 mm VAS. The mean clinically important difference for the HAQ-DI score is -0.22.
 - Change from baseline in each domain of the Short Form (SF-36) Health Status Survey and for the mental and physical component scores: The SF-36 is a validated, 36-item, self-reported questionnaire comprised of 8 subdomains that was used to calculate the 2 summary scores: physical component summary (PCS) and mental component summary (MCS). Average scores in healthy normal population age 55-64 for males and females combined are 47 for PCS and 52 for MCS. Higher scores represent better mental and physical quality of life.
 - Change from baseline in the fatigue subset of the FACIT-F questionnaire: The 13-item fatigue sub-questionnaire from this validated self-administered assessment tool was used to evaluate the effect of fatigue on patient's daily activity and function based on the following 5-point grading system: 0= not at all, 1=a little bit, 2= somewhat, 3 =quite a bit and 4=very much. The overall score was the sum average of the subscales.

Statistical Design, Definitions of Analyzed Populations and Analysis Plan:

Sample Size Calculations

With a projected enrollment of 294 patients randomized via 2:1 (NP01 n=196 subjects; placebo n=98 subjects) this study was to have approximately 90% power to show a 20% difference in the proportion of patients achieving and ACR20 response at Week 24 assuming a placebo response rate of 25% using a two-sided test at a significance level of 0.05. Based on the above listed sample size calculation, the trial was to have approximately 78% power to demonstrate a difference of 30% and 89% power to show a difference of 35% between placebo and NP01 treatment groups for the key secondary endpoint of relative change [%] in morning stiffness.

Study Populations

Three populations were to have been used for analysis. They were defined as follows:

1. Modified Intent-to-Treat (mITT) Population: was defined as all randomized subjects who took at least one dose of study drug. The mITT was to have been used to assess all efficacy endpoints.

2. Per-Protocol (PP) Population: was defined as all randomized patients, treated with study medications, and did not have a major protocol deviation. Major protocol

deviations leading to exclusion from the PP population were defined prior to unblinding during the blind data review meeting. The analyses of the PP population were to have provided supportive evidence (i.e., sensitivity analyses) and were to have been performed for the primary efficacy variable (ACR20).

3. Safety Population: was defined as all randomized subjects who took at least one dose of study drug of the study medication they actually received. The safety population was used for all safety analyses.

The original statistical analysis plan (SAP) submitted on July 17, 2009, stipulated that all efficacy analyses were to have been conducted using the mITT population and the PP population. However, since approximately 5% of the subjects in this trial were not assigned to treatment as randomized due to blinded errors that resulted in the distribution of medications in the wrong order, the data was to have been analyzed according to the treatment actually received (safety population) rather than randomized (mITT). The primary endpoint (ACR20 response rate using the CRP but if unavailable, the ESR) was to have been analyzed using logistic regression with treatment, pooled sites (by country or geographic area), age category and gender as factors using non-responder methodology to account for missing data.

The key secondary endpoint of relative change in morning stiffness was to have been analyzed via Hodges Lehmann methodology due to non-normality of data. Analysis of covariance (ANCOVA) with treatment and sites as factors and the relevant baseline score as a covariate was to have been used to analyze the other secondary endpoints that evaluated the absolute changes in the ACR core set measures, the SF-36, the FACIT-Fatigue, and DAS28 (using CRP). The time to a patient's first response according to the ACR20 criteria was to have been analyzed via Kaplan-Meier methodology and the treatments were to have compared via log-rank testing. The EULAR and the ACR50/70 response rates as well as the proportion of patients taking additional analgesics were to have been analyzed using logistic regression with treatment and pooled sites as factors. All secondary endpoint analyses were to have used last observation carried forward (LOCF) to account for missing data.

Safety Evaluation:

The analysis of safety assessment was to have been conducted on the safety population. Safety assessment was to have included treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), clinical lab data, physical exam findings and vital signs. All TEAEs were to have been coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 11.0). The incidences of TEAEs were to have been summarized by system organ class (SOC) and preferred term by overall and treatment group. If a subject reported the same AE more than once that event was to be counted only once using the most severe intensity.

Clinical lab data results for hematology, serum chemistry and urinalysis testing as well as changes in vital signs and physical exam were to have been reviewed and

summarized for within treatment changes and for changes from baseline for each treatment group. Additionally, shift tables on changes from the normal ranges for lab assessments were to have been created.

Study Conduct:

Listed below are the two protocol amendments to Study NP01-007:

1. Amendment 1 (implemented on April 17, 2008)

This local addendum was made prior to enrollment of any patients in Germany:

- Subjects with a familial predisposition to glaucoma were prohibited from participating in this trial unless a medical ophthalmological exam of intraocular eye pressure measurement reveals normal findings

2. Amendment 2 (implemented on August 4, 2008)

This addendum was made after 73 subjects had been randomized:

- Amended the exclusion criterion that prohibited patients who had used biologicals such as TNF α inhibitors within 3 months prior to screening visit (Visit 0) or other compounds within 1 year prior to screening visit (Visit 0) to within 5 serum half lives prior to the screening visit (Visit 0)
- Clarified the follow-up of AEs that were still ongoing at the final visit
- Increased the number of study centers from 40-45 to 70-80 sites in North America and Europe
- Provided clarification regarding the procedures for the destruction of study medication
- Updated the text regarding the hemocult/guaiac tests
- Included details about the coordinating investigator's affiliation

3. The second SAP (July 1, 2010)

Following unblinding of the study data and completion of the original analyses of the study, a second SAP was submitted by the Applicant based on Agency feedback comments dated August 31, 2009 regarding the original SAP as well as comments received at a preNDA meeting held in February 2010. These comments included the following:

- The primary efficacy analysis should be conducted with patients classified according to the treatment to which they were randomized (mITT population)
- A supportive analysis should also be conducted using the treatments patients actually received (safety population).
- Baseline observation carried forward (BOCF) imputation methodology should be used for continuous variables.

In view of the above recommendations, the second SAP specified the following:

- For patients who prematurely withdrew from the study LOCF methodology was appropriately assigned to the next protocol visit instead of Visit 4
- The change in duration of morning stiffness was not repeated for the regions of US/Canada and Europe

- Subgroup analyses on ACR20 region, gender, age group, and disease duration were performed. A subgroup analysis by study center was not conducted as each center had to be pooled with at least 1 other center in order to have enough ACR20 responders for the model to converge. Due to the extensive pooling, it was not statistically appropriate to do a by center analysis
- In addition to the previously specified imputation methodologies, BOCF imputation was used for continuous efficacy variables. BOCF was not added for the analyses of categorical variables such as the ACR response rates since BOCF was actually the same as the worse case analysis for those variables
- The analysis of the ACR20 for the mITT population was considered the primary analysis. Analyses of all other efficacy variables were considered secondary, while efficacy analyses for the safety and PP populations were considered sensitivity analyses

Study Results:

Disposition:

This study was conducted at 50 centers worldwide located in Poland (n=145; 41%), Hungary (n=102; 29%), the United States (n=75; 21%); Canada (n=13; 4%), the United Kingdom (n=12; 3%), and Germany (n=3; 1%). Of the 389 potential patients screened for this study, 39 were considered to have been screening failures as follows: 24 due to failure to meet entry criteria, 12 due to withdrawal of consent, and 3 due to adverse events. A tabular summary of subjects' disposition for Study NP01-007 is shown in Table 8. Overall, the rate of study completion was higher in the NP01 treatment group as compared to the placebo treatment group (89%). The most common reason for early study withdrawal in both treatment groups was patient request which was higher in the placebo treatment group (7%) as compared to the NP01 treatment group (3%) followed by AE which was similar for the both treatment groups (2% and 2%, respectively).

Table 8 - Subject Disposition for Study NP01-007

	NP01	Placebo	Total
Number of Patients Randomized	231	119	350
Number of Patients Who Completed Visit 4	217 (94%)	106 (89%)	323 (92%)
Number of Patients Withdrawn Prematurely	14(6%)	13 (11%)	27 (8%)
Patient Request	6 (3%)	8 (7%)	14 (4%)
Adverse Event	5 (2%)	2 (2%)	7 (2%)
Lost to Follow-Up	1 (0%)	1 (1%)	2 (1%)
Withdrawal of Consent	1 (0%)	0 (0%)	1 (0%)
Lack of Efficacy	1 (0%)	0 (0%)	1 (0%)
Protocol Violation	0 (0%)	1 (1%)	1 (0%)
Required a Prohibited Medication	0 (0%)	1 (1%)	1 (0%)

Adapted Sponsor's Table 14.1.1 and 14.1.2; p.

Protocol Deviations:

Major protocol deviations were defined in the SAP by the Applicant as those that were likely to affect the validity of the data for the ACR20 and/or duration of morning stiffness. The major protocol deviations leading to exclusion from the PP population are summarized in Table 9. A total of 71 randomized patients incurred one or more protocol deviations over the course of this trial. As shown in Table 9, the rate of protocol violations was comparable for the two treatment groups. The most common major protocol deviation for this trial was due to the use of prohibited medications, specifically NSAIDs which was higher in the placebo treatment group (13%) as compared to the NP01 group (10%), followed by compliance/exposure (3% and 6%, respectively), and misrandomization (4% and 2%, respectively).

Table 9 - Summary of Subjects with Major Protocol Deviations

Type of Protocol Deviation	Number (%) of Patients		
	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Patients With at Least 1 Major Deviation	46 (20%)	25(21%)	71(20%)
Inclusion/Exclusion/Randomization Criteria	8 (4%)	1 (1%)	9 (3%)
Duration of Morning Stiffness at Baseline	3 (1%)	0 (0%)	3 (1%)
Low Tender/Swollen Joint Count at Baseline	2 (1%)	1 (1%)	3 (1%)
DMARD Violation	3 (1%)	0 (0%)	3 (1%)
Misrandomization	5 (2%)	5 (4%)	10 (3%)
Compliance/Exposure	14 (6%)	4(3%)	18 (5%)
Overall Drug Exposure	2 (1%)	0 (0%)	2 (1%)
Overall Non-Compliance	3 (1%)	1 (1%)	4 (1%)
Study Drug Intake Outside of Time Window	9 (4%)	3 (3%)	12 (3%)
Prohibited Medication	24(10%)	17(14%)	41(12%)
Intake of Glucocorticoids	1 (0%)	1 (1%)	2 (1%)
Intake of NSAIDs	23 (10%)	15 (13%)	38 (11%)
Intake of Biologicals	0 (0%)	1 (1%)	1 (0%)

Note: Major deviations were finalized during the Blind Data Review Meeting.
 Sponsor's Table 9; p. 80 Clinical Study Report

Demographics:

Table 10 summarizes the demographic characteristics of the mITT population who participated in this trial. Subjects treated with NP01 were demographically similar to those who received placebo during this study. The patients who participated in this study had a mean age of 57 years and were overwhelmingly female (84%) and Caucasian. Since the majority (75%) of subjects who enrolled in the trial came from European countries, there was a poor representation of other racial or ethnic groups (1% Black, 0% Asian, 3% Hispanic Latino).

Table 10 – Baseline Demographic Characteristics of Subjects Enrolled in Study NP01-007 (mITT Population)

Characteristic	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Age (years): Mean (SD)	57 (10)	58 (10)	57(10)
Age Category:			
Young (≤ 45 years)	24(10%)	12 (10%)	36 (10%)
Middle-aged (>45 to ≤ 65 years)	162 (70%)	83 (70%)	245 (70%)
Elderly (>65 to ≤ 75 years)	35 (15%)	20 (17%)	55 (16%)
Very Elderly >75 years	10 (4%)	4 (3%)	14 (4%)
Gender:			
Female	192 (83%)	102 (86%)	294 (84%)
Male	39 (17%)	17 (14%)	56 (16%)
Ethnicity:			
Not Hispanic/Latino	49 (21%)	23 (19%)	72 (21%)
Hispanic/Latino	6 (3%)	5 (4%)	11 (3%)
Not Assessed (EU, Canada)	175 (76%)	90 (76%)	265 (76%)
Missing	1 (0%)	1 (1%)	1 (1%)
Race:			
White	226 (98%)	118 (99%)	344 (98%)
Black	4 (2%)	1 (1%)	5 (1%)
Asian	1 (0%)	0 (0%)	1 (0%)
BMI (Kg/m²) Mean (SD)	28(6)	28 (6)	28 (6)

SD= standard deviation; BMI=body mass index
 Adapted Sponsor's Table 11; p. 82 Clinical Study Report

Table 11 is a tabular summary of subjects' RA history and disease status. The mean duration of RA disease was 8 years for the study population. The two treatment groups were balanced in terms of baseline disease activity as assessed by a number of parameters. Overall, the study population enrolled in this trial was representative of patients with moderate to very active RA who could potentially benefit from treatment with NP01.

Table 11 – Summary of RA Disease Activity at Baseline for Subjects Enrolled in Study NP01-007 (mITT Population)

Disease Characteristic	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Duration of RA (years):			
Mean (SD)	8 (7)	8 (7)	8 (7)
<2 years	41(18%)	29 (24%)	70 (20%)
≥2 years to <5 years	63 (27%)	25 (21%)	88 (25%)
≥5 years to <10 years	54 (23%)	27 (23%)	81 (23%)
>10 years	73 (32%)	38 (32%)	111(32%)
DAS28:			
Mean (SD)	5.2 (0.8)	5.1 (0.8)	5.2 (0.8)
Range	3.1-7.6	3.5 -7.4	3.1-7.6
Physician’s Assessment of Disease Activity (mm VAS):			
Mean (SD)	55 (16)	54 (17)	55 (17)
Range	8-89	10-99	8-99
Patient’s Assessment of Arthritis Pain Intensity (mm VAS):			
Mean	55 (22)	51 (23)	54 (22)
Range	3-96	0-95	0-96
HAQ-DI score:			
Mean	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
Range	0-2.9	0-2.8	0-2.9
SF-36:			
Physical Component Summary Score			
Mean	31.6 (7.0)	31.5 (6.9)	31.6 (7.0)
Range	13.9-55.7	18.2-48.0	13.9-55.7
Mental Component Summary Score			
Mean	45.3 (10.7)	45.4 (9.6)	45.3 (10.3)
Range	17.1-68.3	22.7-63.8	17.1-68.1

SD= standard deviation

Adapted Sponsor’s Table 12; p. 83 of Clinical Study Report

Besides a high rate of hypertension (43%), the study population reported high rates of co-morbid medical conditions such as osteoarthritis (26%), osteoporosis (15%), hypercholesterolemia (11%), spinal osteoarthritis (10%), gastroesophageal reflux disease (GERD; 10%) and hypothyroidism (10%) which were reasonably balanced between the two treatment groups (Table 12). Some of these co-morbid conditions (e.g., osteoarthritis, spinal osteoarthritis and hypothyroidism) could potentially confound the study’s overall findings as since they are also associated with stiffness and pain.

Table 12 – Summary of Co-Morbid Medical Conditions Reported by > 10% of Subjects Enrolled in Study NP01-007 (mITT Population)

Preferred Term	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Hypertension	92 (40%)	59 (50%)	151 (43%)
Osteoarthritis	59 (26%)	31 (26%)	90 (26%)
Osteoporosis	35 (15%)	17 (14%)	52 (15%)
Hypercholesterolemia	25 (11%)	13 (11%)	38 (11%)
Spinal Osteoarthritis	23 (10%)	13 (11%)	36 (10%)
Gastroesophageal Reflux Disease	19 (8%)	16 (13%)	35 (10%)
Hypothyroidism	21 (9%)	14 (12%)	35 (10%)

Medical history was coded via MedDRA version 11.0
 Modified Sponsor's Table 13; p. 84 Clinical Study Report

The protocol mandated that patients were to continue taking stable doses of concomitant RA medications over the course of the study to treat their underlying disease. This information is summarized in Table 13. Overall, the use of concomitant RA medications was similar for the two treatment groups. The most commonly used medications by the study population were DMARDs (99%) and NSAIDs (73%). A total of 25 subjects (7%) were also taking glucocorticoids for RA, respiratory diseases (e.g., sinusitis and asthma), and skin diseases which were discontinued in 23 of these patients at the screening visit as per the study protocol. The remaining two patients, Subject 12-01 randomized to the NP01 group and Subject 80-01 randomized to placebo, were permitted to continue taking over the course of the trial inhaled glucocorticoids to treat underlying sinusitis and allergic rhinitis, respectively. There were two patients also receiving treatment with therapeutic biologic agents. Subject 62-06 randomized to NP01 treatment discontinued biological therapy as required, however, Subject 90-03 randomized to placebo continued biological treatment during the study and was excluded from the efficacy analysis.

Table 13 - Summary of Baseline RA Medications for Subjects Enrolled in Study NP01-007 (mITT Population)

Drug Category	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Patients Taking Any Concomitant Medication	231 (100%)	119 (100%)	350 (100%)
DMARDs	229 (99%) ^a	119 (100%)	348 (99%)
NSAIDs	166 (72%)	88 (74%)	254 (73%)
Glucocorticoids^b	16 (7%)	9 (8%)	25 (7%)
Other Analgesics:			
Anilides	47 (20%)	30 (25%)	77 (22%)
Other Opioids	19 (8%)	13 (11%)	32 (9%)
Natural Opium Alkaloids	10 (4%)	8 (7%)	18 (5%)
Opium Alkaloids and Derivatives	3 (1%)	2 (2%)	5 (1%)
Other Analgesics and Antipyretics	3 (1%)	1 (1%)	4 (1%)
Drugs Used in Opioid Dependence	1 (0%)	0 (0%)	1 (0%)
Biologics	1 (0%)	1 (1%)	2 (1%)

^aThe missing 2 patients (Patient 23-007 and Patient 23-10) received cyclosporine as DMARDs, however, the respective ATC code was not included.

^bIncludes level glucocorticoids, corticosteroids, and group III potent corticosteroids

Adapted Sponsor's Table 14; p. 85 Clinical Study Report.

Although the protocol prohibited the initiation of medications that could potentially confound the study's results such as glucocorticoids, DMARDs and NSAIDs and encouraged the use of non-narcotic analgesics for pain relief, 41% of the study population started therapy with prohibited medications over the course of the trial as shown in. The overall use of prohibited concomitant medications was similar for the two treatment groups. The three patients (Subjects 23-17, 28-08 and 44-04) randomized to NP01 who reportedly initiated DMARD therapy during the study, received doxycycline as treatment for infections. These 3 subjects should be considered coding mistakes since doxycycline carries the same ATC code as the DMARD minocycline. The seven patients (subjects 13-08, 62-07, 78-01, and 97-03 in the NP01 group and subjects 44-05, 45-01 and 97-02 in the placebo group) who were administered glucocorticoids during the trial required them for treatment of RA exacerbations or for treatment of an insect bite or prophylaxis prior to surgery.

Table 14 – Relevant Concomitant RA Medications Initiated During Study NP01-007 (mITT Population)

Drug Category	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Patients Who Initiated Concomitant RA Medications	92 (40%)	53 (45%)	145 (41%)
NSAIDs	35 (15%)	20 (17%)	55 (16%)
Glucocorticoids	4 (2%)	3 (3%)	7 (2%)
DMARDs	3 (1%)	0 (0%)	3 (1%)
Other Analgesics:			
Anilides	27 (12%)	18 (15%)	45 (13%)
Other Opioids	7 (3%)	4 (3%)	11 (3%)
Natural Opium Alkaloids	1 (0%)	2 (2%)	3 (1%)
Opium Alkaloids and Derivatives	2 (1%)	1 (1%)	3 (1%)
Drugs Used in Opioid Dependence	1 (0%)	0 (0%)	1 (0%)

A patient with multiple occurrences of a medication within a category was counted only once within the total row of this category.

Adapted Sponsor's Table 15; p. 86 Clinical Study Report.

Treatment Compliance:

The protocol specified that patients' compliance with study medication was to have been assessed by their diary recordings and tablet counts performed on the returned blinded study medication. Subjects were also directly queried by the trial investigators regarding the time they ingested their study medication. Table 15 below, summarizes the results of tablet counting to assess patient compliance with study medication. Compliance could not be calculated for one patient in the placebo group (Subject 22-10) as the date of the last dose intake was missing since the patient was lost to follow-up. Overall, the study population's compliance with medication was 99.9% and was balanced between the two treatment groups.

Table 15 – Summary of Compliance with Study Medication for Study NP01-007 (mITT Population)

	NP01 (N=231)	Placebo (N=119)	Total (N=350)
Mean (SD)	99.5% (8)	101% (8)	99.9% (8)
Compliance Categories:			
<80%	3 (1%)	1 (1%)	4 (1%)
≥80% to <95%	15 (7%)	2 (2%)	17 (5%)
≥95% to <105%	199 (86%)	109 (92%)	308 (88%)
≥105% to <120%	9 (4%)	3 (3%)	12 (3%)
>120%	5 (2%)	3 (3%)	8 (2%)

Overall compliance (5) = 100 x {(number of tablets dispensed – number of tablets returned)/ [(date of last dose - date of first dose] + 1)} SD=standard deviation

Modified Sponsor's Table 16; p. 87 Clinical Study Report

Efficacy:

Primary Efficacy Results

The primary efficacy parameter for Study NP01-007 was the ACR20 response rate at Week 12 (Visit 4). The results generated for the primary analysis using nonresponders imputation for missing data (e.g., worse case) are shown in Table 16.

Table 16 – Analysis of the ACR20 Response Rate (Primary Endpoint) and Supportive Sensitivity Analyses for Study NP01-007

Imputation scheme	NP01 n/N (%)	Placebo n/N (%)	% Difference in proportions ^a (95% CI) ^b		Odds Ratio (95% CI) ^c	P-value ^d
Primary analysis						
Worse case^e	108/231 (46.8%)	34/119 (28.6%)	18.2	17.4 (7.23, 27.64)	2.25 (1.39, 3.64)	0.0010
Secondary analysis						
Observed case	108/224 (48.2%)	35/116 (30.2%)	18.0	17.3 (6.83, 27.78)	2.21 (1.36, 3.58)	0.0013
LOCF^f	110/229 (48.0%)	35/119 (29.4%)	18.6	17.9 (7.66, 28.22)	2.30 (1.42, 3.72)	0.0007
Withdrawal^g	108/230 (47.0%)	35/119 (29.4%)	17.5	16.9 (6.58, 27.16)	2.18 (1.35, 3.51)	0.0014

Source: Study NP01-007, Clinical Study Report Section 11.4.1.1 Table 18.

CI = confidence interval; N = total number of patients per treatment group and imputation scheme at corresponding visit; n = number of responders.

Note: Visit 4 includes early withdrawal patients.

^a The observed difference between treatments (first value) and the estimate of the treatment difference from the generalized linear model (second value) are reported.

^b The 95% CI was calculated from a generalized linear model with a binomial probability function and an identity link with treatment, geographic region, gender, and median age class as factors.

^c Asymptotic 95% CIs based on asymptotic normality of the estimated odds ratio.

^d The p-value was based on logistic regression with treatment, geographic region, gender, and median age class as factors.

^e Worse case imputation: all missing values were imputed as non-responders.

^f LOCF imputation: last observation (post-baseline) was carried forward.

^g Withdrawal imputation: missing values for withdrawn patients were imputed as non-responders.

Table courtesy of Dr. Kiya Hamilton

A statistically higher response rate for the ACR20 was observed in patients administered NP01 as compared to placebo at the Week 4 visit. The results from multiple sensitivity analyses which involved the application of different imputation

methodologies for missing data were supportive of the primary efficacy results (refer to Table 16).

Secondary Efficacy Endpoints

The results of the analyses of the key secondary endpoint, the relative change from baseline in duration of morning stiffness at Visit 4 for the mITT population using LOCF and BOCF imputation for missing data, are shown in Table 17. Subjects with missing baseline values were excluded by the Applicant in this analysis resulting in a smaller sample size. The median relative rate of change from baseline in the duration of morning stiffness was greater in patients administered NP01 as compared to placebo treated patients at Visit 4 for both analyses.

Table 17 - Analyses of the Relative Change from Baseline in Duration of Morning Stiffness at Visit 4 (Key Secondary Endpoint) for Study NP01-007 (mITT Population)

Imputation scheme	Relative Change (%)				Difference in median ^a [%] (95% CI) ^a	P-value ^b
	NP01		Placebo			
	N	Median	N	Median		
LOCF	216	-55	107	-34	-20 (-32, -6)	0.0015
BOCF	215	-55	107	-33	-20 (-32, -7)	0.0013

Source: Study NP01-007, Clinical Study Report Section 11.4.1.2.1 Table 22.

CI = confidence interval; LOCF = last observation carried forward; N = number in analysis (i.e., excluding the missing).

Note: Visit 4 includes early withdrawal patients.

^a Difference in median and its 95% CI were estimated using Hodges-Lehmann method.

^b Wilcoxon signed rank test p-value (for information only).

As different methods were applied to compute the p-value and the 95% CI, the difference between treatment groups was assessed using the 95% CI.

Note: LOCF and BOCF imputation algorithms were implemented up to the next visit following the last diary data. LOCF (last observation carried forward) was computed using the last 7 days prior to the visit day with non-missing values for the duration of morning stiffness.

BOCF: Baseline observation was carried forward.

Table courtesy of Dr. Kiya Hamilton

However, the above analysis of the key secondary endpoint provided by the Applicant did not include the entire mITT population. As per the Agency’s statistician’s request, the applicant conducted additional analyses of the relative change from baseline in duration of morning stiffness for the full mITT population shown in Table 18. Since some patients were missing the baseline value for the key secondary efficacy endpoint for the mITT population, this resulted in a reduction in the sample size for the analysis of this endpoint from 231 to 216 subjects in the NP01 group and from 119 to 107 subjects in the placebo group (full mITT population) for the LOCF analysis. For the BOCF analysis, sample size was reduced further to 215 subjects in the NP01 group and 107 subjects in the placebo group. In the additional analyses, if the baseline value was missing the applicant replaced it with the patients screening value and LOCF and BOCF imputations

were applied. The results from these additional analyses were similar to the original analyses of this endpoint. The validity of these findings, however, are highly questionable since this endpoint was found to lack definitions for resolution of morning stiffness and recurrence of stiffness to be used by patients to answer the question consistently in addition to lacking information necessary to support its reliability and construct validity.

Table 18 – Additional Analyses of the Relative Change from Baseline in Duration of Morning Stiffness at Visit 4 (Key Secondary Endpoint) for Study NP01-007 (full mITT Population)

Imputation scheme	Relative Change (%)				Difference in median ^a [%] (95% CI) ^a	P-value ^b
	NP01		Placebo			
	N	Median	N	Median		
LOCF	230	-54.2	119	-28.6	-20.8 (-32.5, -7.6)	0.0006
BOCF	231	-51.4	119	-24.6	-18.7 (-31.3, -6.0)	0.0011

Source: Response to Information Request dated April 4, 2012

CI = confidence interval; LOCF = last observation carried forward; N = number in analysis (i.e., excluding the missing).

Note: Visit 4 includes early withdrawal patients.

^a Difference in median and its 95% CI were estimated using Hodges-Lehmann method.

^b Wilcoxon signed rank test p-value (for information only).

As different methods were applied to compute the p-value and the 95% CI, the difference between treatment groups was assessed using the 95% CI.

Note: LOCF and BOCF imputation algorithms were implemented up to the next visit following the last diary data.

LOCF (last observation carried forward) was computed using the last 7 days prior to the visit day with non-missing values for the duration of morning stiffness.

BOCF: Baseline observation was carried forward.

Table courtesy of Dr. Kiya Hamilton

Other Secondary Efficacy Endpoints:

There were multiple secondary endpoints analyzed which are summarized in Table 17 below. The analyses of these endpoints were conducted using LOCF imputation for missing data unless otherwise noted. No multiplicity correction was planned in the protocol or implemented here for the other secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

**Table 19 – Tabular Summary of Secondary Endpoint Analyses for Study NP01-007
(not adjusted for multiplicity)**

Secondary Efficacy Variable	Comment	P-value
ACR20 Response Rate at Each Visit	The proportion of patients who were responders at any visit was higher for the NP01 group (50% , 138 patients) as compared to PLO (42%, 50 patients)	p<0.002 All visits
ACR50 Response Rate at Each Visit	The proportion of patients who were responders at any visit was higher for the NP01 group (22% Visit 4) as compared to PLO (10% Visit 4)	p<0.05 Visits 3 and 4
ACR70 Response Rate at Each Visit	The proportion of patients who were responders at any visit was higher for the NP01 group (7% Visit 4) as compared to PLO (3% Visit 4)	N.S.
Tender Joint Count	Absolute change from baseline at Visit 4: NP01: -4.8 vs. PLO: -2.8	p=0.0014
Swollen Joint Count	Absolute change from baseline at Visit 4: NP01: -3.7 vs. PLO: -2.5	p=0.0085
Patient’s Assessment of Pain	Mean pain score decreased over time in the NP01 group to -22.1 mm at Visit 4; Mean pain score for PLO group did not decrease until later in the trial (Visit 3) and was -11.4 mm at Visit 4	p=0.0011
Patient’s Global Assessment of Disease Activity	Mean change over baseline score at Visit 4 of -21.1 mm for NP01 group vs. -7.8 mm for the PLO group	p=0.0003
Physician’s Global Assessment of Disease Activity	Mean change over baseline score at Visit 4 of -23.5 mm for NP01 group vs. -13.2 mm for the PLO group	p<0.0001
Time to Response Based on ACR Criteria	The median time to the first time the ACR20 criteria were met (using responders only n=188 patients) was 84 days for NP01 vs. 44 days for PLO group	
HAQ-DI score	Mean HAQ-DI score at Visit 4 for NP01 group was -0.222 vs. -0.049 for PLO group.	p<0.0001
CRP	Mean absolute change from baseline to Visit 4 for NP01 group -1.74 mg/L vs. -3.21mg/L for PLO	N.S.
ESR	Mean absolute change from baseline to Visit 4 for NP01 group -8.3 mm vs. -6.7 mm for PLO	N.S.
TNFα	Mean absolute change from baseline to Visit 4 for NP01 group -0.7 pg/mL vs. -0.1 pg/mL for PLO (observed case)	N.S.
IL-6 levels	Mean decrease in IL-6 levels was greater in the NP01 group at Visit 4 as compared to the PLO group (mean titer ratio: 0.8 (95% CI 0.7, 0.9)	p=0.001
DAS28	Mean absolute change from baseline DAS28 score was greater in NP01 group at Visit 4 (-1.16) vs. PLO (-0.64)	p<0.0001
EULAR Response	Although no patients had a “good response” by this criterion, a higher proportion of subjects in the NP01 group (57%) had a moderate response as compared to PLO group (40%)	p=0.0014

Table 20 – Tabular Summary of Secondary Endpoint Analyses for Study NP01-007 (not adjusted for multiplicity) (cont.)

Secondary Efficacy Variable	Comment	P-value
Change in Duration of Morning Stiffness Between Baseline and Each Visit	Median relative change from baseline was greater in the NP01 group than in the PLO group at each visit. Median relative change from baseline at visit 4 for the NP01 group was 45.6 minutes vs. 79.3 minutes for the PLO group.	p=0.0015
Severity of Morning Stiffness	Mean change from baseline at Visit 4 in the NP01 group was -28.6 mm vs. -19.2 mm for PLO group	p=0.0066
Reoccurrence of Morning Stiffness	Mean change from baseline at Visit 4 for the NP01 group was 23.7% days vs. 11.8% days for PLO group	p=0.0026
Patient Assessment of Morning Pain	Mean change from baseline to Visit 4 for NP01 was -24 mm vs. -15 mm for PLO group	p=0.0121
Patient Assessment of Evening Pain	Mean change from baseline to Visit 4 for NP01 was -21 mm vs. -15 mm for PLO group	p=0.0489
Additional Analgesics	Mean number of days with additional analgesics over the 12 weeks of the trial was comparable (NP01: 14 days vs. PLO 15 days)	N.S.
FACIT-F Fatigue Score	Mean absolute increase in fatigue subset score from baseline to Visit 4 for NP01 group 3.76 vs. 1.40 for PLO group	p=0.0028
SF-36 Score	Mean improvement in PCS score for NP01 group was 3.53 vs. 105 for PLO (LOCF); Mean improvement in MCS score for NP01 was 1.50 vs. 0.47 for PLO group	p=0.001 for PCS; N.S. for MCS
Urine CTX-1	Mean absolute change from baseline to Visit 4 for NP01 group 67.8 µg/mmol creatinine vs. 162.3 µg/mmol creatinine for PLO (observed case)	N.S.

Efficacy Conclusions:

Treatment of RA patients with NP01 resulted in a significantly higher ACR20 response rate (47%) as compared to placebo (29%) after 12 weeks of therapy. This result is expected given the known efficacy of prednisone in the treatment of RA. Patients treated with NP01 also experienced a relative decrease over baseline in the duration of morning stiffness of approximately 20 minutes compared to placebo patients which was also statistically significant. However, both the validity and clinical meaningfulness of this key secondary endpoint finding are questionable in view of the lack of information necessary to support the reliability and construct validity of this patient reported outcome (PRO) and the overall decrease in the magnitude in morning stiffness observed in this trial. The majority of the other secondary endpoints assessed in this study trended in favor of NP01 therapy, but declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate due to multiplicity concerns.

5.3.2 EMR 62215-003

Title: A New Timed-Released Tablet Formulation of Prednisone Compared to Standard Prednisone in Patients with Rheumatoid Arthritis (Prednisone TRT Study) – A Randomized, Multicenter, Double-Blind, Active Controlled Study with an Open Extension on the New Drug Only

Dates Conducted: The double-blind portion of this trial was started on August 4, 2004 and completed on April 6, 2006. The open label extension was started on November 3, 2004 and completed January 5, 2007.

Objectives:

Primary Objective (double-blind portion):

- To evaluate the superiority of the new timed-release tablet formulation of prednisone (for administration in the evening) to standard morning administration of prednisone in reducing duration of morning stiffness

Secondary Objectives (double-blind portion):

- To compare the two prednisone formulations on all standard parameters for the assessment of RA in a 3 month, double-blind study phase
- To demonstrate maintained efficacy and safety

Objectives for OLE portion:

- To demonstrate maintained efficacy and safety over 9 months of open-label treatment with NP01

Overall Design:

This Phase 3 study was to have been conducted in 2 parts. The first portion was to have been a 3-month, multicenter, randomized, double-blind, double-dummy, actively controlled, parallel-group study that evaluated the efficacy and safety of 3-10 mg daily doses of NP01 when administered in the evening versus 3-10 mg daily doses of immediate release (IR) prednisone administered in the morning to approximately 280 patients with RA on concomitant DMARD therapy. It was to have been followed by a 9-month, open-label extension that evaluated the long-term safety of NP01. A small subgroup study in 32 patients was to have been conducted concurrently that evaluated adrenocortical function in subjects over the course of the study. The overall duration of the entire trial was to have been 2 years. The duration of participation for each patient was to have been 1 year which included the 3-month double-blind phase and the 9-month open label extension. As apart of the 1-2 screening process for this trial, eligible study candidates were to have completed a minimum of 7 days of diary recordings regarding their daily duration of morning stiff and pain intensity in order to generate baseline disease data necessary for study entry.

Patients who successfully completed the screening process were to have been randomized via 1:1 ratio to treatment with either 3-10 mg daily dose of NP01

administered in the evening or 3-10 mg daily dose of IR prednisone administered in the morning. Due to the double-dummy medication blind, the protocol mandated that all subjects had to take study medication twice daily (e.g., in the mornings and evenings).

Subjects who completed the double-blind portion of the trial and did not develop any exclusion criteria during the double-blind portion of the trial were eligible to continue receiving treatment with NP01 in the open-label extension.

Patients (n=16 subjects per treatment group) who gave consent to participate in the concurrent adrenocortical function subgroup study were to have undergone CRH-stimulation testing at screening, upon completion of the 3-month double-blind treatment and at the end study.

Major Inclusion Criteria:

Subjects were to have met the following criteria:

- Aged 18 to 80 years
- Documented history of RA (sero-negative or sero-positive) in agreement with the ACR criteria, including the symptoms morning stiffness, joint pain, tender and swollen joints, inflammatory state with elevated ESR or CRP
- Symptomatic status required for inclusion:
 - a. Morning stiffness of ≥ 45 minutes (average daily duration during the last 7 days of the screening period prior to randomization)
 - b. Intensity of pain on VAS of ≥ 30 mm (average of daily maximum scores during the last 7 days of the screening period prior to randomization)
 - c. Swollen joint count ≥ 3
 - d. Tender joint count ≥ 1
 - e. Signs of inflammatory processes, i.e., ESR ≥ 28 mm (1st hour) and/or CRP ≥ 1.5 times above the normal age- and sex-related range
- On DMARD treatment for at least 3 months. Patients with prednisone/prednisolone therapy alone could be included into the study (if DMARDs previously not tolerated)
- On stable doses of DMARDs for at least 1 month (or no DMARDs if not tolerated)
- On corticoid medication for at least 3 months
- With stable doses of ≥ 2.5 and ≤ 10 mg prednisone/prednisolone per day for at least 1 month (methylprednisolone doses were converted into prednisone doses as follows: prednisone dose = methylprednisolone dose x 1.25)

Exclusion Criteria:

Potential trial candidates were to have been prohibited from participating in either portion of this trial if any of the following criteria applied:

1. Suffered from another disease, which required glucocorticoid treatment during the study period, e.g., asthma, neurodermatitis
2. Synoviorthesis within 4 months prior to study start

3. Crystalloid injections into joints within the last 4 months prior to start of the study
4. Parenteral treatment with corticoids within the last 4 months prior to the start of the study
5. Use of biologicals within last 4 months prior to start of the study
6. Requirement of non-permitted concomitant medication
7. Known hypersensitivity to prednisone or prednisolone
8. Presence of a contra-indication to corticoids, e.g., established new osteoporotic fractures, florid ulcers in the GI-tract during the previous 2 months, history of corticoid psychosis, herpes simplex and herpes zoster infection (viremic phase)
9. Pregnancy or nursing
10. Participated in another clinical study (use of an investigational product) within 30 days
11. Significant renal impairment (serum creatinine >150 µmol/L)
12. Significant hepatic impairment based on investigator's opinion
13. Significant concomitant disease which would exclude the subject from the study in the investigator's opinion

Treatment:

Study medication (NP01) and active comparator (Decortin IR prednisone) to have been used in this trial consisted of two dose strengths, i.e. 1-mg and 5-mg tablets. Matching placebo tablets for both NP01 and Decortin were to have been also used in order to comply with the double-dummy blind. During the screening phase, patients continued to take their stable daily doses of glucocorticoids with their concomitant DMARD therapy. Following randomization, individual dosages of study glucocorticoids were adjusted to subjects' pre-study dosage by using the required amount of 1-mg and 5-mg tablets of NP01 or IR prednisone (Decortin). However, patients who were taking 2.5 mg or 7.5 mg of prednisone at study entry were given 3 mg or 7 mg of study medication. All study medications were to have been taken twice daily in the morning (between 6 and 8 AM) and in the evening (between 9:00 and 11:00 PM) with or after a light meal and swallowed whole (unchewed and unbroken) with sufficient liquid. In the event that more than 2-3 hours had passed since the evening meal, patients were instructed to take the study tablets with a light meal or snack. No changes in study medication dose were permitted during the 12-week double-blind portion of the trial.

During the OLE portion of the trial, all patients were to have continued taking the same dose of NP01 in the evening after a light meal as they did during the double-blind part of study. Partial dose reductions were permitted during this phase.

Rescue Medications:

In the event of an acute exacerbation of pain, the protocol permitted patients to use a non-anti-inflammatory analgesic such as acetaminophen/paracetamol as rescue medication. Subjects were required to record the use of all rescue medication in their study diaries.

Concomitant Medications:

The protocol permitted the concomitant use of DMARD therapy that had been administered at stable doses for at least 1 month prior to the study. In addition to continuing their stable doses of DMARDs therapy, patients were also allowed to continue taking stable doses of NSAIDs and participate in physical therapy provided that either of these treatment modalities had been started prior to entering the trial. The use of all other medications as treatment for concomitant diseases was permitted as long as their dosages remained stable throughout the study.

Use of the following concomitant treatments by patients was prohibited while participating in the trial:

- Glucocorticoids other than the study medication
- Intra-articular injections, synoviorthesis and cryotherapy
- Biologicals

Removal of Patients from Treatment or Assessment:

Patients were to have been withdrawn from the study if they withdrew consent, developed an exclusion criterion which was clinically relevant and affected the subject's safety, if discontinuation was considered necessary by the investigator or sponsor, were a therapeutic failure requiring urgent additional medication, developed an AE, became pregnant, unblinding of study drug occurred, or were repeatedly (more than once) unreliable in keeping study appointments, i.e., > 3 days during double-blind phase, >1 month behind schedule in the open follow-up phase of the study.

Study Procedures:

The following Table 22 and Table 23 are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations for both portions of this trial:

Table 21 - Schedule of Procedures and Evaluations for Double-Blind Portion of Study EMR62215-003

PROCEDURES	schedule of procedures during double-blind phase				
	visit 1	visit 2	visit 3	visit 4	visit 5
weeks	-1(2)	0	2	6	12
	screening	baseline			end db
informed consent	x				
medical history*	x				
entry criteria	(x)	x			x (FU)
physical examination	(x)	x			x
check diary		x	x	x	x
Physician's Global assessment	x	x	x	x	x
Disease Activity Score (DAS)**	x	x	x	x	x
Health Assessment Questionnaire (HAQ)	x	x			x
Quality of Life (SF36)		x			x
ESR** and CRP	x	x	x	x	x
safety laboratory**** + hematology + IL-6	x				x
adrenocortical function (CRH-test)***	x				x
collect diary visit set		x	x	x	x
dispense medication		x		x	x (FU)
collect medication / pill count				x	x (db)
adverse events	x	x	x	x	x
changes of concomitant medication	x	x	x	x	x

* including documentation of previous treatments and concomitant medication

** all factors needed to calculate DAS, including swollen and tender joint counts, patient's global assessment of disease activity

*** to be assessed in a subset of subjects only (after Screening and before Visit 2 and 1 day after Visit 5)

**** safety laboratory also includes urinalysis

FU = Follow-up, db = double-blind

Sponsor's Table 9.2; p. 56 of Clinical Study Report

Table 22 - Schedule of Procedures and Evaluations for OLE for Study EMR62215-003

PROCEDURES	Schedule of procedures during open follow-up phase			
	Visit 5	Visit 6	Visit 7	Visit 8
Month	0 (Start of Follow-up)	3	6	9 (End of study)
Entry criteria	x			
Physical examination	(x)			x
Morning stiffness, diary	(x)	x	x	x
Pain score (VAS), diary	(x)	x	x	x
Physician's Global Assessment	(X)	x	x	x
Disease Activity Score (DAS)*	(x)	x	x	x
Health Assessment Questionnaire (HAQ)	(x)	x	x	x
Quality of Life (SF36)	(x)			x
ESR** and CRP	(x)	x	x	x
Safety laboratory*** + hematology	(x)			x
Adrenocortical function (CRH test)**	(x)			x
Collect diary	(x)	x	x	x
Dispense medication, TRT only	x	x	x	
Collect medication / pill count	(x)	x	x	x
Adverse Events	(x)	x	x	x
Changes of concomitant medication	(x)	x	x	x
Complete end-of-study procedures				x

* all factors needed to calculate DAS, including swollen and tender joint counts, patient's global assessment of disease activity

** to be assessed in a subset of subjects and in additional subjects of the German centers at Visit 8 only (Amendment No.1)

*** safety laboratory also includes IL-6 and urinalysis

(x) as part of double-blind phase

Sponsor's Table 9.2; p. 49 of Clinical Study Report

Outcome Measures:

The following efficacy assessments were to have been performed:

Primary efficacy endpoint:

The primary efficacy endpoint was to have been the comparison of the relative change (%) in the duration of morning stiffness between baseline and Visit 4 (Week 12) for NP01 versus IR prednisone. Data for this nonvalidated endpoint was to have been obtained from patients' diary cards which contained the following questions concerning stiffness: waking up time, stiffness of joints (yes/no), and time of resolution of morning

stiffness. Duration of morning stiffness was the difference between the time of resolution of morning stiffness and the time of wake-up.

Secondary efficacy endpoints:

This study had a number of secondary endpoints defined as follows:

- Morning stiffness in terms of mean daily duration (minutes) per week: This endpoint was to have been generated in a similar manner as the primary endpoint based on data captured in patients' diary cards, however, it was calculated on a weekly basis compared to baseline.
- Change from baseline in terms of reoccurrence of stiffness during day (while performing routine activities): Every evening during the treatment phase, patients were to record in their diaries if they had reoccurrence of stiffness (yes/no). Reoccurrence of stiffness during the day was assessed as the percentage of days with reoccurrence of stiffness over the last 7 days prior to each visit (if 4 or more responses were missing, the percentage was set to missing)
- Change in mean daily pain intensity (100 mm VAS): Patients were to have assessed their maximum pain intensity during the day via a 100 mm VAS (0=no pain and 100 mm = very intense pain) every evening. This information was to have been recorded in their patient diary card. This assessment was to have been computed as the change in percentage of occurrence of pain over the last 7 days prior to each visit (if 4 or more responses were missing, the percentage was set to missing).
- Change from baseline to Week 12 in patient assessment of the pain intensity: In addition to performing a daily pain assessment, subjects were also required to assess their pain via a 100 mm VAS (0=no pain and 100 mm = very intense pain) at the end of the double-blind phase.
- Quality of sleep in terms of mean daily VAS quality of sleep score per week: This was assessed by patients every morning via a 100 mm VAS (0= very good and 100= very bad) and recorded in their dairy cards. .
- Change from baseline in the use of additional analgesics: Patients were to have recorded in their diary cards the use of analgesics over the last 24 hours (yes/no). Positive responses also required recording the type, dose and time the analgesic was taken by subjects in their diaries. This endpoint was computed as the change from baseline in percentage of days with the event over the last 7 days prior to each visit (if 4 or more responses were missing, the percentage was set to missing).
- Change from baseline in DAS28 at each visit: The DAS28 score is another validated, regulatory standard endpoint commonly used by foreign regulatory authorities to assess efficacy of treatments in RA trials. It is a composite index score comprised of the number of tender and swollen joints based on a 28 joint count, an acute phase reactant (e.g., ESR or CRP), and the patient's global disease assessment based on a 100 mm VAS. Its score is calculated via a standardized formula and ranges from 0-10 with higher scores consistent with higher disease activity.

- Change from baseline in physician's global assessments of disease activity at each visit: At each study visit, the investigator was required to assess the patient's overall disease activity via a 100 mm VAS (0=no disease activity and 100 mm = high disease activity).
- Patient Reported Outcome (PRO) - Two patient reported health-related quality of life assessment tool were to have been evaluated:
 - Change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) at each visit: This is a validated, self-reported functional status instrument that was used to measure disability over the 12-weeks of the treatment phase as assessed by 8 domains of functionality. The highest scores from the 8 domains (range: 0-24) are summed and divided by 8 to yield a Functional Disability Index (range: 0-3 with higher scores indicative of increased functional disability). Subject's global well being and pain severity were to have also been evaluated via a 100 mm VAS.
 - Change from baseline in each domain of the Short Form (SF-36) Health Status Survey and for the mental and physical component scores: The SF-36 is a validated, 36-item, self-reported questionnaire comprised of 8 subdomains that was used to calculate the 2 summary scores: physical component summary (PCS) and mental component summary (MCS). Average scores in healthy normal population age 55-64 for males and females combined are 47 for PCS and 52 for MCS. Higher scores represent better mental and physical quality of life.
- Inflammatory parameters - Three inflammatory parameters were to have been assessed at each visit and were to have been compared to baseline levels:
 - CRP, IL-6 and osteocalcin: CRP and IL-6 levels were to have been analyzed from patients' blood and serum samples collected in the morning following ingestion of the morning dose of study medication.

Statistical Design, Definitions of Analyzed Populations and Analysis Plan:

Sample Size Calculations

With a projected enrollment of 280 patients randomized via 1:1 (NP01 n=140 subjects; active comparator n=140 subjects) this study was to have approximately 90% power to show a 27% difference in the relative change in morning stiffness between the two treatment groups using a one-sided test at a significance level of 0.025. A protocol mandated interim sample size adjustment based on review of blinded data generated conducted when 50% of the subjects had completed the study resulted in no adjustment in the study's sample size.

Study Populations

Three populations were to have been used for analysis. They were defined as follows:
1. **Intention-to-Treat (ITT) Population**: was defined as all randomized subjects as randomized. The ITT was to have been used to assess all efficacy endpoints.

2. Per-Protocol (PP) Population: was defined as all randomized patients as randomized who had been treated according to the protocol, treated with study medications, and fulfilled the following criteria:

- Morning stiffness at baseline was not missing and \geq 45 minutes in duration
- Duration of treatment was 12 weeks +/- 3 days (e.g., 12 weeks data of morning stiffness available)
- Time of intake of evening medication was between 9:00 and 11:00 PM (a deviation from this time window was allowed for a maximum of 7 days during the double blind phase)

3. Safety Population: was defined as all randomized subjects who took at least one dose of study drug of the study medication they actually received. The safety population was used for all safety analyses.

The statistical analysis plan (SAP) submitted on May 24, 2006, stipulated that the primary efficacy analysis was to have been the only confirmatory result of statistical testing and the secondary variables were purely exploratory. The efficacy analysis for the primary endpoint was to have been conducted on the ITT population via ANOVA with treatment and site as factors. Sensitivity analyses for this endpoint were to have been performed on the PP population. Missing data was to have been imputed via LOCF.

The exploratory secondary endpoint of mean daily VAS quality of sleep score per week was to have been analyzed using the same ANOVA model used for the primary endpoint. Analysis of covariance (ANCOVA) with treatment and sites as factors and the relevant baseline score as a covariate was to have been used to analyze the other exploratory secondary endpoints. All secondary endpoint analyses were to have used LOCF to account for missing data.

Safety Evaluation:

The analysis of safety assessment was to have been conducted on the safety population. Safety assessment was to have included treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), clinical lab data, physical exam findings and vital signs. All TEAEs were to have been coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 11.0). The incidences of TEAEs were to have been summarized by system organ class (SOC) and preferred term by overall and treatment group. If a subject reported the same AE more than once that event was to be counted only once using the most severe intensity.

Clinical lab data results for hematology, serum chemistry and urinalysis testing as well as changes in vital signs and physical exam were to have been reviewed and summarized for within treatment changes and for changes from baseline for each treatment group. Additionally, shift tables on changes from the normal ranges for lab assessments were to have been created.

Study Conduct:

Listed below are the two protocol amendments to Study NP01-007:

1. Amendment 1 (implemented on September 29, 2005)

- Due to slow recruitment at the original 4 German sites conducting the adrenal cortical subgroup test, an additional optional CRH-test was included for study subjects at German sites who did not participate in the original CRH-test subgroup

2. Amendment 2 (implemented on November 29, 2005)

In addition to minor editorial changes to the study protocol the following changes were made:

- Increased the number of study sites in Germany from 16-20 to 25 and in Poland from 4-6 to 14 sites
- Inclusion criteria were amended to permit the enrollment of DMARD intolerant subjects who are receiving stable doses of prednisone as the sole treatment for RA
- Exclusion criteria were changed to exclude subjects requiring concomitant treatment with biological agents or who have received treatment with a biological agent within the preceding 4 weeks prior to study enrollment
- Clarification of the instructions for emergency code breaks.
- Addition of a conversion chart to switch patients taking methylprednisolone to prednisone
- Clarification regarding the prohibition of biologicals during the double-blind phase
- Clarification that the results of the baseline assessments for CRP, IL-6 and osteocalcin were not going to be shared with investigators
- Clarification of the central lab's responsibilities (e.g., responsible for all lab tests except ESR, hematology and urinalysis)
- Clarifying information regarding the handling of patient diaries by investigators
- Patients who do not fulfill the required criterion for CRP/ESR at study entry can be enrolled if reassessment at Visit 2 confirmed inflammatory state
- Changes in the responsibilities of the clinical study team

Study Results:

Disposition:

This study was conducted at 29 centers located in Europe: 17 centers in Germany and 12 centers in Poland. Of the 375 potential patients screened for this study, 61 did not meet entry criteria, 7 withdrew consent, 6 failed to meet screening criteria due to other reasons, 1 experienced an adverse event during screening, and 12 were listed as missing. A tabular summary of subjects' disposition for Study NP01-007 is shown in Table 23. Overall, the rate of study completion during the double-blind portion was higher in the IR prednisone treatment group (90%) as compared to the NP01 treatment group (84%). The most common reason for early study withdrawal in both treatment

groups during this phase was withdrawal of consent which was higher in the NP01 treatment group (6%) as compared to the IR prednisone group (2%) followed by AE which was similar for the both treatment groups (3% and 2%, respectively).

Table 23 –Subject Disposition for Study EMR62-215-003

Double-Blind Portion	NP01	IR Prednisone	Total
Number of Patients Randomized	144	144	288
Number of Patients Who Completed Visit 4	121 (84%)	130 (90%)	251(87%)
Number of Patients Withdrawn Prematurely	23(16%)	14 (10%)	37 (13%)
Adverse Event	4 (3%)	3 (2%)	7 (2%)
Withdrawal of Consent	8 (6%)	3 (2%)	11 (4%)
Inclusion/exclusion Criteria	1 (<1%)	0 (0%)	1 (<1%)
Lack of Efficacy	1 (<1%)	0 (0%)	1 (<1%)
Other Reason(s)	0 (0%)	1 (<1%)	1 (<1%)
Open-Label Follow-Up Portion			NP01
Number of Patients Enrolled in Open-Label Follow-Up			249 (100%)
Number of Patients Who Completed Open-Label Follow-Up			219 (88%)
Number of Patients Withdrawn Prematurely from Open Label Follow-Up			20 (12%)
Adverse Event			12 (5%)
Took a Prohibited Concomitant Medication			1 (<1%)
Insufficient Efficacy			5 (2%)
Other Reason			1 (<1%)
Protocol Violation			1 (<1%)
Withdrawal of Consent			10 (4%)

Modified Sponsor's Tables 10.2 and 10.2; p. 70-71 and Tables 10.1 and 10.2 p. 59-60 of the Clinical Study Reports

A total of 219 subjects who completed the double-blind portion enrolled in the open-label extension out of which 88% completed 9-months of open-label treatment (Table 23). The reasons and rates for premature withdrawal of subjects from the open-label extension were similar to that observed in the double-blind portion.

Protocol Deviations:

Major protocol deviations were defined by the Applicant as those that were likely to affect the validity of the data for the duration of morning stiffness (primary endpoint of the double-blind phase). The major protocol deviations leading to exclusion from the PP population are summarized in Table 24. A total of 135 randomized patients incurred one or more protocol deviations over the course of the double-blind portion of the trial. As shown in Table 24, the rate of protocol violations was higher in the NP01 treatment group (52%) as compared to the IR prednisone treatment group (42%). The most common major protocol deviation for this part of the study was due to the duration of treatment was out of range (outside 84 ± days). According to the Applicant this category also included 37 subjects who withdrew prematurely from the study (23 patients from the NP01 treatment group and 14 from the IR prednisone group) as well as subjects who shifted their Visit 5 to earlier or later dates without violation of medication

compliance or due to an adverse event. Too short a duration of morning stiffness (<45 minutes) (14%) was the next most common reason for a major protocol violation followed by timing of evening medication out of range (patient failed to take it between 9:00 and 11:00 PM) (13%).

Table 24 - Summary of Subjects with Major Protocol Deviations Enrolled in Study EMR62-215-003

Type of Protocol Deviation	Number (%) of Patients		
	NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Patients With at Least 1 Major Deviation	75 (52%)	60 (42%)	135 (47%)
Duration of Treatment Out of Range^a	47 (33%)	40 (28%)	87 (30%)
Morning Stiffness at Baseline Too Short (< 45% min.)	23 (16%)	18 (13%)	41 (14%)
Timing of Evening Medication Out of Range^b	21 (15%)	15 (10%)	36 (13%)

Subjects might have had more than one major protocol violation. The numbers include subjects who dropped out.

^aOutside 84 ± 3 days.

^bNot between 9:00 and 11:00 PM

Modified Sponsor's Table 9; p. 80 Clinical Study Report

Protocol violations were not applicable to the open-label extension of this trial.

Demographics:

Table 25 summarizes the demographic characteristics of the ITT population who participated in this trial. Subjects treated with NP01 were demographically similar to those who received IR prednisone during this study. The patients who participated in this study had a mean age of 55 years and were overwhelmingly female (86%) and Caucasian. There was a poor representation of other racial groups due to the geographic location of the study sites (e.g., Europe).

Table 25 – Baseline Demographic Characteristics of Subjects Enrolled in Study EMR62-215-003 (ITT Population)

Characteristic	NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Age (years): Mean (SD)	55 (11)	55 (10)	55 (11)
Age Category:			
Young (≤ 45 years)	26 (18%)	23 (16%)	49 (17%)
Middle-aged (>45 to ≤ 65 years)	93 (65%)	92 (64%)	185 (64%)
Elderly (>65 to ≤ 75 years)	23 (16%)	26 (18%)	49 (17%)
Very Elderly >75 years	2 (1%)	3 (2%)	5 (2%)
Gender:			
Female	125 (87%)	122 (85%)	247 (86%)
Male	19 (13%)	22 (15%)	41 (14%)
Race:			
White	143 (99%)	144 (100%)	287 (100%)
Black	0	0	0
Asian	1 (1%)	0	1(0%)
Weight (kg) Mean (SD)	70 (13.5)	72 (16)	71 (15)
Height (cm) Mean (SD)	163 (7)	164 (8)	163 (8)

SD= standard deviation;

Adapted Sponsor's Table 11.2; p. 74 Clinical Study Report

The demographic characteristics of the 249 patients who continued treatment in the open-label phase of this trial were similar to those observed in the double-blind portion of the trial. Table 26 is a tabular summary of subjects' RA history and disease status. The mean duration of RA disease was 115 months for the double-blind study population. The two treatment groups were balanced in terms of baseline disease activity as assessed by a number of parameters. Overall, the study population enrolled in this trial was representative of patients with moderate to severe RA who could potentially benefit from treatment with NP01. The disease characteristics of patients who enrolled in the open-label study were comparable to those of the double-blind portion.

Table 26 – Summary of RA Disease Activity at Baseline for Subjects Enrolled in Study EMR62-215-003 (ITT Population)

Disease Characteristic		NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Prednisone dose (mg)		6.7	6.7	6.6
Duration of RA (months): Mean (SD)		115	115	115
<2 years		19 (13%)	18 (13%)	37 (13%)
≥2 years to <5 years		37 (26%)	37 (26%)	74 (26%)
≥5 years to <10 years		33 (23%)	31 (22%)	64 (22%)
≥10 years		55 (38%)	58 (40%)	113 (39%)
DAS28: Mean (SD)		5.8 (0.8)	5.9 (0.9)	5.9 (0.8)
Range		3.3-81	3.7-7.7	3.3-8.1
Physician's Assessment of Disease Activity (mm VAS):				
Asymptomatic		0	0	0
Mild		13 (9%)	14 (10%)	27 (9%)
Moderate		103 (72%)	102 (71%)	205 (71%)
Severe		28 (19%)	28 (19%)	58 (19%)
Very Severe		0	0	0
Patient's Assessment of Arthritis Pain Intensity (mm VAS):				
Mean (SD)		58 (14.8)	59.7 (15.8)	58.8 (15.3)
Range		18-95	25-96	18-96
HAQ-DI score: Mean (SD)		1.5 (0.6)	1.5 (0.5)	1.5 (0.50)
Range		0-2.9	0-2.8	0-2.9
SF-36:				
Reported Health Transition:	Mean (SD)	58 (26)	61 (25)	60 (25)
	Range	0-100	0-100	0-100
Physical Functioning:	Mean (SD)	40 (19)	43 (22)	42 (21)
	Range	0-90	0-100	0-100
Role Physical:	Mean (SD)	15 (29)	17 (31)	16 (30)
	Range	0-100	0-100	0-100
Role Emotional:	Mean (SD)	39 (45)	40 (45)	39 (45)
	Range	0-100	0-100	0-100
Social Functioning:	Mean (SD)	56 (24)	55 (24)	55 (24)
	Range	0-100	0-100	0-100
Bodily Pain:	Mean (SD)	31 (13)	29 (14)	30 (13)
	Range	0-64	0-72	0-72
Vitality	Mean (SD)	42 (14)	41 (16)	42 (15)
	Range	15-95	5-85	5-95
Mental Health	Mean (SD)	58 (17)	58 (17)	58 (17)
	Range	20-96	20-100	20-100
General Health	Mean (SD)	36 (16)	36 (14)	36 (15)
	Range	5-75	0-77	0-77

SD= standard deviation Adapted Sponsor's Table 11.3.1 and 11.3.2; p. 75-76 of Clinical Study Report

Besides a high rate of hypertension (38%), the study population reported high rates of co-morbid medical conditions such as osteoporosis (18%), obesity (10%), goiter (7%) and synovectomy (7%) which were reasonably balanced between the two treatment groups (Table 27). Some of these co-morbid conditions (e.g., local osteoarthritis, osteoarthritis, spinal osteoarthritis and hypothyroidism) could potentially confound the study's overall findings as since they are also associated with stiffness and pain.

Table 27 – Summary of Co-Morbid Medical Conditions Reported by > 10% of Subjects Enrolled in Study EMR62-215-003 (ITT Population)

Preferred Term	NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Hypertension	52 (36%)	57 (40%)	109 (38%)
Osteoporosis	24 (17%)	29 (20%)	53 (18%)
Obesity	15 (10%)	14 (10%)	29 (10%)
Goiter	13 (9%)	8 (6%)	21 (7%)
Synovectomy	11 (8%)	9 (6%)	20 (7%)
Localized Osteoarthritis	11 (8%)	8 (6%)	19 (7%)
Hypothyroidism	10 (7%)	8 (6%)	18 (6%)
Varicose Vein	10 (7%)	8 (6%)	18 (6%)
Hypercholesterolemia	9 (6%)	18 (13%)	27 (9%)
Thyroidectomy	9 (6%)	7 (5%)	16 (6%)
Osteoarthritis	8 (6%)	7 (5%)	15 (5%)
Spinal Osteoarthritis	7 (5%)	12 (8%)	19 (7%)
Knee Arthroplasty	7 (5%)	9 (6%)	16 (6%)

Medical history was coded via MedDRA Preferred Term
 Modified Sponsor's Table 11.4; p. 77 Clinical Study Report

The protocol mandated that patients were to continue taking stable doses of concomitant RA medications over the course of the study to treat their underlying disease. This information regarding baseline use of concomitant RA medications is summarized in Table 28. Overall, the use of concomitant RA medications was similar for the two treatment groups. The most commonly used RA medications by the study population were DMARDs (94%) and NSAIDs (80%). Sixteen patients who participated in this trial did not take concomitant DMARDs due to intolerance to these agents. Overall the use of concomitant baseline RA medications was similar between the two groups. No changes were observed in the concomitant medications taken by patients who enrolled in the open-label extension.

Table 28 – Summary of Concomitant RA Medications Taken at Baseline for Subjects Enrolled in Study EMR62-215-003 (ITT Population)

Drug Category	NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Patients Taking Any Concomitant Medication	144 (100%)	143 (99%)	287 (100%)
DMARDs	133 (92%)	139 (97%)	272 (94%)
NSAIDs	118 (82%)	113 (79%)	231 (80%)
Analgesics:	55 (38%)	52 (36%)	107 (37%)
Other RA Medication^a	106 (74%)	101 (70%)	207 (72%)
Other Medications for Treatment of non-RA Diseases	116 (81%)	22 (85%)	238 (83%)

Note: If a subject had more than one medication within a WHO Preferred Term class, the subject was counted once in that class.

Includes bisphosphonates, risedronic acid, calcium supplements, folate, minerals and vitamins

Adapted Sponsor's Table 111.5; p. 78 Clinical Study Report.

The protocol prohibited the initiation of medications that could potentially confound the study's results. As shown in Table 29, there was very little change in the concomitant medications taken during this trial by subjects as compared to baseline (refer to Table 28).

Table 29 – Relevant Concomitant RA Medications Taken During Study EMR62-215-003 (ITT Population)

Drug Category	NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Patients Taking Any Concomitant Medication	122 (85%)	113 (79%)	237 (82%)
DMARDs	133 (92%)	139 (97%)	272 (94%)
NSAIDs	120 (83%)	114 (79%)	234 (81%)
Analgesics:	69 (48%)	64 (44%)	133 (46%)
Other RA Medication	110 (76%)	101 (70%)	211 (73%)
Other	118 (82%)	126 (88%)	244 (85%)

Note: If a subject had more than one medication within a WHO Preferred Term class, the subject was counted once in that class.

Adapted Sponsor's Table 11.6 p. 79 Clinical Study Report.

Treatment Compliance:

The protocol specified that patients' compliance with study medication was to have been assessed by their diary recordings and tablet counts performed on the returned blinded study medication. Subjects were also directly queried by the trial investigators regarding the time they ingested their study medication. Table 30 below, summarizes the results of tablet counting to assess patient compliance with study medication. Compliance could not be calculated for one patient in the placebo group (Subject 22-10) as the date of the last dose intake was missing since the patient was lost to follow-up.

Overall, the study population's compliance with medication was 99.9% and was balanced between the two treatment groups. A higher percentage of subjects in the NP01 group took their evening dose outside the permitted time period as compared to subjects in the prednisone IR group. Similarly, a high rate of compliance with study medication was also observed in the open-label extension.

Table 30 – Summary of Compliance with Study Medication for Study EMR62-215-003 (ITT Population)

	NP01 (N=144)	IR Prednisone (N=144)	Total (N=288)
Morning Compliance	98%	99%	99.9%
Evening Compliance	98%	98%	98%
Morning Dose (IR Prednisone)			
<80%	9 (6%)	5 (4%)	14 (5%)
≥80% to ≤120%	131 (91%)	132 (92%)	263 (91%)
>120%	3 (2%)	5 (4%)	8 (3%)
Evening Dose (NP01)			
<80%	5 (4%)	7 (5%)	12 (4%)
≥80% to ≤120%	136 (95%)	132 (92%)	268 (93%)
>120%	2 (1%)	3 (2%)	(1%)
Intake of Study Medication Outside of the Permitted Time Range for Evening Intake (10:00 ± 30 minutes)			
Week 2	28 (20%)	21 (15%)	49 (17%)
Week 6	23 (18%)	14 (10%)	37 (13%)
Week 12	22 (19%)	18 (14%)	40 (14%)

Modified Sponsor's Tables 11.7 and 14.3.2.2 from the Clinical Study Report

Efficacy:

Primary Efficacy Results

IN EMR 62215-003, the primary endpoint was the relative change in the duration of morning stiffness after 12 weeks of treatment. Table 31 shows both the results of this analysis on the ITT population and the PP population. Although the difference in the relative change in duration of morning stiffness was shown to be statistically different for the two treatment groups based on the ITT population analysis, the results based on the PP population were less robust as the result of the impact from the high percentage of protocol violations affecting this outcome.

Table 31 – Analysis of the Relative Change in Duration of Morning Stiffness (Primary Endpoint) and Sensitivity Analyses Results for Study EMR 62215-003

Duration of Morning Stiffness at Week 12 (ITT Population)						
Imputation Scheme	Relative Change (%)				Treatment Difference LS Mean (SE) [%] Lower Limit of 95% CI	P-value (one-sided)
	NP01		Decortin			
	N	Median	N	Median		
LOCF	125	-22.66	129	-0.39	22.4 (11.1) 0.493	0.0226
Duration of Morning Stiffness at Week 12 (Per Protocol Population)						
LOCF	69	-22.65	84	-1.43	21.2 (15.2) -8.79	0.0822

LS = Least square; SE = standard error

Note: The statistical tests were performed two-sided at a significance level of 5%. One-sided p-values were transformed from the two-sided p-values.

Other Secondary Efficacy Endpoints:

There were multiple exploratory secondary endpoints analyzed for this trial which are summarized in Table 29 below. The analyses of these endpoints were conducted using LOCF imputation for missing data unless otherwise noted.

Table 32 – Tabular Summary of Secondary Endpoint Analyses for Study EMR 62215-003

Secondary Efficacy Variable	Comment
Patient’s Assessment of Pain	Mean pain score decreased over time in the NP01 group to -22.1 mm at Visit 4; Mean pain score for PLO group did not decrease until later in the trial (Visit 3) and was -11.4 mm at Visit 4
Additional Analgesics	Mean number of days with additional analgesics over the 12 weeks of the trial was comparable (NP01: 14 days vs. PLO 15 days)
Quality of Sleep	Relative change from baseline score in NP01 group at Visit 5 was 2.84 vs. -3.62 for prednisone IR group
Mean Daily Quality of Sleep	Relative change from baseline score in NP01 group at Visit 5 was 4.63 vs. 0.13 for prednisone IR group
DAS28	Relative change from baseline score in NP01 group at Visit 5 was -9.02 and was comparable vs. -12.3 for prednisone IR group
Tender Joint Count	Relative change from baseline at Visit 5 for NP01 group was -12.5 and was comparable vs. -15.2 for prednisone IR group
Swollen Joint Count	Relative change from baseline at Visit 5 for NP01 group was -17.7 and was comparable vs. -16.2 for prednisone IR group
ESR	Relative change from baseline to Visit 5 for NP01 group -5.6 mm vs. -20.5 mm for prednisone IR
Patient’s Global Assessment of Disease Activity	Relative change over baseline score at Visit 5 of -9.1 mm for NP01 group vs. -15.0 mm for the prednisone IR group
Physician’s Global Assessment of Disease Activity	Mean change over baseline score at Visit 4 of -23.5 mm for NP01 group vs. -13.2 mm for the prednisone IR group
HAQ-DI score	Relative change from baseline score at Visit 5 for NP01 group was -0.1 vs. -4.7 for prednisone IR group.
SF-36	Use of non-validated Polish translation precluded analysis of data collected
CRP	Relative change from baseline to Visit 4 for NP01 group 2.4 mg/L vs. 0 mg/L for prednisone IR group
IL-6 levels	Relative change in IL-6 levels at Visit 4 in NP01 group -28.6 vs. 0.0 prednisone IR group
Osteocalcin	Relative change from baseline to Visit 5 for NP01 group -1.7 vs. 3.9 prednisone IR group (observed case)
ACR20	The percentage of patients who achieved an ACR20 response at Visit 5 for the NP01 group (15%; 21 subjects) was comparable to the prednisone IR group (17%; 25 subjects)

Efficacy Conclusions:

Treatment of RA patients with NP01 resulted in a relative decrease over baseline in the duration of morning stiffness of approximately 22 minutes compared to placebo patients which was statistically significant. However, both the robustness and validity of these findings are questionable after accounting for the large percentage of protocol violations (47%) that occurred over the course of this trial as well as the lack of information necessary to support the reliability and construct validity of this patient reported outcome (PRO). The overall decrease in the magnitude in morning stiffness observed in this trial may not be representative of a clinically meaningful outcome. The other secondary endpoints assessed in this study were designated as exploratory in nature and resulted in comparable outcomes for both NP01 and prednisone IR for a majority of these assessments.

6 Review of Efficacy

Efficacy Summary

While originally proposed for only an RA indication, the CMC and clinical pharmacology data support the use of NP01 for the full range of other indications currently approved for the reference immediate-release prednisone.

The clinical data submitted in support of NP01 for the treatment of RA in adult patients was generated from one Phase 3 trial, NP01-007. This was an international, multicenter, randomized, double-blind, placebo-controlled parallel group study in approximately 294 patients with RA on concomitant DMARD therapy that evaluated the efficacy and safety of low dose (≤ 5 mg/day) NP01 therapy when administered once daily in the evening. The primary endpoint for this study was the ACR20 response rate at Week 12 (Visit 4) observed for NP01 versus placebo treated patients. A higher proportion of patients treated with NP01 (47%) achieved an ACR20 response rate as compared to placebo patients (29%) in this study. The difference in ACR20 response rates was statistically significant in favor of NP01 ($p=0.0010$ using worst case imputation for missing data). The results from sensitivity analyses involving the application of different imputation methodologies for missing data were supportive of the primary efficacy results. The results from the primary analysis are not unexpected given prednisone's proven efficacy as a treatment for RA.

The results from the key secondary endpoint analysis of the patient reported outcome (PRO) of the relative rate of change from baseline in the duration of morning stiffness was also in favor of patients treated with NP01 as compared to placebo at Visit 4 as demonstrated via a variety of analyses performed using multiple imputation techniques in different populations of subjects with missing baseline data. However, the validity of these results are questionable since the instrument used to collect data for the analysis of the key secondary endpoint and other supportive secondary endpoints that also

assessed morning stiffness was found to be inadequate as per a SEALD consultative review dated December 4, 2007. According to the SEALD consultant, this endpoint lacked definitions for resolution of morning stiffness and recurrence of stiffness to be used by patients to answer the question consistently. It also lacked the information necessary to support reliability and construct validity of the endpoint. In view of these issues, the Applicant was advised to review the Agency's PRO guidance document and submit documentation of validation and justification of the instrument used to measure morning stiffness in the NDA, but failed to do so. Additionally, the Applicant did not provide any discussion regarding translation or cultural adaptation of this endpoint or a scientific justification for a responder definition, thus raising a question regarding the clinical meaningfulness of the approximate 20 minute difference observed in the duration of morning stiffness between the two treatment groups. Most importantly, positive results from a second adequate and well-controlled study to support the robustness of the key secondary endpoint results were not submitted by the Applicant for review which they were told would be necessary for approval of a morning stiffness marketing claim for NP01 at the EOP2 meeting held with the Agency. In the time that it took for NP01-007 to be completed, morning stiffness has been removed from the updated 2010 ACR/EULAR Disease Classification Criteria for RA as a result of this parameter's lack of discriminatory capability to discern between inflammatory versus non-inflammatory disease as well as treated versus untreated RA. The introduction of therapeutic biologics and triple therapy for RA has also resulted in better disease control and symptomatic relief so that morning stiffness is no longer an issue in patients receiving adequate therapy for their disease.

The majority of the other secondary endpoints assessed in this study trended in favor of treatment with NP0 and were supportive of the results from the primary endpoint analysis. However, declaring statistical significance of the secondary endpoints evaluated in these trials using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocols or implemented during the analyses of the secondary endpoints other than for the key secondary endpoint.

The risk benefit assessment is in favor of approving NP01 for the general indications already approved for the reference immediate-release prednisone product with similar labeling. There are issues and questions raised regarding the validity of the results from the morning stiffness outcome, however, the clinical data are not needed to support the application given the adequate CMC and clinical pharmacology data. The clinical trial data for the ACR20 endpoint, while generally supportive of efficacy, do not warrant inclusion in the label under 6.1 Indication. The original proposed indication for NP01 is the treatment of RA in adult patients. Based on review of the CMC and clinical pharmacology data, the clinical review recommends that the list of indications be broadened to include all the indications listed in the reference product as follows:

- allergic conditions: atopic dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness

- dermatologic diseases: bullous dermatitis herpetiformis, contact dermatitis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome)
- endocrine conditions: congenital adrenal hyperplasia, hypercalcemia of malignancy, nonsuppurative thyroiditis, primary or secondary adrenocortical insufficiency
- gastrointestinal conditions: Crohn's disease, ulcerative colitis
- hematologic diseases: acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, secondary thrombocytopenia in adults
- neoplastic conditions: acute leukemia, aggressive lymphoma
- nervous system conditions: acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury
- ophthalmic conditions: sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical steroids
- conditions related to organ transplantation: acute or chronic solid organ rejection
- pulmonary diseases: COPD, allergic bronchopulmonary aspergillosis, aspiration pneumonia, asthma, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy, hypersensitivity pneumonitis, idiopathic bronchiolitis obliterans with organizing pneumonia, idiopathic eosinophilic pneumonias, idiopathic pulmonary fibrosis, pneumocystis carinii pneumonia (PCP) associated with hypoxemia, occurring in an HIV+ individual who is also under treatment with appropriate anti-PCP antibiotics, symptomatic sarcoidosis
- renal conditions: to induce diuresis or remission of proteinuria in nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
- rheumatologic conditions: acute gouty arthritis, ankylosing spondylitis, dermatomyositis/polymyositis, polymyalgia rheumatica, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis including juvenile rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, vasculitis

- specific infectious conditions: trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy

These indications are consistent with the indications approved for the reference immediate-release prednisone tablet and a related, immediate-release prednisolone product (Flo-Pred).

6.1.1 Methods

Efficacy data contained in the submission from the 3-month, multicenter, randomized, double-blind, placebo-controlled, parallel group trial NP01-007 conducted in patients with active RA were reviewed to assess this application. Analyses of pertinent subgroups were also conducted. All primary and secondary analyses were confirmed by the FDA's statistical reviewer. The design of the protocol was discussed in Section 5.3.1.

6.1.2 Demographics

Demographic information for the efficacy study is presented in detail in Table 10 in Section 5.3.

6.1.3 Subject Disposition

Patient disposition is described in detail in Table 8 in Section 5.3.1.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint for Study NP01-007 was the ACR20 response rate at Week 12 (Visit 4). The results generated for the primary analysis using nonresponder imputation for missing data (e.g., worse case) are shown in Table 33:

Table 33 - Analysis of the ACR20 Response Rate (Primary Endpoint) and Supportive Sensitivity Analyses for Study NP01-007

Imputation scheme	NP01 n/N (%)	Placebo n/N (%)	% Difference in proportions ^a (95% CI) ^b		Odds Ratio (95% CI) ^c	P-value ^d
Primary analysis						
Worse case^e	108/231 (46.8%)	34/119 (28.6%)	18.2	17.4 (7.23, 27.64)	2.25 (1.39, 3.64)	0.0010
Secondary analysis						
Observed case	108/224 (48.2%)	35/116 (30.2%)	18.0	17.3 (6.83, 27.78)	2.21 (1.36, 3.58)	0.0013
LOCF^f	110/229 (48.0%)	35/119 (29.4%)	18.6	17.9 (7.66, 28.22)	2.30 (1.42, 3.72)	0.0007
Withdrawal^g	108/230 (47.0%)	35/119 (29.4%)	17.5	16.9 (6.58, 27.16)	2.18 (1.35, 3.51)	0.0014

Source: Study NP01-007, Clinical Study Report Section 11.4.1.1 Table 18.

CI = confidence interval; N = total number of patients per treatment group and imputation scheme at corresponding visit; n = number of responders.

Note: Visit 4 includes early withdrawal patients.

^a The observed difference between treatments (first value) and the estimate of the treatment difference from the generalized linear model (second value) are reported.

^b The 95% CI was calculated from a generalized linear model with a binomial probability function and an identity link with treatment, geographic region, gender, and median age class as factors.

^c Asymptotic 95% CIs based on asymptotic normality of the estimated odds ratio.

^d The p-value was based on logistic regression with treatment, geographic region, gender, and median age class as factors.

^e Worse case imputation: all missing values were imputed as non-responders.

^f LOCF imputation: last observation (post-baseline) was carried forward.

^g Withdrawal imputation: missing values for withdrawn patients were imputed as non-responders.

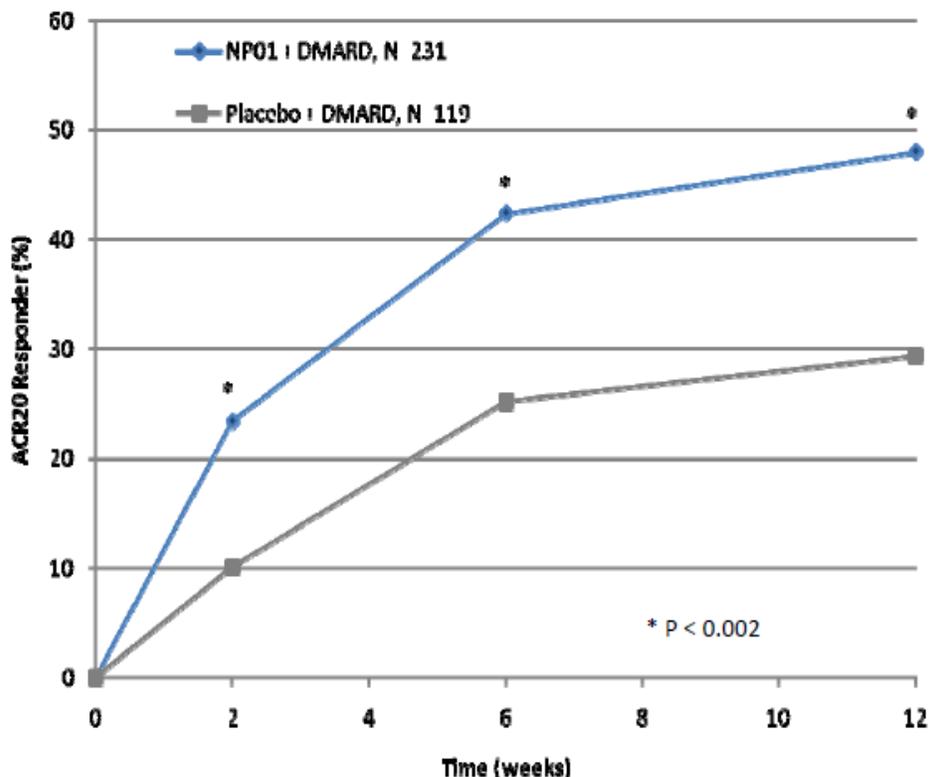
Table courtesy of Dr. Kiya Hamilton

A statistically higher response rate for the ACR20 was observed in patients administered NP01 as compared to placebo at the Week 4 visit. The results from multiple secondary or sensitivity analyses which involved the application of different imputation methodologies for missing data were supportive of the primary efficacy results (refer to Table 33).

Figure 3 below graphically depicts the time course of the ACR responder rate for the mITT population using LOCF imputation over the 12 weeks of study treatment. The NP01 treatment group separates early from the placebo group as a result of higher

ACR20 responses in this treatment group that are maintained over the 12 weeks of study assessment.

Figure 3 – Time Course of the ACR20 Responder Rate (mITT Population, LOCF)



Sponsor's Fig. 4; p. 97 Clinical Study Report

6.1.5 Analysis of Secondary Endpoints

The results of the analyses of the key secondary endpoint, the relative change from baseline in duration of morning stiffness at Visit 4 for the mITT population using LOCF and BOCF imputation for missing data, are shown in Table 35. Subjects with missing baseline values were excluded by the Applicant in this analysis resulting in a smaller sample size. The median relative rate of change from baseline in the duration of morning stiffness was greater in patients administered NP01 as compared to placebo treated patients at Visit 4 for both analyses.

Table 34 - Analyses of the Relative Change from Baseline in Duration of Morning Stiffness at Visit 4 (Key Secondary Endpoint) for Study NP01-007 (mITT Population)

Imputation scheme	Relative Change (%)				Difference in median ^a [%] (95% CI) ^a	P-value ^b
	NP01		Placebo			
	N	Median	N	Median		
LOCF	216	-55	107	-34	-20 (-32, -6)	0.0015
BOCF	215	-55	107	-33	-20 (-32, -7)	0.0013

Source: Study NP01-007, Clinical Study Report Section 11.4.1.2.1 Table 22.

CI = confidence interval; LOCF = last observation carried forward; N = number in analysis (i.e., excluding the missing).

Note: Visit 4 includes early withdrawal patients.

^a Difference in median and its 95% CI were estimated using Hodges-Lehmann method.

^b Wilcoxon signed rank test p-value (for information only).

As different methods were applied to compute the p-value and the 95% CI, the difference between treatment groups was assessed using the 95% CI.

Note: LOCF and BOCF imputation algorithms were implemented up to the next visit following the last diary data. LOCF (last observation carried forward) was computed using the last 7 days prior to the visit day with non-missing values for the duration of morning stiffness.

BOCF: Baseline observation was carried forward.

Table courtesy of Dr. Kiya Hamilton

However, the above analysis of the key secondary endpoint provided by the Applicant did not include the entire mITT population. As per the Agency's statistician's request, the applicant conducted additional analyses of the relative change from baseline in duration of morning stiffness for the full mITT population shown in Table 35. Since some patients were missing the baseline value for the key secondary efficacy endpoint for the mITT population, this resulted in a reduction in the sample size for the analysis of this endpoint from 231 to 216 subjects in the NP01 group and from 119 to 107 subjects in the placebo group (full mITT population) for the LOCF analysis. For the BOCF analysis, sample size was reduced further to 215 subjects in the NP01 group and 107 subjects in the placebo group. In the additional analyses, if the baseline value was missing the applicant replaced it with the patients screening value and LOCF and BOCF imputations were applied. The results from these additional analyses were similar to the original analyses of this endpoint.

Table 35 – Additional Analyses of the Relative Change from Baseline in Duration of Morning Stiffness at Visit 4 (Key Secondary Endpoint) for Study NP01-007 (full mITT Population)

Imputation scheme	Relative Change (%)				Difference in median ^a [%] (95% CI) ^a	P-value ^b
	NP01		Placebo			
	N	Median	N	Median		
LOCF	230	-54.2	119	-28.6	-20.8 (-32.5, -7.6)	0.0006
BOCF	231	-51.4	119	-24.6	-18.7 (-31.3, -6.0)	0.0011

Source: Response to Information Request dated April 4, 2012

CI = confidence interval; LOCF = last observation carried forward; N = number in analysis (i.e., excluding the missing).

Note: Visit 4 includes early withdrawal patients.

^a Difference in median and its 95% CI were estimated using Hodges-Lehmann method.

^b Wilcoxon signed rank test p-value (for information only).

As different methods were applied to compute the p-value and the 95% CI, the difference between treatment groups was assessed using the 95% CI.

Note: LOCF and BOCF imputation algorithms were implemented up to the next visit following the last diary data.

LOCF (last observation carried forward) was computed using the last 7 days prior to the visit day with non-missing values for the duration of morning stiffness.

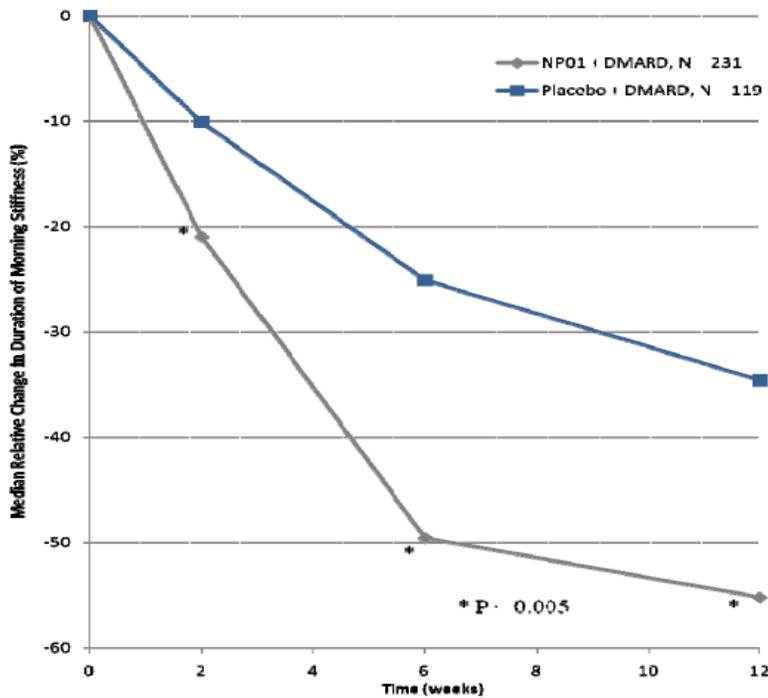
BOCF: Baseline observation was carried forward.

Table courtesy of Dr. Kiya Hamilton

The validity of these findings are highly questionable since this endpoint was found to lack definitions for resolution of morning stiffness and recurrence of stiffness to be used by patients to answer the question consistently in addition to lacking information necessary to support its reliability and construct validity.

Figure 4 depicts the time course of the relative change in duration of morning stiffness for the mITT population using LOCF imputation for missing data over the 12 weeks of study treatment. The NP01 treatment group again separates early from the placebo group as a result of greater decreases in duration of morning stiffness experienced by this treatment group that are maintained over the 12 weeks of study assessment. The clinical meaningfulness of the approximate 20 minute difference observed in the duration of morning stiffness between the two treatment groups is also questionable since no scientific justification for a responder definition was provided by the Applicant.

Figure 4 – Time Course of the Relative Change in Duration of Morning Stiffness (mITT Population, LOCF)



Sponsor's Fig. 5; p. 126 Clinical Study Report

6.1.6 Other Endpoints

The results from the secondary endpoints supportive of both the primary and key secondary endpoints are shown in the following Table 36:

Table 36 - Tabular Summary of Other Secondary Endpoint Analyses at the Visit 4 Timepoint Supportive of Both the Primary and Key Secondary Endpoints for Study NP01-007

Secondary Efficacy Variable	Comment	P-value
ACR20 Response Rate at Each Visit	The proportion of patients who were responders at any visit was higher for the NP01 group (50% , 138 patients) as compared to PLO (42%, 50 patients)	p<0.002 All visits
ACR50 Response Rate at Each Visit	The proportion of patients who were responders at any visit was higher for the NP01 group (22% Visit 4) as compared to PLO (10% Visit 4)	p<0.05 Visits 3 and 4
ACR70 Response Rate at Each Visit	The proportion of patients who were responders at any visit was higher for the NP01 group (7% Visit 4) as compared to PLO (3% Visit 4)	N.S.
Tender Joint Count	Absolute change from baseline at Visit 4: NP01: -4.8 vs. PLO: -2.8	p=0.0014
Swollen Joint Count	Absolute change from baseline at Visit 4: NP01: -3.7 vs. PLO: -2.5	p=0.0085
Patient's Assessment of Pain	Mean pain score decreased over time in the NP01 group to -22.1 mm at Visit 4; Mean pain score for PLO group did not decrease until later in the trial (Visit 3) and was -11.4 mm at Visit 4	p=0.0011
Patient's Global Assessment of Disease Activity	Mean change over baseline score at Visit 4 of -21.1 mm for NP01 group vs. -7.8 mm for the PLO group	p=0.0003
Physician's Global Assessment of Disease Activity	Mean change over baseline score at Visit 4 of -23.5 mm for NP01 group vs. -13.2 mm for the PLO group	p<0.0001
Time to Response Based on ACR Criteria	The median time to the first time the ACR20 criteria were met (using responders only n=188 patients) was 84 days for NP01 vs. 44 days for PLO group	
HAQ-DI score	Mean HAQ-DI score at Visit 4 for NP01 group was -0.222 vs. -0.049 for PLO group.	p<0.0001
CRP	Mean absolute change from baseline to Visit 4 for NP01 group -1.74 mg/L vs. -3.21mg/L for PLO	N.S.
ESR	Mean absolute change from baseline to Visit 4 for NP01 group -8.3 mm vs. -6.7 mm for PLO	N.S.
TNFα	Mean absolute change from baseline to Visit 4 for NP01 group -0.7 pg/mL vs. -0.1 pg/mL for PLO (observed case)	N.S.
IL-6 levels	Mean decrease in IL-6 levels was greater in the NP01 group at Visit 4 as compared to the PLO group (mean titer ratio: 0.8 (95% CI 0.7, 0.9)	p=0.001
DAS28	Mean absolute change from baseline DAS28 score was greater in NP01 group at Visit 4 (-1.16) vs. PLO (-0.64)	p<0.0001

Table 37 - Tabular Summary of Other Secondary Endpoint Analyses at the Visit 4 Timepoint Supportive of Both the Primary and Key Secondary Endpoints for Study NP01-007 (cont.)

Secondary Efficacy Variable	Comment	P-value
EULAR Response	Although no patients had a “good response” by this criterion, a higher proportion of subjects in the NP01 group (57%) had a moderate response as compared to PLO group (40%)	p=0.0014
Change in Duration of Morning Stiffness Between Baseline and Each Visit	Median relative change from baseline was greater in the NP01 group than in the PLO group at each visit. Median relative change from baseline at visit 4 for the NP01 group was 45.6 minutes vs. 79.3 minutes for the PLO group.	p=0.0015
Severity of Morning Stiffness	Mean change from baseline at Visit 4 in the NP01 group was -28.6 mm vs. -19.2 mm for PLO group	p=0.0066
Reoccurrence of Morning Stiffness	Mean change from baseline at Visit 4 for the NP01 group was 23.7% days vs. 11.8% days for PLO group	p=0.0026
Patient Assessment of Morning Pain	Mean change from baseline to Visit 4 for NP01 was -24 mm vs. -15 mm for PLO group	p=0.0121
Patient Assessment of Evening Pain	Mean change from baseline to Visit 4 for NP01 was -21 mm vs. -15 mm for PLO group	p=0.0489
Additional Analgesics	Mean number of days with additional analgesics over the 12 weeks of the trial was comparable (NP01: 14 days vs. PLO 15 days)	N.S.
FACIT-F Fatigue Score	Mean absolute increase in fatigue subset score from baseline to Visit 4 for NP01 group 3.76 vs. 1.40 for PLO group	p=0.0028
SF-36 Score	Mean improvement in PCS score for NP01 group was 3.53 vs. 105 for PLO (LOCF); Mean improvement in MCS score for NP01 was 1.50 vs. 0.47 for PLO group	p=0.001 for PCS; N.S. for MCS
Urine CTX-1	Mean absolute change from baseline to Visit 4 for NP01 group 67.8 µg/mmol creatinine vs. 162.3 µg/mmol creatinine for PLO (observed case)	N.S.

With exception of ACR70 response rate at Visit 4, the change in inflammatory biomarkers (CRP, ESR and TNF- α), change in the mental summary component (MSC) of the SF-36 and use of additional analgesics, the majority of these other secondary endpoints trended towards improvement in favor of the NP01 group as compared to the placebo group. No correction for multiplicity was prespecified by the statistical analysis plan (SAP) for NP01-007 for use in conducting the analyses of the secondary endpoints other than the key major secondary endpoint of duration of morning stiffness. Therefore, declaring statistical significance of the non-key secondary endpoints for this trial using unadjusted p-values may be inappropriate.

6.1.7 Subpopulations

The Agency's statistical reviewer verified that the efficacy findings in Study NP01-007 were not significantly affected by age, sex, disease duration or region. Since participants in this study was overwhelming Caucasian, a subgroup analysis for race was not performed. There were no clinically meaningful treatment-by-subgroup interactions.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant also conducted a small subgroup study assessing HPA axis suppression in support of the night time administration of NP01. The design and results of this subgroup study are discussed in Section 7.4.5.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance effects were not evaluated by the Applicant since this is 505(b)(2) application and these issues as related to the administration of low-dose corticosteroid therapy in RA are well documented.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety of NP01 is primarily supported by the CMC and clinical pharmacology data which form the basis for the 505(b)(2) reference to the established safety profile for immediate-release prednisone. The Applicant has provided additional safety information from the placebo-controlled controlled Phase 3 trial NP01-007 and the actively controlled Phase 3 trial EMR 62215-003 which evaluated doses of 1 to 10 mg/day of NP01 in adult patients with RA. The overall rate of serious adverse events associated with NP01 and the active comparator, prednisone immediate release, were low and consistent with historical clinical experience with low dose corticosteroid therapy. The majority of the serious adverse events including deaths contained in the safety database submitted in support of NP01's safety profile were the type of events (e.g., chest pain, myocardial ischemia/infarctions, injuries due to falls, orthopedic surgery, etc...) expected to occur in an older population with long-standing RA at risk due to other co-morbid conditions. However, the overall low incidence of serious adverse events observed in the double-blind safety population may have been influenced by the large imbalance in the number of patients taking ≤ 5 mg/day (n= 379

subjects) versus > 5 mg/day (n= 125 subjects) of NP01 in view of the well documented dose-dependency of adverse events associated with corticosteroid administration and the relatively short duration of double-blind exposure (3 months).

Review of the adverse events of special interest (e.g., infections, gastrointestinal cardiovascular, metabolic, CNS and eye adverse events) did not identify any potential safety issues associated with NP01's delayed mechanism of release, however, none of the trials that evaluated this drug were powered to specifically determine safety risk.

Additionally, there was no evidence of NP01 having any clinically meaningful adverse effect on clinical lab test parameters or vital signs, but this again may be a result of the short duration of exposure to the drug since corticosteroids are known to have toxic effects on blood pressure, weight (e.g., gain), serum potassium and glucose levels.

Additional supportive data from the open label study LOD 9577 and the open label extension of EMR 62215-003, which also evaluated the same low dose range of NP01 in adult patients with RA, did not reveal any new or unexpected safety signals associated with the chronic administration of this drug. However, there are concerns that reporting bias for adverse events associated with the chronic administration of NP01 may have been introduced as a result of a design flaw in the protocol for LOD 9577. According to the protocol for this study, no uniform methodology was used to collect treatment emergent adverse events which were only captured if they were recorded as part of the routine medical visit by the study investigators. Since this study was conducted post-approval in the EU, there are also concerns that investigator bias may have been introduced as well during the determination process for the types of safety data to be recorded at each visit. There are also concerns related to the validity of the safety findings for the double-blind portion of EMR 62215-003 since no financial disclosure information was submitted for the investigators who participated in this trial as required under 21 CFR §54 needed to minimize the potential for the introduction of bias.

Review of the postmarketing data and the worldwide literature reviews also failed to identify any new potential safety signals associated with the oral administration of low dose NP01.

In view of the small number of subjects, the lack of adequately matched control subjects for dose and duration of corticosteroid exposure, and incomplete testing of subgroup participants, the clinical validity of the findings from the HPA substudy are questionable at best and should not be included in the drug's label.

As stated previously, the overall safety profile of NP01 is consistent with historical clinical experience with low dose corticosteroid therapy. In view of the imbalance in exposure data that resulted in more patients being treated with \leq 5 mg/day of NP01 than with > 5 mg/day, the short duration of double-blind exposure, the lack of

adequately powered studies to determine safety risk, as well as the possible introduction of reporting and investigator bias, the drug's safety profile may not have been adequately characterized based on review of the data contained in this safety database. Since the safety profile of prednisone is well documented, this medical reviewer recommends that NP01's label reflect the safety data contained in the RLD label and descriptions of the safety findings from the clinical studies should not be included as these data may be potentially misleading and not useful to health care providers for the reasons cited.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of the safety of this 505(b)(2) application for NP01, the Applicant submitted safety data from a total of 13 clinical studies: nine Phase 1 trials (EMR 62215-001, EMR 62215-002, EMR 62215-005, NP01-006, NP01-008, NP01-009, NP01-010, NP01-013, NP01-14 and NP01-015), one Phase 2a trial (NP01-201) and two Phase 3 trials (NP01-007 and EMR 62215-003) and one open-label, quality of life postmarketing study (LOD 9577). A tabular summary of these trials can be found in Table 3 in Section 5.

In addition to the safety database generated from these 14 studies, the submission contained other supportive safety data for the drug including a tabular summary of spontaneously reported postmarketing reports for other corticosteroids collected by the Agency's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS), and a periodic safety update (PSURs) submitted to the EMA where this drug is currently registered for marketing. These data were updated with new safety information contained in the 120-day safety update that also contained an abbreviated safety report of the ongoing Phase 1 study NP01-015, the most recent submitted PSUR, and 2 citations from an abbreviated literature review update.

Safety data from the 13 studies were summarized in the individual trial reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs. All safety analyses were performed on the double-blind safety population from the controlled studies (NP01-007 and EMR 62215-003), the single and multiple dose Phase 1 and 2 studies, and ongoing open label studies in RA conducted by the Applicant as well as the data contained in the PSURs, postmarketing adverse event review, and 120-day safety update were examined by this medical officer.

7.1.2 Categorization of Adverse Events

Verbatim terms of AEs recorded in the case report forms (CRF) by investigators was coded by the Applicant using MedDRA dictionary Preferred Term and System Organ Class (SOC) (version 12.0). A listing of all AEs coded in this manner including the corresponding verbatim terms was included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This application contained 12-weeks of double-blind safety data generated from the following 2 trials: NP01-007 and EMR 62215-003. These trials were of sufficiently similar design to allow for pooled analyses of the controlled safety data by treatment group. Analyses of the safety data were performed on the safety population which was defined as all patients who were randomized and who received at least one dose of study medication in these trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Cumulative exposure data by NP01 dose (≤ 5 mg or > 5 mg per day) for the combined controlled and uncontrolled multiple dose Phase 3 trials are presented in Table 38. A total of 504 RA patients were treated in these trials with the to-be-marketed formulation of NP01 as follows: 379 patients with ≤ 5 mg/day and 125 patients with > 5 mg/day. Median duration of NP01 exposure was 89 days (range 4 to 406 days). A total of 101 subjects were exposed for ≥ 336 days which meets the International Conference on Harmonization (ICH) E1A guideline for a minimum of a 100 patients treated for 1 year.

Table 38 – Summary of Study Drug Exposure in the Overall Combined Safety Population

	NP01		
	≤ 5 mg (N=379)	>5 mg (N=125)	Total (N=504)
Daily Dose (mg):			
Mean (SD)	5 (0.6)	8 (1.5)	6 (1.7)
Median (Range)	5 (2, 9)	8 (6,10)	5 (2, 10)
Total Dose (mg):			
Mean (SD)	803 (629)	2211 (923)	1152 (937)
Median (Range)	415 (25, 3100)	2451 (42, 3680)	450 (25, 3680)
Duration of Treatment (days):			
Mean (SD)	159 (115)	266 (102)	185 (121)
Median (Range)	84 (5, 406)	279 (6, 371)	89 (5, 406)
<30 days	14 (4%)	6 (5%)	20 (4%)
≥ 30 days to <90 days	225 (59%)	8 (6%)	233 (46%)
≥ 90 days to <180 days	11 (3%)	8 (6%)	19 (4%)
≥ 180 days to <270 days	24 (6%)	16 (13%)	40 (8%)
≥ 270 days to <336 days	46 (12%)	45 (36%)	91 (18%)
> 336 days	59 (16%)	42 (34%)	101 (20%)

Modified Sponsor's Table 8; p. 57 Summary of Clinical Safety

Included in this application was safety data collected from Study LOD 9577 which was a 9-month, open-label, postmarketing trial required by the German regulatory authorities that assessed quality of life in RA patients treated with low dose NP01. The abbreviated safety report for this study contained exposure and safety information for an additional 2,676 patients, which when added to the overall combined safety population exposed to NP01 during clinical development, satisfies the other ICH E1A requirement for an overall safety database of 1500 patients for drugs administered chronically.

7.2.2 Explorations for Dose Response

Since this is a 505 (b)(2) application, and prednisone is traditionally administered as individualized doses based on the severity of the patient's underlying condition and response to treatment, the Applicant did not conduct any dose response explorations in support of NP01.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant did not conduct any special animal and/or in vitro testing with NP01 to support its safety profile.

7.2.4 Routine Clinical Testing

The following clinical and lab testing were conducted at screening and the final study visits (Week 12) in studies NP01-007 and EMR 62215-003 (except where noted) and submitted in support of NP01's safety profile:

- Physical exam, weight and height
- Vital signs: systolic and diastolic blood pressure, and heart rate (sitting)
- Complete cell count (CBC) with differential and platelet count, hemoglobin and hematocrit
- Serum chemistries; albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, GGT, glucose, potassium, sodium, total bilirubin, total protein, total cholesterol and triglycerides
- Urinalysis: including pH, specific gravity, protein, glucose, ketones, nitrite, occult blood, bilirubin, urobilinogen
- Pregnancy testing
- Hemocult/Guaiac testing (NP01-007 only)

Patients who participated in the adrenocortical function subgroup study were to have CRH testing at screening, Week 12 (Visit 5) and at Month 12 (Visit 8).

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the population studied in these trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The results from the two pharmacokinetic studies that assessed food effect (NP01-006) and relative bioavailability (EMR 62215-005) conducted by the Applicant are presented and discussed in the preceding section 4.4.3 of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety profile of prednisone has been well documented and includes toxic effects on cardiovascular and renal functions (e.g., hypertension, salt and water retention, and electrolyte imbalances), the gastrointestinal system (e.g., increase risk for perforation and fatty infiltration of the liver), and the central nervous system (e.g., mood swings, insomnia, euphoria, depression, frank psychosis, etc...). This drug can also cause osteoporosis, hyperglycemia, decreased wound healing, cataracts, and glaucoma as well as increasing the risk for infection due to its immunosuppressive capabilities. Chronic administration of prednisone can result in hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome. In view of these drug-induced toxicities, the clinical studies conducted in support of NP01 included hepatic, renal, hematological and blood pressure monitoring. Additionally, subjects with underlying renal or hepatic impairment, and uncontrolled diabetes or hypertension were prohibited from

participating in the pivotal studies conducted in support of NP01. At the request of the German regulatory authorities, the Applicant also conducted a subgroup study to evaluate the effects of NP01 administration on the HPA axis, the results of which are discussed under Section 7.4.5. In view of the drug-induced toxicities associated with prednisone, the Applicant also submitted analyses of adverse events of interest that included infections, gastrointestinal (upper abdominal pain, dyspepsia, abdominal discomfort, and abdominal pain), cardiovascular (hypertension and secondary hypertension), sleep disorders (insomnia and sleep disorder), metabolic weight increased, blood glucose increased, occult blood positive, diabetes mellitus and glycosuria), central nervous system (depression and delirium) and eye problems (cataracts and glaucoma) in support of NP01's safety profile. The results of these analyses are discussed in section 7.3.3 of this review.

7.3 Major Safety Results

All safety analyses were performed on the safety population which was defined as all randomized subjects who took at least one dose of study drug of the study medication they actually received. Analyses of adverse events (AEs) were performed only for those events considered to be treatment emergent. (Note: The Applicant defined treatment-emergent AEs as events that occurred or worsened after initiation of study medication.) A summary of AEs that were reported in the NP01 safety database for the controlled trials NP01-007 and EMR 62215-003 is presented in Table 39. Nearly half of the subjects experienced at least 1 AE while participating in these trials. The rates for serious (NP01: 1%; prednisone IR 3%; and placebo: 2%) and severe (NP01: 1%; prednisone IR: 3%; and placebo: 1%) treatment-emergent AEs were similar across the three treatment groups. During the controlled trials, more patients withdrew from the NP01 (13 subjects; 4%) and active control prednisone IR (7 subjects; 5%) treatment groups than from the placebo group (1 subject; 1%). There was one death reported in the safety population that occurred in the prednisone IR treatment group. This death will be discussed in the following section 7.31.

Table 39 – Summary of Treatment Emergent Adverse Events for Subjects in the Controlled Phase 3 Studies (Safety Population)

	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Number of Subjects with Any TEAE:	157 (42%)	57 (50%)	58 (49%)
Number of Subjects with Any Serious TEAE:	5 (1%)	4 (3%)	2 (2%)
Number of Subjects with Any Severe TEAE:	4 (1%)	4 (3%)	1 (1%)
Deaths:	0	1 (1%)	0
Number of Subjects Who Discontinued Due to TEAE:	13 (4%)	7 (5%)	1 (1%)

7.3.1 Deaths

There was one death reported in the NP01 clinical development program that occurred in EMR 62215-003 due to sudden death. Additionally, there were 4 deaths reported in the postmarketing study LOD 9577 conducted in Germany as follows: 2 deaths due to unknown causes, 1 death status post fall, and 1 death due to myocardial infarction. For completeness, summaries of these 4 post-marketing deaths are provided below along with the death that occurred during the drug's clinical development program. A review of the case narratives failed to identify any substantial evidence that these deaths were related to treatment with NP01.

Individual Patient Death Summaries:

Subject 6012079 (Protocol EMR 62215-003)

Cause of Death: Sudden death due to myocardial infarction

Subject 6012079 was a 64 year-old female randomized to treatment with prednisone IR. She died suddenly at home 18 days after initiating study medication. An autopsy was not performed. Her past medical history was significant for RA, recurrent respiratory tract infections, and episodic chest pain with intermittent tachycardia (with salves up to 180 beats/min), atrial tachycardia and supraventricular premature beats documented on Holter monitoring. Concomitant medications included: leflunomid, methotrexate, acetamin, metoprolol succinate and glyceroltrinitrat. The patient was a nonsmoker with no prior history of hypertension or hyperlipidemia. Approximately 3 weeks prior to her death, the patient experienced symptoms of stenocardia (angina pectoris). Results of her cardiac work-up included right bundle branch block on ECG with slight modification on stress ECG. Echocardiography was consistent with a slightly enlarged left atrium and slight myocardial hypertrophy. Doppler studies of her supra-aortic vessels were unremarkable. The patient' cardiologist recommended repeat Holter monitoring and a Nitrotest but she died prior to undergoing these tests.

Impression: The cause of death for this subject was most likely cardiovascular in etiology in view of her recent cardiac problems and unrelated to study therapy.

Subject 25521 (Protocol LOD 9577)

Cause of Death: Unknown

Subject 25521 was a 75 year-old female who died at home status 10 days post (S/P) hospital discharge following non-surgical revision of a dislocated hip prosthesis. No information was provided regarding the circumstances of her death. Her past medical history was remarkable for RA, luxation of right hip joint prosthesis following falls, malignant skin neoplasm, arthrosis of hand and shoulder and mixed hyperlipidemia. Concomitant medications included; metoprolol, enoxaparin, leflunomide, and 5 mg per day of NP01.

Impression: The cause of death for this subject is unknown due to the paucity of the information provided. However, in view of her recent hospitalization it is unlikely to have been related to NP01.

Subject 35561 (Protocol LOD 9577)
Cause of Death: Unknown

Subject 35561 was a 69 year-old female who died while participating in this study. No information was provided regarding the circumstances of her death, past medical history or concomitant medications other than she was taking 5 mg a day of NP01.

Impression: The cause of death for this subject is unknown due to the paucity of the information provided.

Subject 53766 (Protocol LOD 9577)
Cause of Death: Injuries S/P fall

Subject 53766 was an 83 year-old female who died as a result of injuries sustained in a fall while participating in this study. No information was provided regarding the circumstances of her death, past medical history or concomitant medications other than she was taking NP01 8 mg per day.

Impression: The cause of death for this subject was due to the injuries she sustained in the fall and is unlikely to have been related to NP01.

Subject 30766 (Protocol LOD 9577)
Cause of Death: Myocardial infarction

Subject 30766 was an 82 year-old female who died as a result of a myocardial infarction while participating in this study. No information was provided regarding the patient's past medical history. Concomitant medications included: alendronate, colecalciferol, calcium carbonate, and NP01 1 mg a day.

Impression: The cause of death for this subject was due to myocardial infarction and is unlikely to be related to NP01.

7.3.2 Nonfatal Serious Adverse Events

The following Table 40 summarizes the treatment-emergent serious adverse events (SAEs) reported in the safety population. Overall, the numbers of SAEs reported for both controlled trials were low. The proportion of patients who experienced treatment-emergent SAEs in the NP01 group was 1% which was comparable to the 2% observed in the placebo group but lower than the 3% reported in the prednisone IR group. Review

of the SAEs by system organ class (SOC) did not reveal any potential patterns or safety signals due to the small numbers of SAEs observed during the controlled trials.

Examination of the narratives for the five subjects who experienced a SAE during treatment with NP01 failed to reveal an association between these events and exposure to drug. Located below Table 40 are summaries of the SAEs for all five NP01-treated subjects. Summaries of the four prednisone IR subjects and the two placebo subjects who experienced SAEs are not included in this review.

Review of safety data from the OLE of EMR 62215-003 and LOD 9577 conducted in RA patients, NP01-201 conducted in adult asthmatics and the 14 single dose Phase 1 PK studies in healthy volunteers also did not reveal any unexpected safety signals associated with the administration of NP01.

Table 40 – Serious Adverse Events Reported During the Controlled Phase 3 Studies (Safety Population)

Adverse Event by MedDRA System Organ Class (SOC)/ Preferred Term	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Any System Organ Class	5 (1%)	4 (3%)	2 (2%)
Cardiac Disorders:	1 (<1%)	0 (0%)	1 (1%)
Myocardial Infarction	1 (<1%)	0 (0%)	0 (0%)
Myocardial Ischemia	0 (0%)	0 (0%)	1 (1%)
Gastrointestinal Disorders:	0 (0%)	1 (<1%)	0 (0%)
Abdominal Pain	0 (0%)	1 (<1%)	0 (0%)
General Disorders and Administration Site Cond.:	1 (<1%)	2 (1%)	0 (0%)
Chest Pain	1 (<1%)	1 (<1%)	0 (0%)
Sudden Death	0 (0%)	1 (<1%)	0 (0%)
Injury, Poisoning and Procedural Complications:	0 (0%)	1 (<1%)	0 (0%)
Tendon Rupture	0 (0%)	1 (<1%)	0 (0%)
Investigations:	0 (0%)	0 (0%)	1 (1%)
Cervical Smear Abnormal	0 (0%)	0 (0%)	1 (1%)
Musculoskeletal and Connective Tissue Dis.:	2 (1%)	0 (0%)	0 (0%)
Osteoarthritis	1 (<1%)	0 (0%)	0 (0%)
Synovial Cyst	1 (<1%)	0 (0%)	0 (0%)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	1 (<1%)	0 (0%)	0 (0%)
Squamous Cell Carcinoma	1 (<1%)	0 (0%)	0 (0%)
Nervous System Disorders:	0 (0%)	1 (<1%)	0 (0%)
Depressed Level of Consciousness	0 (0%)	1 (<1%)	0 (0%)
Respiratory, Thoracic, and Mediastinal Disorders:	0 (0%)	1 (<1%)	0 (0%)
Pulmonary Embolism	0 (0%)	1 (<1%)	0 (0%)
Surgical and Medical Procedures:	2 (1%)	0 (0%)	0 (0%)
Hospitalization	1 (<1%)	0 (0%)	0 (0%)
Limb Operation	1 (<1%)	0 (0%)	0 (0%)

Adapted Sponsor's Table 33; p. Clinical Safety Summary

Individual Nonfatal Serious Adverse Event Summaries:

Subject 66-15 (Protocol NP01-007)

Nonfatal SAE: Chest Pain and Palpitations

Subject 66-15 was a 56 year-old female non-smoker randomized to treatment with NP01. Past medical history was remarkable for ulcerative colitis, GERD, dyspepsia, osteoarthritis, hypertension, neutropenia and S/P exploratory laparotomy with tubal ligation and uterine ablation. Concomitant medications included: mesalazine, calcium carbonate, docusate sodium meloxicam, pantoprazole, and acetaminophen. On 19 February 2009, eight days after initiating study medications, the patient presented to the

emergency room (ER) complaining of intermittent chest pain and palpitations which she reported had going on for approximately 1 week, lasted approximately 30 minutes with radiation to the jaw and responded to nitroglycerin administered in the ER. Blood pressure was 149/89. Serial cardiac enzymes and ECG were negative. The patient was started on atenolol prior to discharge for hypertension. Cardiac stress test performed on 25 February 2009 was negative for ischemia. Myocardial perfusion imaging with SPECT analysis did not demonstrate any perfusion defects.

Impression: The chest pain and palpitations were unlikely related to NP01.

Subject 5605 (Protocol EMR62215-003)
Nonfatal SAE: Myocardial ischemia

Subject 5605 was a 55 year-old male randomized to NP01. Past medical history was remarkable for gout. Concomitant medications included: diclofenac, allopurinol, sulfasalazine and chloroquine phosphate. After 4 days of study medication, the patient was hospitalized on [REDACTED] (b) (6) for acute chest pain. A diagnosis of inferior wall myocardial infarction was made on coronary angiography and the patient underwent percutaneous transluminal coronary angioplasty with stent placement. The patient recovered and was discharged.

Impression: Myocardial infarction was unlikely to have been related to NP01 in view of atherosclerotic coronary disease.

Subject 224 (Protocol EMR62215-003)
Nonfatal SAE: Localized osteoarthritis and limb operation

Subject 224 was a 55 year-old female randomized to NP01. Past medical history was remarkable for hypertension, GERD, chronic bronchitis, osteoporosis and S/P multiple orthopedic surgical procedures including rhizarthosis bilaterally, meniscus surgery of right knee twice, bilateral bunionectomy, and claw toe surgery. Concomitant medications included: metamizol, tramadol, diclofenac, and ibuprofen. The patient was hospitalized on [REDACTED] (b) (6) after receiving study medications for 49 days for rhizarthosis due to osteoarthritis.

Impression: Localized osteoarthritis and hand surgery unlikely to have been related to NP01 in view of her extensive surgical history.

Subject 507 (Protocol EMR62215-003)
Nonfatal SAE: Squamous cell carcinoma

Subject 507 was a 67 year-old female randomized to NP01. Past medical history was remarkable for osteoporosis, hypertension, nephrolithiasis with chronic pyelonephritis, coronary heart disease, lung embolism, anemia, and S/P total knee replacement. Concomitant medications included: ranitidine, talinol, amitriptylinoxide, phenprocoumon, buprenorphine, risedronic acid, methotrexate, folate, celecoxib and ramipril. On (b) (6) the patient was hospitalized on Day 71 of study treatment for excision of a spinaliom of the right cheek that had been increasing in size over the past few months. Histopathology was consistent with an invading spinocellular carcinoma which required additional excision. The patient was discharged without sequelae.

Impression: Squamous cell carcinoma of the face unlikely to have been related to NP01.

Subject 5108 (Protocol EMR62215-003)
Nonfatal SAE: Bursitis

Subject 5108 was a 47 year-old female randomized to NP01. Past medical history was remarkable for anemia, atherosclerosis of aorta, diabetes mellitus and uterine myoma. Concomitant medications included: cyclosporine A, meloxicam, omeprazole, methotrexate, enoxaprin, diosmin and paracetamol. On (b) (6) Day 17 of study treatment, the patient developed pain in her right leg and knee . Ultrasound revealed a large Baker's cyst of the right popliteal fossa. A surgical excision was performed on (b) (6). Patient was discharged without sequelae.

Impression: The Baker's cyst (bursitis) was unlikely to have been related to NP01.

7.3.3 Dropouts and/or Discontinuations

Since AEs can directly influence the disposition of patients in clinical trials, the safety database for NP01 was examined to determine if there were any safety signals generated by subjects who prematurely withdrew from the trials conducted by the Applicant due to NP01-related AEs. Table 41 below is a tabular summary of the AEs experienced by the subjects who discontinued study treatment during the combined controlled trials. The overall proportion of patients who discontinued due to TEAEs during the controlled studies was comparable for the NP01 and prednisone IR treatment groups (4% and 5%, respectively) but these proportions were both higher as compared to the placebo group (1%). Review of these data failed to identify any potential safety signal since all of the subjects who withdrew prematurely from treatment with NP01 did so due to individual AEs with the exception of headaches (2 subjects) and insomnia (2 subjects).

The rate of early subject withdrawal from the open-label trial LOD 9577 (6%) was similar to that of NP01-treated patients in the combined controlled studies (4%). Examination of

these data as well as the study drop-out data from the OLE of EMR 62215-003 revealed similar patterns of AEs leading to patient withdrawal from treatment as those observed in the controlled trials.

Table 41 – Discontinuations Due to Adverse Events in the Controlled Phase 3 Studies (Safety Population)

Adverse Event by MedDRA System Organ Class (SOC)/ Preferred Term	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Any System Organ Class	13 (4%)	7 (5%)	1 (1%)
Cardiac Disorders:	1 (<1%)	0 (0%)	0 (0%)
Palpitations	1 (<1%)	0 (0%)	0 (0%)
Ear and Labyrinth Disorders:	0 (0%)	1 (1%)	0 (0%)
Vertigo	0 (0%)	1 (1%)	0 (0%)
Eye Disorders:	1 (<1%)	0 (0%)	0 (0%)
Glaucoma	1 (<1%)	0 (0%)	0 (0%)
Gastrointestinal Disorders:	3 (1%)	3 (2%)	0 (0%)
Abdominal Pain	1 (<1%)	0 (0%)	0 (0%)
Abdominal Pain Upper	0 (0%)	2 (1%)	0 (0%)
Constipation	1 (<1%)	0 (0%)	0 (0%)
Dyspepsia	1 (<1%)	0 (0%)	0 (0%)
Gastroesophageal Reflux Disease	0 (0%)	1 (1%)	0 (0%)
Intestinal Functional Disorder	0 (0%)	1 (1%)	0 (0%)
Nausea	0 (0%)	2 (1%)	0 (0%)
Vomiting	1 (<1%)	0 (0%)	0 (0%)
General Disorders and Administration Site Conditions:	0 (0%)	1 (1%)	0 (0%)
Sudden Death	0 (0%)	1 (1%)	0 (0%)
Musculoskeletal and Connective Tissue Disord.:	5 (1%)	2 (1%)	0 (0%)
Rheumatoid Arthritis	5 (1%)	2 (1%)	0 (0%)
Nervous System Disorders:	2 (1%)	2 (1%)	1 (1%)
Aphasia	0 (0%)	1 (1%)	0 (0%)
Depressed Level of Consciousness	0 (0%)	1 (1%)	0 (0%)
Dizziness	0 (0%)	1 (1%)	0 (0%)
Headache	2 (1%)	1 (1%)	1 (1%)
Psychiatric Disorders:	4 (1%)	0 (0%)	0 (0%)
Anxiety	1 (<1%)	0 (0%)	0 (0%)
Insomnia	2 (1%)	0 (0%)	0 (0%)
Sleep Disorder	1 (<1%)	0 (0%)	0 (0%)
Renal and Urinary Disorders:	0 (0%)	1 (1%)	0 (0%)
Renal Pain	0 (0%)	1 (1%)	0 (0%)
Vascular Disorders:	1 (<1%)	0 (0%)	0 (0%)
Secondary Hypertension	1 (<1%)	0 (0%)	0 (0%)

Adapted Sponsor's Table 39; p. Clinical Safety Summary

7.3.4 Significant Adverse Events

Discussed in section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

- a. Infections, Gastrointestinal, Cardiovascular, Metabolic, Central Nervous System (CNS) and Eye Adverse Events

In view of the well documented drug-induced toxicities associated with prednisone, the Applicant also submitted analyses of adverse events of interest that included infections, gastrointestinal (upper abdominal pain, dyspepsia, abdominal discomfort, and abdominal pain), cardiovascular (hypertension and secondary hypertension), sleep disorders (insomnia and sleep disorder), metabolic (weight increased, blood glucose increased, occult blood positive, diabetes mellitus and glycosuria), central nervous system (CNS) (depression and delirium) and eye problems (cataracts and glaucoma) in support of NP01's safety profile. The results of these analyses are shown in Table 38.. Overall, the proportions of patients who reported cardiovascular, metabolic, CNS and eye TEAEs were similar for all three treatment groups. Higher proportions of patients treated with prednisone IR reported treatment-emergent infections (13%) and TEAEs involving the gastrointestinal tract (8%) as compared to the NP01 treatment group (9% and 4%, respectively) and placebo group (2% and 8%, respectively). The higher rate of infections is not an unexpected finding in view of the immunosuppressive capabilities of corticosteroids. The higher rate of gastrointestinal AEs observed in the prednisone IR group is due to higher rates of upper abdominal pain (6%) and dyspepsia (2%) reported by subjects in this treatment group as compared to NP01 treated patients (2% and 1%, respectively). Due to the small number of cases reported, it is unclear if this finding is due to less localized gastrointestinal toxicity associated with NP01 as a result of its delayed release which may occur lower down in the intestinal tract or an artifact of a fairly limited sample size.

Table 42 - Analyses of Adverse Events of Interest from the Controlled Phase 3 Studies (Safety Population)

Adverse Event by MedDRA System Organ Class (SOC)/ Preferred Term	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Infections:	35 (9%)	18 (13%)	10 (8%)
Nasopharyngitis	5 (1%)	8 (6%)	4 (3%)
Bronchitis	5 (1%)	5 (4%)	5 (4%)
Urinary Tract Infection	2 (1%)	2 (1%)	0 (0%)
Upper Respiratory Tract Infection	2 (1%)	3 (2%)	1 (1%)
Pharyngitis	1 (<1%)	0 (0%)	1 (1%)
Sinusitis	1 (<1%)	1 (1%)	1 (1%)
Acute Tonsillitis	1 (<1%)	0 (0%)	0 (0%)
Pharyngitis Streptococcal	1 (<1%)	0 (0%)	0 (0%)
Respiratory Tract Infection	1 (<1%)	0 (0%)	0 (0%)
Rhinitis	1 (<1%)	0 (0%)	0 (0%)
Viral Upper Respiratory Tract Infections	0 (0%)	1 (1%)	0 (0%)
Gastrointestinal	13 (4%)	11 (8%)	2 (2%)
Abdominal Pain Upper	6 (2%)	8 (6%)	2 (2%)
Dyspepsia	3 (1%)	3 (2%)	0 (0%)
Abdominal Discomfort	3 (1%)	0 (0%)	0 (0%)
Abdominal Pain	2 (<1%)	1 (1%)	0 (0%)
Occult Blood Positive	1 (<1%)	0 (0%)	1 (1%)
Cardiovascular	8 (2%)	2 (1%)	1 (1%)
Hypertension	7 (2%)	2 (1%)	1 (1%)
Secondary Hypertension	1 (<1%)	0 (0%)	0 (0%)
Sleep Disorder	7 (2%)	2 (1%)	0 (0%)
Insomnia	4 (1%)	1 (1%)	0 (0%)
Sleep Disorder	3 (1%)	1 (1%)	0 (0%)
Metabolic	5 (1%)	2 (1%)	1 (1%)
Weight Increased	1 (<1%)	2 (1%)	0 (0%)
Blood Glucose Increased	2 (1%)	0 (0%)	0 (0%)
Diabetes Mellitus	1 (<1%)	0 (0%)	0 (0%)
Glycosuria	0 (0%)	1 (1%)	0 (0%)
Central Nervous System	2 (1%)	1 (1%)	0 (0%)
Depression	2 (1%)	1 (1%)	0 (0%)
Eye Problems	1 (<1%)	1 (1%)	0 (0%)
Cataract	0 (0%)	1 (1%)	0 (0%)
Glaucoma	1 (<1%)	0 (0%)	0 (0%)

Modified Sponsor's Table 35; p. Clinical Safety Summary

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As was shown in the preceding Table 39, approximately 50% of the patients experienced an adverse event while participating in the controlled studies. Table 43 summarizes the most commonly reported TEAEs reported by >2% of patients during the controlled studies NP01-007 and EMR 62215-003. The AEs by preferred MedDRA term most commonly reported by NP01-treated subjects were: rheumatoid arthritis (13%), nasopharyngitis (4%), headache (4%) and nausea (2%). Overall, the rates of commonly occurring TEAEs were comparable with those observed in the placebo treatment group with the exception of rheumatoid arthritis which occurred at a much higher rate (26%) and is not an unexpected finding in controlled studies assessing the efficacy of a disease treatment. The etiology of the overall higher rates of gastrointestinal disorders (11%) and infections (10%) observed in the prednisone IR treatment group is unclear. As suggested previously, NP0's delayed release may be associated with less localized toxicity of the upper gastrointestinal tract, but the number of cases is too small to draw a valid conclusion. Review of the safety data from the OLE of EMR 62215-003 and LOD 9577 did not result in the identification of any new or unexpected safety findings.

Table 43 – Incidence of TEAEs Occurring in >2% of Patients Treated with NP01 in Controlled Phase 3 Studies (Safety Population)

Adverse Event by MedDRA System Organ Class (SOC)/ Preferred Term	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Gastrointestinal Disorders:	19 (5%)	16 (11%)	3 (3%)
Abdominal Pain Upper	6 (<2%)	8 (6%)	2 (2%)
Diarrhea	4 (1%)	4 (3%)	1 (<1%)
Nausea	8 (2%)	4 (3%)	0 (0%)
Dyspepsia	0 (0%)	3 (2%)	0 (0%)
Infection and Infestations:	23 (6%)	15 (10%)	10 (8%)
Nasopharyngitis	16 (4%)	8 (6%)	4 (3%)
Bronchitis	5 (1%)	5 (4%)	5 (4%)
Upper Respiratory Tract Infection	2 (<1%)	3 (2%)	1 (<1%)
Musculoskeletal and Connective Tissue Disorders:	48 (13%)	14 (10%)	31 (26%)
Rheumatoid Arthritis	48 (13%)	14 (10%)	31 (26%)
Ear and Labyrinth Disorders:	4 (1%)	5 (4%)	0 (0%)
Vertigo	4 (1%)	5 (4%)	0 (0%)
Nervous System Disorders:	15 (4%)	5 (4%)	5 (4%)
Headache	15 (4%)	5 (4%)	5 (4%)
General Disorders and Administration Site Conditions:	2 (<1%)	0 (0%)	0 (0%)
Chest Pain	2 (<1%)	0 (0%)	0 (0%)

Modified Sponsor's Table 1.6.5 Clinical Safety Summary

7.4.2 Laboratory Findings

Laboratory data from the two controlled Phase 3 trials were presented as follows: actual values, change from baseline by parameter and the incidence of treatment-emergent shifts from normal range relative to baseline for selected parameters of clinical interest. The Applicant provided normal range of values for each lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate.

a. Hematology:

Table 45 shows there was no evidence of any clinically relevant mean changes from baseline or clinically relevant shifts from baseline in any of the hematological parameters across treatment groups for the controlled safety population. Similar findings were noted on examination of these data from the open label studies.

Table 44- Mean Change in Hematology Parameters for Subjects in the Controlled Phase 3 Studies (Safety Population)

Indice	NP01 (N=375)		Prednisone IR (N=144)		Placebo (N=119)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Hemoglobin (g/L)						
<i>N</i>	368	356	143	135	118	116
<i>Mean (SD)</i>	131 (15)	133 (16)	129 (15)	131 (20)	130 (14)	131 (12)
<i>Median</i>	131	132	130	130	133	133
<i>(Min, Max)</i>	(88, 214)	(78, 229)	(85, 216)	(86, 229)	(88, 159)	(100, 153)
WBC (x10³/mcl)						
<i>N</i>	368	356	143	135	118	116
<i>Mean (SD)</i>	7.8 (2.5)	7.6 (2.3)	8.7 (2.7)	8.9 (2.5)	7.6 (2.8)	7.3 (2.9)
<i>Median</i>	7.5	7.2	8.6	8.6	7.0	6.9
<i>(Min, Max)</i>	(2.6, 20)	(3.0, 16)	(4.1, 22)	(3.9, 18)	(2.9, 22)	(3.3, 20)
Basophils (%)						
<i>N</i>	228	221			117	116
<i>Mean (SD)</i>	0.7 (0.4)	0.7 (0.4)	Not available	Not available	0.8 (0.5)	0.8 (0.5)
<i>Median</i>	0.7	0.6			0.7	0.7
<i>(Min, Max)</i>	(0, 2.0)	(0, 2.7)			(0, 2.7)	(0, 2.9)
Eosinophils (%)						
<i>N</i>	228	221			117	116
<i>Mean (SD)</i>	2.4 (2.0)	1.8 (1.4)	Not available	Not available	2.3 91.5)	2.5 (1.6)
<i>Median</i>	2.0	1.4			2.0	2.3
<i>(Min, Max)</i>	(0, 24)	(0.2, 11)			(0.1, 9.2)	(0, 8.5)
Lymphocytes (%)						
<i>N</i>	228	221			117	116
<i>Mean (SD)</i>	26 (8)	24 (7)	Not available	Not available	24 (8)	25 (8)
<i>Median</i>	25	23			25	25
<i>(Min, Max)</i>	(8.5, 53)	(8.7, 51)			(8.5, 44)	(9.9, 47)
Monocytes (%)						
<i>N</i>	228	221			117	116
<i>Mean (SD)</i>	5.5 (1.8)	4.8 (1.7)	Not available	Not available	5.4 (3.3)	5.2 (2.0)
<i>Median</i>	5.3	4.4			4.8	4.8
<i>(Min, Max)</i>	(1.7, 14)	(1.5, 11)			(2.0, 35)	(1.0, 16)
Neutrophils (%)						
<i>N</i>	228	221			117	116
<i>Mean (SD)</i>	66 (8.9)	69 (8.3)	Not available	Not available	67 (9.5)	66 (9.6)
<i>Median</i>	66	70			67	67
<i>(Min, Max)</i>	(34, 87)	(39, 87)			(37, 88)	(45, 85)
Platelets (x10³/mcl)						
<i>N</i>	366	355	143	135	117	116
<i>Mean (SD)</i>	312 (96)	315 (93)	301 (93)	296 (88)	327 (98)	320 (97)
<i>Median</i>	304	307	282	285	312	316
<i>(Min, Max)</i>	(74, 700)	(18, 826)	(146, 558)	(131, 659)	(138, 675)	(133, 714)

Modified Sponsor's Table 1.12.1.1 from the Clinical safety Summary

Table 45 - Hematology Reference Range Shifts from Baseline for Subjects in the Controlled Phase 3 Studies (Safety Population)

Indice	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Hemoglobin (g/L)			
Shift from Normal to Low	10 (3%)	11 (8%)	3 (3%)
Shift from Normal to High	2 (1%)	0 (0%)	0 (0%)
Shift from High to Low	1 (0%)	0 (0%)	0 (0%)
WBC (x10³/mcl)			
Shift from Normal to Low	3 (1%)	0 (0%)	11 (9%)
Shift from Normal to High	18 (5%)	16 (11%)	0 (0%)
Shift from High to Low	0 (0%)	0 (0%)	0 (0%)
Basophils (%)			
Shift from Normal to Low	0 (0%)	Not available	0 (0%)
Shift from Normal to High	11 (3%)	Not available	9 (8%)
Shift from High to Low	0 (0%)	Not available	0 (0%)
Eosinophils (%)			
Shift from Normal to Low	0 (0%)	Not available	0 (0%)
Shift from Normal to High	2 (1%)	Not available	0 (0%)
Shift from High to Low	0 (0%)	Not available	0 (0%)
Lymphocytes (%)			
Shift from Normal to Low	32 (9%)	Not available	1 (1%)
Shift from Normal to High	1 (0%)	Not available	1 (1%)
Shift from High to Low	0 (0%)	Not available	0 (0%)
Monocytes (%)			
Shift from Normal to Low	23 (6%)	Not available	8 (7%)
Shift from Normal to High	3 (1%)	Not available	2 (2%)
Shift from High to Low	1 (0%)	Not available	1 (1%)
Neutrophils (%)			
Shift from Normal to Low	1 (0%)	Not available	0 (0%)
Shift from Normal to High	41 (11%)	Not available	10 (8%)
Shift from High to Low	0 (0%)	Not available	0 (0%)
Platelets (x10³/mcl)			
Shift from Normal to Low	1 (0%)	1 (1%)	0 (0%)
Shift from Normal to High	24 (6%)	3 (2%)	6 (5%)
Shift from High to Low	0 (0%)	0 (0%)	0 (0%)

Modified Sponsor's Table 1.12.2.1.4 from the Clinical Safety Summary

b. Clinical Chemistry:

Table 46 and Table 47 show there was no evidence of any clinically relevant mean changes from baseline in clinical chemistries parameters for the three treatment groups in the controlled safety population. Review of the shift analyses provided for the NP01 and prednisone IR groups shown in

Table 48 reveals clinically relevant shifts occurred in both treatment groups for the following parameters: cholesterol, triglycerides, and glucose. These findings are consistent with the well documented toxicity profile for corticosteroids. Similar findings were noted on examination of these data from the open label studies.

Table 46 – Mean Change in Liver and Lipid Parameters for Subjects in the Controlled Phase 3 Studies (Safety Population)

Indice	NP01 (N=375)		Prednisone IR (N=144)		Placebo (N=119)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Alk phos (U/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	83 (31)	81 (27)	77 (23)	74 (21)	82 (22)	81 (20)
<i>Median</i>	79	78	72	69	80	79
<i>(Min, Max)</i>	(38, 455)	(37, 319)	(32, 174)	(34, 162)	(37, 180)	(41, 144)
ALT/SGPT (U/L)						
<i>N</i>	373	363	144	138	116	113
<i>Mean (SD)</i>	24 (16)	24 (18)	21 (13)	22 (19)	24 (14)	26 (15)
<i>Median</i>	19	19	19	18	20	22
<i>(Min, Max)</i>	(6, 114)	(5, 156)	(8, 102)	(6, 211)	(8, 95)	(8, 101)
AST/SGOT (U/L)						
<i>N</i>	373	363	144	138	116	113
<i>Mean (SD)</i>	22 (10)	23 (12)	19 (7)	20 (9)	24 (10)	26 (13)
<i>Median</i>	21	21	18	18	22	23
<i>(Min, Max)</i>	(10, 81)	(8, 158)	(7, 49)	(9, 89)	(7, 74)	(12, 89)
GGT (U/L)						
<i>N</i>	374	363	144	138	116	113
<i>Mean (SD)</i>	31 (33)	30 (33)	28 (21)	27 (21)	29 (32)	32 (53)
<i>Median</i>	20	20	22	21	19	20
<i>(Min, Max)</i>	(5, 307)	(5, 334)	(4, 122)	(5, 144)	(7, 283)	(5, 518)
Bilirubin (umg/dL)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	7 (3)	7 (3)	6 (3)	6 (3)	7 (3)	7 (4)
<i>Median</i>	7	7	6	6	7	7
<i>(Min, Max)</i>	(2, 20)	(2, 22)	(2, 20)	(2, 17)	(2, 19)	(2, 22)
Albumin (g/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	43 (3)	44 (3)	43 (3)	42 (3)	44 (3)	44 (3)
<i>Median</i>	43	44	43	42	44	44
<i>(Min, Max)</i>	(34, 51)	(28, 51)	(35, 55)	(34, 49)	(34, 53)	(37, 52)
Protein (g/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	71 (5)	72 (5)	72 (5)	72 (4)	70 (4)	70 (4)
<i>Median</i>	71	71	73	72	70	70
<i>(Min, Max)</i>	(60, 89)	(57, 84)	(59, 90)	(58, 86)	(59, 80)	(59, 79)
Cholesterol (mmol/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	5.5 (1)	5.8 (1)	5.7 (1)	5.6 (1)	5.5 (1)	5.6 (1)
<i>Median</i>	5.5	5.7	5.7	5.7	5.4	5.5
<i>(Min, Max)</i>	(2.9, 11)	(3, 11)	(3, 9)	(3, 9)	(3, 9)	(3, 9)
Triglycerides (mmol/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	1.5 (0.9)	1.4 (0.7)	1.6 (0.9)	1.7 (0.8)	1.6 (0.9)	1.6 (1)
<i>Median</i>	1	1	1.5	1.6	1.5	1.4
<i>(Min, Max)</i>	(0.4, 7)	(0.4, 5)	(0.5, 8)	(0.5, 5)	(0.3, 7)	(0.5, 8)

Modified Sponsor's Table 1.12.1.2 from the Clinical Safety Summary

Table 47 - Mean Change in Renal and Electrolyte Parameters for Subjects in the Controlled Phase 3 Studies (Safety Population)

Indice	NP01 (N=375)		Prednisone IR (N=144)		Placebo (N=119)	
	Baseline	Week 12	Baseline	Baseline	Week 12	Baseline
BUN (mmol/L)						
<i>N</i>	230	225	Not available	Not available	116	114
<i>Mean (SD)</i>	5.2 (1.6)	5.5 (1.6)	Not available	Not available	5.4 (1.6)	5.4 (1.8)
<i>Median</i>	5.4	5.4			5.0	5.4
<i>(Min, Max)</i>	(1.8, 14)	(2.5, 11)			(1.8, 10)	(2.5, 12)
Creatinine (umol/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	69 (17)	69 (16)	71 (16)	70 (14)	67 (14)	68 (14)
<i>Median</i>	65	66	68	69	66	71
<i>(Min, Max)</i>	(42, 168)	(35, 168)	(45, 128)	(41, 114)	(35, 115)	(35, 115)
Glucose (mmol/L)						
<i>N</i>	369	356	143	135	116	113
<i>Mean (SD)</i>	5 (1)	6 (1)	5 (1)	5 (2)	6 (2)	6 (1)
<i>Median</i>	5	5	5	5	5	5
<i>(Min, Max)</i>	(3, 17)	(3, 15)	(4, 15)	(3, 17)	(4, 18)	(3, 13)
Calcium (mmol/L)						
<i>N</i>	374	363	144	138	116	114
<i>Mean (SD)</i>	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
<i>Median</i>	2	2	2	2	2	2
<i>(Min, Max)</i>	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)
Chloride (mmol/L)						
<i>N</i>	374	363	143	138	116	114
<i>Mean (SD)</i>	104 (2)	104 (2)	105 (3)	105 (2)	104 (3)	104 (2)
<i>Median</i>	104	104	105	105	104	105
<i>(Min, Max)</i>	(96, 111)	(96, 111)	(94, 113)	(96, 112)	(95, 110)	(95, 109)
Potassium (mmol/L)						
<i>N</i>	372	362	143	138	116	112
<i>Mean (SD)</i>	4 (0.4)	4 (0.4)	4 (0.3)	4 (0.4)	4 (0.4)	4 (0.4)
<i>Median</i>	4	4	4	4	4	4
<i>(Min, Max)</i>	(3, 6)	(3, 6)	(3, 5)	(3, 5)	(3, 6)	(3, 6)
Sodium (mmol/L)						
<i>N</i>	374	363	143	138	116	114
<i>Mean (SD)</i>	141 (2)	141 (2)	142 (2)	143 (2)	140 (2)	141 (2)
<i>Median</i>	141	141	142	143	141	141
<i>(Min, Max)</i>	(134, 149)	(133, 149)	(137, 147)	(137, 147)	(133, 146)	(129, 146)

Modified Sponsor's Table 1.12.1.2 from the Clinical Safety Summary

Table 48 - Chemistry Reference Range Shifts from Baseline for Subjects in the Controlled Phase 3 Studies (Safety Population)

Indice Shift from Normal to High	NP01 (N=375)	Prednisone IR (N=144)	Placebo (N=119)
Alk phos (U/L)	6 (2%)	2 (1%)	2 (2%)
ALT/SGPT (U/L)	13 (4%)	5 (4%)	6 (5%)
AST/SGOT (U/L)	13 (4%)	7 (5%)	9 (8%)
GGT (U/L)	15 (4%)	8 (5%)	2 (2%)
Bilirubin (umg/dL)	2 (<1%)	0 (0%)	2 (2%)
Albumin (g/L)	2 (<1%)	0 (0%)	2 (2%)
Protein (g/L)	3 (1%)	1 (<1%)	0 (0%)
Cholesterol (mmol/L)	54 (14%)	15 (10%)	9 (8%)
Triglycerides (mmol/L)	17 (5%)	15 (10%)	8 (7%)
BUN (mmol/L)	7 (2%)	0 (0%)	5 (4%)
Creatinine (umol/L)	9 (2%)	3 (2%)	2 (2%)
Glucose (mmol/L)	28 (8%)	18 (13%)	3 (3%)
Calcium (mmol/L)	1 (<1%)	0 (0%)	2 (2%)
Chloride (mmol/L)	3 (1%)	2 (1%)	0 (0%)
Potassium (mmol/L)	6 (2%)	1 (<1%)	3 (3%)
Sodium (mmol/L)	8 (2%)	1 (<1%)	0 (0%)

Modified Sponsor's Tables 1.12.2.2.4 and 1.12.2.2.1 from Clinical Safety Summary

c. Urinalysis:

Review of the mean changes from baseline and shift change from baseline analyses for urinalysis parameters failed to identify any clinically relevant changes in the controlled safety population associated with NP01 treatment.

7.4.3 Vital Signs

According to the protocols for the two controlled Phase 3 trials, patients' vital signs (systolic and diastolic blood pressure, heart rate, and body weight) were collected at the screening and baseline visits as well as at Weeks 2, 6 and 12 in NP01-007 and at the screening, baseline and Week 12 visit in EMR 62215-003. Vital signs from the pooled safety population were presented as mean change from baseline as shown in Table 49. No clinically meaningful changes were noted on review of these data associated with the administration of NP01.

Table 49 – Mean Change in Vital Sign and Weight Parameters for Subjects in the Controlled Phase 3 Studies (Safety Population)

Indice	NP01 (N=375)		Prednisone IR (N=144)		Placebo (N=119)	
	Baseline	Week 12	Baseline	Baseline	Week 12	Baseline
Systolic BP (mmHg)						
<i>N</i>	375	367	144	139	119	116
<i>Mean (SD)</i>	130 (14)	129 (14)	128 (14)	130 (15)	128 (12)	131 (13)
<i>Median</i>	130	130	130	130	130	130
<i>(Min, Max)</i>	(90, 183)	(90, 183)	(85, 180)	(100, 180)	(100, 164)	(90, 163)
Diastolic BP (mmHg)						
<i>N</i>	375	367	144	139	119	116
<i>Mean (SD)</i>	80 (8)	80 (9)	79 (9)	80 (9)	80 (7)	79 (8)
<i>Median</i>	80	80	80	80	80	80
<i>(Min, Max)</i>	(55, 119)	(60, 110)	(40, 100)	(55, 120)	(65, 98)	(60, 113)
Pulse (bpm)						
<i>N</i>	375	367	144	139	119	116
<i>Mean (SD)</i>	75 (8)	75 (8)	77 (8)	77 (8)	74 (9)	74 (7)
<i>Median</i>	74	74	76	76	74	74
<i>(Min, Max)</i>	(49, 110)	(49, 104)	(57, 108)	(56, 100)	(41, 101)	(60, 99)
Weight (kg)						
<i>N</i>	375	366	144	138	119	116
<i>Mean (SD)</i>	73 (16)	73 (16)	72 (16)	72 (16)	74 (16)	74 (16)
<i>Median</i>	70	70	71	72	71	71
<i>(Min, Max)</i>	(42, 158)	(44, 150)	(43, 114)	(44, 1140)	(45, 129)	(45, 130)

Modified Sponsor's Tables 1.13.1 and 1.13.2 from the Clinical Safety Summary

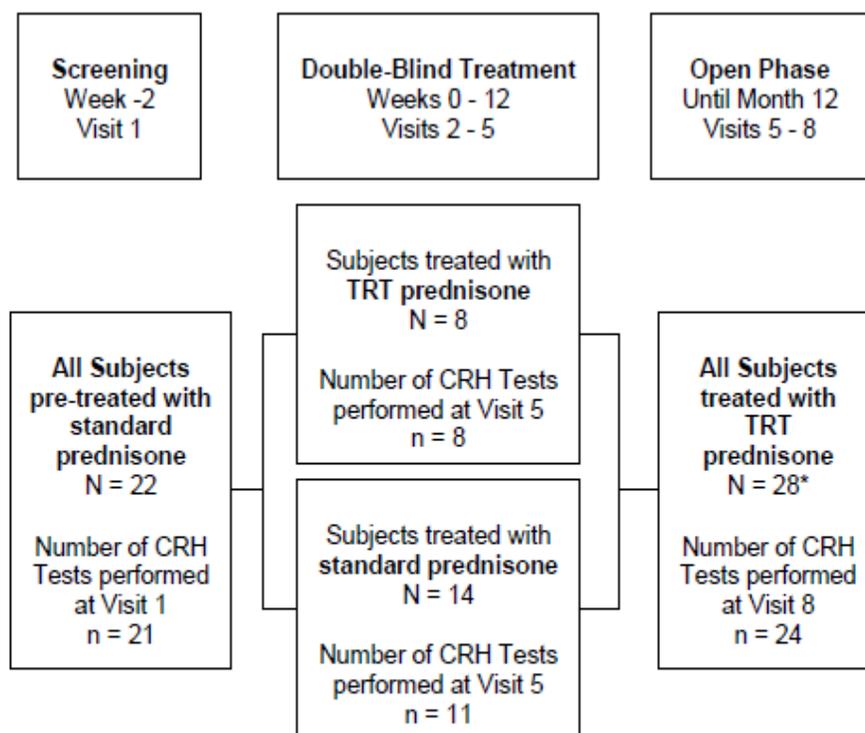
7.4.4 Electrocardiograms (ECGs)

The Applicant was not required to do QT prolongation studies as part of their clinical development program. Serial ECG 's were also not performed on subjects who participated in the trials conducted in support of the safety profile of this drug.

7.4.5 Special Safety Studies/Clinical Trials

Due to potential safety concerns related to suppression of the HPA as a result of the night time administration of NP01, the Applicant was required by the German regulatory authorities to conduct CRH testing in patients taking NP01 at bedtime. Pursuant to this, the Applicant conducted a CRH substudy as part of EMR 622-003 in which 28 patients taking a dose of ≥ 5 mg per day of NP01 or prednisone IR were subjected to CRH testing at three time points over the course of the study. The design of the substudy and disposition of subjects are shown in Fig. 5:

Figure 5 – Schemata of CRH Substudy



Source: Section 17, Listing 17.1

N = number of Subjects, n = number of CRH tests.

* at Visit 8 six additional subjects performed the CRH test, who had not been previously included in the test series of the CRH test substudy.

TRT prednisone = NP01

Standard prednisone = immediate release prednisone

Sponsor's Fig. 12.1; p. 57 Clinical Trial Report

Demographically, these subjects were predominantly female (89%), with a mean age of 56 years (range 33 to 69 years) and all were Caucasian. A total of 64 CRH tests were conducted over the course of the substudy, but not all subjects completed testing at all time points (see Figure 5). CRH testing was performed within 24 hours of prednisone administration and patients' serum cortisol levels were measured 15 minutes before, immediately before, and at 60 and 90 minutes post-injection of human corticotropin (CRH manufactured by Ferring). Review of the CRH test data collected in this substudy revealed no clinically relevant differences in CRH test responses in subjects treated with NP01 versus prednisone IR. Additionally, the amount of HPA axis suppression observed in patients taking 2-10 mg/day of NP01 for up to 12 months was similar to that observed in the active control patients who received prednisone IR for 3 months. In view of the small number of subjects, the lack adequately matched control subjects for dose

and duration of corticosteroid exposure, and incomplete testing, the validity of these findings is questionable.

7.4.6 Immunogenicity

Not applicable for this application since NP01 is a small molecular entity that does not contain proteins or protein derivatives that would elicit an immunogenic response.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Since corticosteroids historically have been shown to exhibit dose-dependent toxicity, the Applicant also performed all safety analyses subgrouped by pooled NP01 dose (e.g., ≤ 5 mg/day and > 5 mg/day). The overall incidence of treatment-emergent AEs in the pooled double-blind Phase 3 studies was higher in the NP01 ≤ 5 mg/day subgroup (43%) as compared to the > 5 mg/day subgroup (36%). Further examination of safety analyses by NP01 dose subgroup revealed inconsistent results that may have been impacted by the imbalance in the number of patients in the dose subgroups (≤ 5 mg/day subgroup: n=313 versus > 5 mg/day subgroup n=62).

7.5.2 Time Dependency for Adverse Events

In support of the safety profile of NP01, the Applicant performed analyses of treatment emergent events of special interest (e.g., CNS, cardiovascular, eye, gastrointestinal, etc...) by exposure time on the pooled data generated from the Phase 3 double-blind studies. The results of the cumulative incidence of any AE of special interest overall by treatment group by exposure time are shown in Table 50:

Table 50 – Cumulative Incidence of Treatment Emergent Events of Special Interest by Exposure Time for Patients in the Controlled Phase 3 Studies (Safety Population)

Any AE of Special Interest by Treatment	Exposure Duration			
	Days 1-30	Days 31-60	Days 61-90	Days 91-180
NP01 (N=375)				
N of Events/ N at Risk	31/375	16/331	15/303	0/18
Cumulative Estimate Event-Free Probability of Event (SE)	1.000	0.916	0.871	0.793
Hazard Rate	0.084 (0.0145)	0.049 (0.0120)	0.089 (0.0220)	0.000 (0.000)
Prednisone IR (N=144)				
N of Events/ N at Risk	19/144	8/119	5/108	0/13
Cumulative Estimate Event-Free Probability of Event (SE)	1.000	0.865	0.806	0.742
Hazard Rate	0.135 (0.288)	0.068 (0.232)	0.079 (0.0341)	0.000 (0.000)
Placebo (N=119)				
N of Events/ N at Risk	6/119	3/104	4/98	0/4
Cumulative Estimate Event-Free Probability of Event (SE)	1.000	0.948	0.920	0.850
Hazard Rate	0.052 (0.0208)	0.029 (0.0166)	0.075 (0.0363)	0.000 (0.000)

Modified Sponsor's table 1.7.4 Clinical Safety Assessment

No time dependency relationship was observed in the overall hazard rate analysis shown in Table 50 or on examination of the hazard rate analyses of the individual events of special interest.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of AEs were conducted by the Applicant on pooled data generated from the Phase 3 double-blind studies in order to determine if there were any drug-demographic interactions. Subgroup analysis was limited by small sample sizes for race and gender. Due to the paucity of Asian subjects (n=2) and Black/African American subjects (n=5) as well as male subjects (n=638; 15%) who participated in these trials no definitive conclusions regarding the risk for developing AEs associated with NP01 treatment can be made for any of these demographic groups.

The Applicant also conducted age-based analyses on safety data generated from the pooled Phase 3 double-blind studies for the following age subgroups: ≤ 45 years old (13%), >45 to 65 years old (68%), >65 to 75 years old (16%) and > 75 years old (3%). Despite the imbalances in the numbers of patients in the four age subgroups, no clinically meaningful age-related relationships for the occurrence of NP01 associated adverse events was observed on review of these analyses.

Of the two Phase 3 controlled studies, only NP01-007 included subjects (n=56) from North America who were all treated at doses \leq 5 mg/day of NP01 resulting in a limited analysis of AEs by geographic region from which no valid conclusions could be drawn.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were noted during the review of the safety data submitted in support of this application.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted by the Applicant in support of NP01's safety. Review of the database did not identify any AEs that appeared related to an interaction with concomitant medications. The Applicant referenced the current product labeling for both the RLD prednisone (PredniSONE Tablets) (NDA 17109) and Flo-Pred (prednisolone acetate) (NDA 22067) for background information on drug-drug interactions with prednisone IR.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no reports of malignancy associated with the use of NP01 in the safety database submitted in support of this indication by the Applicant. Human carcinogenicity studies were not required as the carcinogenicity and genotoxicity for prednisone IR is well documented.

7.6.2 Human Reproduction and Pregnancy Data

All of the study protocols that evaluated NP01 prohibited pregnant or breast feeding females from participating in these trials. Although these studies' entry criteria required women of reproductive potential to practice effective forms of contraception for the duration of the trials, there were a total of 2 pregnancies that occurred in the open-label phases of EMR 62215-003 summarized in Table 51:

Table 51 – Summary of Pregnancies in NP01 Safety Database

Subject Number	Demographics	Dose	Exposure	Concomitant Medications	Outcome
5502 OLE	33 yo female	7 mg/day	4 th week of pregnancy	Aurothiomalate sodium, diclofenac, omeprazole, calcium carbonate	Delivered healthy male without sequelae
5708 OLE	29 yo female	10 mg/day	1 st trimester	Cyclosporin, diclofenac, ranitidine, APAP and omeprazole	Delivered healthy male without sequelae

There were also three reports of pregnancies identified in the literature summarized in the PSUR submitted in support of NP01's safety profile in which no safety issues were identified.

The effects of prednisone IR on pregnant and lactating females are well documented, resulting in its classification as a Pregnancy Category D drug similar to the labeling for prednisolone. For completeness, the Applicant referenced the current product labeling for the RLD prednisone (PredniSONE Tablets) (NDA 17109) and Flo-Pred (prednisolone acetate) (NDA 22067) for background information on pregnancy, birth and lactation effects of NP01.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application did not contain any data generated from assessments of NP01's effect on growth. The potential for a negative impact on growth and development in children is described in the current labeling for the reference drug.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses occurred with NP01 over the course of its development. NP01 is a delay-release formulation of prednisone. Prednisone IR has no known potential for abuse or withdrawal, however, it is well documented that glucocorticoids can cause hypothalamic-pituitary adrenal (HPA) axis suppression resulting in adrenal insufficiency following withdrawal of treatment. In support of this, the Applicant referenced the current product labeling for the RLD prednisone (PredniSONE Tablets) (NDA 17109) and Flo-Pred (prednisolone acetate) (NDA 22067) for background information on overdose, abuse potential, withdrawal or rebound effects of prednisone IR. The Applicant's

proposed label contains appropriate information to health care prescribers regarding the need to gradually taper treatment and to avoid abrupt withdrawal of therapy.

7.7 Additional Submissions / Safety Issues

Additional safety information that was contained in the Applicant's 120-day safety update submitted on March 3, 2010 has been incorporated into the postmarketing and literature review subsections of this review.

8 Postmarket Experience

In support of NP01's safety profile, the Applicant submitted the results of a postmarketing review they conducted of AEs reports associated with any dose of "prednisone" or "prednisolone" that had been spontaneously submitted to the FDA's Spontaneous Reporting System (SRS) and the Adverse Event Reporting System (AERS database) for the time periods from January 1, 1969 through October 31, 1997 and November 1, 1997 to March 31, 2010, respectively. A total of 965,454 AE reports were identified during this search in which "prednisone" or "prednisolone" were listed as the suspected drug. Given the volume of data collected, the Applicant only included postmarketing AEs reported at a frequency $\geq 0.5\%$ of the total events collected by the FDA's AERS database which are summarized in Table 52:

Table 52 – Spontaneous Adverse Events Reported in > 0.5% of the Total Events in the SRS and AERS Databases for Prednisone and Prednisolone

System Organ Class Preferred Term	Number of Reports N (%)
AERS Total Number of Events	965,454 (100%)
Gastrointestinal Disorders:	
Diarrhea	5293 (0.5%)
Nausea	8419 (0.9%)
Vomiting	4889 (0.5%)
General Disorders and Administration Site Conditions:	
Asthenia	5541 (0.6%)
Condition Aggravated	5774 (0.6%)
Drug Ineffective	6078 (0.6%)
Fatigue	5877 (0.6%)
Pyrexia	11692 (1.2%)
Infection and Infestations:	
Pneumonia	6305 (0.7%)
Musculoskeletal and Connective Tissue Disorders:	
Arthralgia	5240 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders:	
Dyspnea	7570 (0.8%)

Adapted Sponsor's table 43; p. 298 Summary of Clinical Safety

No new safety signals were identified on review of these data.

Since March 2009, NP01 has been marketed in Germany and 13 other EU countries as well as Israel and Switzerland under the trade names, "Lodotra" and "Nocasio" for the treatment of moderate to severe, active rheumatoid arthritis in adults particularly when accompanied by morning stiffness. Marketing authorization for "Nocasio" has been subsequently withdrawn in all of these countries for commercial reasons only. For completeness, the Applicant submitted the fifth Annual Periodic Safety Update (PSUR) that covered the time period from October 18, 2010 through April 17, 2011 which reviewed all relevant Adverse Drug Reactions (ADRs) received from any source associated with Lodotra/Nocasio. Included in the 120-day safety update was the updated sixth PSUR which covered the 6-month period from April 18, 2011 through October 17, 2011. A cumulative total of 41 case reports and 11 literature reports of ADRs were reviewed and discussed in these PSURs. Included in the 120-day safety update were six additional case reports submitted after the data lock for the sixth PSUR. These reports were examined by this reviewer and no particular safety issues or concerns were identified for Lodotra/Nocasio.

9 Appendices

9.1 Literature Review/References

In support of NP01's safety profile, the Applicant provided a review of the worldwide literature that was limited to adverse events of special interest in addition to literature reviews included in the two PSURs discussed in Section 8. However, explanations of how these literature searches were conducted were not included for review.

Examination of the numerous articles cited in the original submission as well as the 13 citations from the worldwide literature published during the time periods covered by the fifth and sixth PSURs did not reveal any new safety signals associated with corticosteroid therapy. The Applicant did submit in the 120-day update, a line listing for one article from the scientific literature describing the reactivation of hepatitis B in two patients as a result of glucocorticoid treatment that resulted in the death of one patient. Reactivation of viruses is a known adverse effect of this drug class and is already listed in the class labeling.

9.2 Labeling Recommendations

Based on the review of data submitted in support of this application, this medical officer has the following recommendations for the product's label:

1. The trade name Rayos[®] is acceptable. It has been deemed acceptable by the Division of Medication Error Prevention and Analysis
2. The drug's label should be consistent with the current product labeling for the RLD prednisone (PredniSONE Tablets) (NDA 17109) as well as the recent updates in the label for Flo-Pred (prednisolone acetate) (NDA 22067)
3. Since NP01 is a member of the corticosteroid class of drugs, it is not considered to be a DMARD. Therefore, all connotations as such need to be omitted from the drug's label.
4. Since the drug will be labeled for all of the indications listed in the RLD, it does not need to be taken at bedtime. All instructions pertaining to the latter need to be omitted from the drug's label.
5. Unlike the labeling for immediate release formulations of prednisone, the Dosing and Administration section should state that NP01 needs to be taken with food in view of the drug's decreased bioavailability in the fasted state
6. Section 6.1 which describes the clinical trial experience for this drug should be omitted
7. Information describing potential drug-drug interactions for bupropion and fluoroquinolones should be included in Section 7

8. Pertinent CMC information related to NP0's delayed released should be included
9. Pertinent bioavailability data for NP01 should be included
10. It should state that NP01 is a Pregnancy Category D drug to be consistent with the June 2007 recommendations made by the Pediatric and Maternal Health Staff for prednisolone labeling
11. For consistency, the label should contain the same information for Pediatric Use as the RLD
12. The description of the results from NP01-007 should be omitted from Clinical Studies Section 14

9.3 Advisory Committee Meeting

In lieu of an advisory committee meeting, a regulatory briefing for this application was held on May 18, 2012 with CDER's senior management. Based on the presentations of data submitted in support of this application and the ensuing discussions, the committee's consensus was that there was adequate evidence in support of NP01's efficacy as a treatment for RA. A marketing claim for relief of morning stiffness could be entertained provided there was adequate evidence to support the validity of this endpoint as well as the instrument used to assess it. If not, the panel generally recommended that the drug be approved with the same generalized indications and labeling as the RLD.

10 Individual Study Reviews

10.1 Individual Study Reports

Protocol EMR 062215-500 CL016 LOD9577

Title: Non-Interventional study (NIS) to determine the improvement of the activity status and quality of life in patients with rheumatoid arthritis under treatment with the TEMPUS tablet.

Dates Conducted: This trial was started on April 15, 2009 and completed on October 29, 2010. Study enrollment was prematurely stopped at the end of 2009 in order to submit study results to the Reference Member State regulatory authority BfArM Germany as per the postmarketing commitments timeline for the drug.

Study Sites: A total of 461 centers (283 general practitioners and 178 rheumatologists) located in Germany.

Objectives:

Primary Objective:

- Determine how patients can directly benefit from a reduction of the morning stiffness symptoms in terms of an improvement of quality of life and activity status in 3 different areas
 - Occupational activities
 - Household duties
 - Leisure time activities

Secondary Objectives:

- Assess the safety of NP01(Lodotra) when used under every day conditions in addition to collecting socio-economic data such as medical aids/service
- Assess quality of life by HAQ-DI

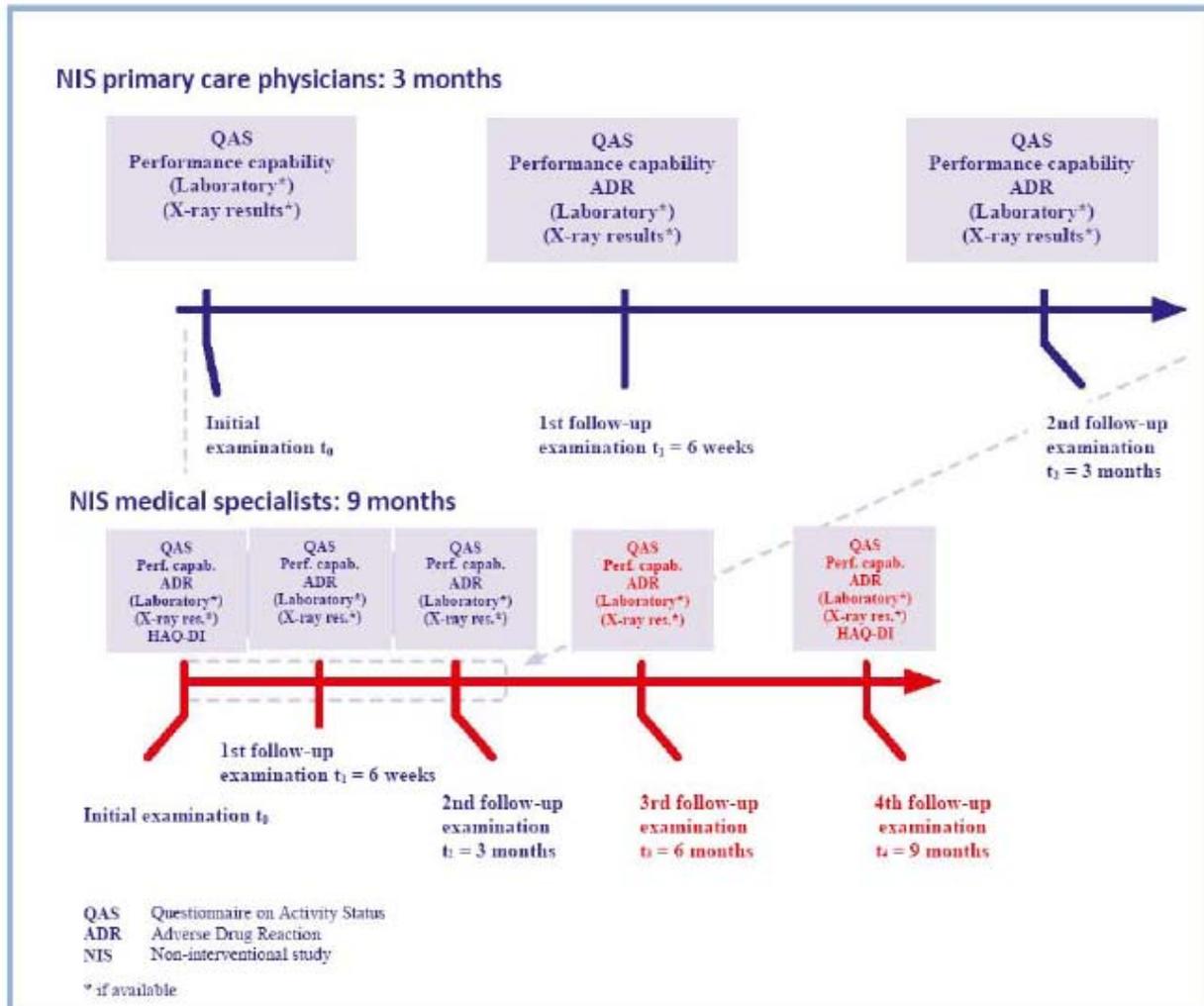
Overall Design:

This was to have been a multicenter, uncontrolled, non-interventional postmarketing study to evaluate improvement of activity status and quality of life in 8,000 patients treated with NP01 (Lodotra) or on recently initiated, stable doses of glucocorticoids. The trial was to have been comprised of two groups:

- Patients under the treatment of primary care physicians who were to have been observed for 3 months
- Patients under the treatment of rheumatologists who were to have been observed for 9 months

All assessment parameters for this study were to have been only collected if they were recorded routinely during medical check-ups.

Figure 6 - Schemata of EMR 062215-500 CL016 LOD9577



Sponsor's Fig. 9-1; p. 16 Clinical Study Report

Major Inclusion Criteria:

All subjects who met the approved indication for Lodotra (NP01) as well as:

1. Age 18 years or older
2. Diagnosis of active RA with accompanying symptoms such as morning stiffness
3. Already being treated with low-dose glucocorticoids or on recently initiated, stable glucocorticoid therapy

Exclusion Criteria:

Participation was at the discretion of the treating physician who checked for contraindications on an individual basis

Treatment:

NP01 (Lodotra) was to have been administered as specified in the approved European label (SmPC) for the drug. All patients were to have remained on their respective pre-study dose of NP01 (Lodotra). Newly diagnosed subjects starting glucocorticoid therapy were to have received the drug as prescribed by the study investigator. NP01 (Lodotra) was to have been prescribed for each patient under the health insurance provision.

Concomitant Medications:

There were to have been no restrictions regarding prior and concomitant medication used during the study. All medications taken within 12 months prior to the study and any concomitant medication taken during the trial were to have been recorded in the patients' CRF.

Study Procedures:

The following Table 53 is a tabular flow chart of the scheduled study visits as well as protocol specified procedures and evaluations. Patients followed by primary care physicians were to have undergone three evaluations over three months: the initial examination, at 6 weeks and after 3 months (Visits 1-3 [t₀-t₃]). Subjects followed by rheumatologists were to have undergone five evaluations over nine months: the initial examination, after 6 weeks, and at 3, 6 and 9 months (Visits 1-3 [t₀-t₄]).

Table 53 – Schedule of Assessments for Study EMR 062215-500 CL016 LOD9577

Assessment	Visit ^a				
	Visit 1 (t ₀)	Visit 2 (t ₁)	Visit 3 (t ₂)	Visit 4 (t ₃)	Visit 5 (t ₄)
Demographics	X				
Disease data					
RA	X				
Onset complaints	X				
Medication					
Lodotra ® dose	X	X	X	X	X
LAB findings					
CRP	X	X	X	X	X
ESR	X	X	X	X	X
X-ray	X	X	X	X	X
Concomitant /basic medication	X	X	X	X	X
Medical aids/services	X	X	X	X	X
Study endpoints					
QAS	X	X	X	X	X
Performance capability (VAS)	X	X	X	X	X
Side effects/ adverse events		X	X	X	X
HAQ-DI (patient questionnaire)	X				X

a: t₀ = initial examination; t₁= follow-up examination (FE) 6 weeks; t₂= FE 3 months; t₃= FE 6 months; t₄ = FE 9 months
 Sponsor's Table 9-2; p. 21 Clinical Study Report

Outcome Measures:

Primary Endpoint:

The primary endpoint was to have been the change at 3 months over baseline functionality as assessed via the Questionnaire on Activity Status (QAS) The QAS is a patient directed short questionnaire that quires subjects regarding their daily activities for the preceding 7 days.

Secondary Endpoints:

These were to have included:

- QAS comparison after 9 months
- Performance capability as assessed via 100 mm VAS
- Use of concomitant medication
- HAQ-DI score
- Lab findings (CRP, ESR, x-rays if available)

- Side effects and adverse events

Statistical Analysis:

Sample size calculations were based on exploratory data of the Questionnaire on Activity Status (QAS) score with $\alpha=0.01667$ following the application of a Bonferroni correction. This resulted in a study with 90% power and sample size of 5407 subjects. In view of a projected loss to follow-up of approximately 1/3 of study subjects based on prior experience with observational trials, the study's sample size was recalculated to be approximately 8000 subjects to compensate for the latter.

The safety population was to have been used in the analysis of safety and was to have included all patients who had at least one on-study visit.

Demographic, baseline characteristics, patient disposition, and safety data were to have been analyzed and summarized by descriptive statistics and presented in tabular form. MedDRA version 14.0 terminology was to have been used to classify adverse events which will be summarized by preferred term and system organ class.

Study Conduct:

There were no amendments to the protocol or protocol deviations reported for the safety population. Study enrollment was prematurely discontinued at the end of 2009 in order to have a report ready for submission to fulfill the postmarketing commitment timeline for this study.

Results:

A total of 2,730 subjects were enrolled in this trial (Table 54). Since trial enrollment was prematurely halted, the abbreviated study report contained the results of safety analyses conducted on data collected from the 2676 participating subjects who comprised the safety population. Table 54 summarizes the disposition of the safety population for this study. Overall rate of study completion was 74%. The most common reason for withdrawing prematurely from the study was due to insufficient efficacy (7%), experiencing an AE (6%), lost to follow-up (5%) and withdrawal of consent (4%). There were 4 deaths and 22 patients (1%) reported experiencing a SAE over the course of the study.

Table 54 - Subject Disposition for Study EMR 062215-500 CL016 LOD9577

	NP01 N (%)
Number of Patients Enrolled in Study	2730
Number of Patients in the Safety Population	2676
Number of Patients in Safety Population Who Completed Study	1971 (74%)
Number of Patients in Safety Population With Incomplete Data	39 (2%)
Number of Patients Who Experienced Any SAE	22 (1%)
Deaths	4 (<1%)
Number of Patients Who Prematurely Withdrew:	666 (25%)
Any AE	158 (6%)
Insufficient Efficacy	185 (7%)
Withdrawal of Consent	94 (4%)
Lost of Follow-up	144 (5%)
Noncompliance	52 (2%)
PI Decision	2 (<1%)
Therapy Break	12 (<1%)
Remission	14 (1%)
Other	5 (<1%)

The safety population includes all patients who are enrolled in the study and had at least one documented on-study visit.

Percentages are based on the number of patients in the Safety Population.

Modified Table 1a of Clinical Study Report Tables

A summary of the baseline demographics of patients who participated in this trial is shown in Table 55. Patients who participate in this study had a mean age of 60 years and were overwhelming female (72%) consistent with the sex distribution for RA. The mean duration of RA disease was approximately 8 years.

Table 55 – Demographic Characteristics of Patients Who Participated in EMR 062215-500 CL016 LOD9577 (Safety Population)

Demographic Characteristic	Total (N=2676)
Age (years)	
Mean (SD)	60 (13)
Median (Range)	60 (18, 97)
Gender:	
Male	748 (28%)
Female	1928 (72%)
Weight (kg)	
Mean (SD)	76 (15)
Median (Range)	75 (40, 165)
Height (cm)	
Mean (SD)	168 (8.6)
Median (Range)	168 (137, 204)
Disease Duration (years)	
Mean (SD)	7.9 (8.3)
Median (Range)	5.1 (0, 58)

Sponsor's Table 12-1; P. 26 Clinical Study Report

As shown in Table 56, the mean baseline dose of NP01 (Lodotra) was 5 mg/day and decreased over the course of the trial to approximately 3.8 mg/day.

Table 56 – Exposure to NP01 (Lodotra) in EMR 062215-500 CL016 LOD9577 (Safety Population)

Doses	Visit 1	Visit 2	Visit 3 ³	Visit 4	Visit 5 ³	Endpoint ¹
Total Patients	2676	2453	2341	1321	1186	2580
Mean (SD)	5.0 (2.4)	4.6 (2.2)	4.4 (2.2)	4.2 (2.0)	4.1(2.0)	3.8 (2.4)
Median (Range)	5 (1, 25)	5 (0,15)	5 (0, 15)	5 (0, 10)	5 (0, 20)	5 (0, 20)
Change²						
Mean (SD)		-0.4 (2.1)	-0.6 (2.4)	-0.8 (2.3)	-0.9 (2.4)	-1.2 (2.8)

¹Endpoint is the last visit information available for a patient (LOCF)

²Change is based on change in dose from Visit 1

³General practitioners' patients (N=929) study period was up to 3 months (Visit 1-3 only) and Rheumatologist patients (N=1747) study period was up to 9 months (Visit 1-5)

Study 12-2; p. 27 Clinical Study Report

Efficacy data results were not provided in the abbreviated study report included in support of this application. In terms of safety outcomes, 4 patients died while participating in this trial as follows: 1 patient died status post a fall, 1 patient died as a result of a myocardial infarction, and the circumstances surrounding the deaths of 2 remaining patients could not be determined. (Refer to Section 7.3.1 for additional information concerning these deaths.) Twenty-two subjects reported a total of 35 SAEs.

The most frequently reported SAEs involved the following system organ classes (SOC): gastrointestinal disorders (5 SAEs, <1%), general disorders and administration site conditions (4 SAEs; <1%), injury, poisoning and procedural complications (3 SAEs; <1%) and skin and subcutaneous disorders (3 SAEs; <1%). SAEs of concern included 1 case of GI bleeding, 1 case of hemorrhagic proctitis, 1 case of stomach pain/ache, and 1 case of red skin. A total of 281 AEs reported by a 158 patients (6 %) resulted in the premature withdrawal of these patients. The SOCs most commonly involved in patient withdrawal were: gastrointestinal disorders (54 subjects; 2%), psychiatric disorders (29 subjects; 1%), nervous system disorders (17 subjects; 1%), general disorders and administration site conditions (15 subjects; 1%) and skin and subcutaneous tissue disorders (15 subjects; 6%). Further examination of these data revealed that the most frequently reported AEs leading to premature withdrawal of subjects were: nausea (22 patients; 1%), upper abdominal pain (18 subjects; 1%), sleep disorders (16 patients; 1%), RA (11 patients; <1%), headache (9 patients; <1%), dizziness (6 patients; <1%) and glucose metabolism (3 patients with diabetes; <1%, and 3 patients with blood glucose increased; <1%). No new safety signal or unexpected pattern of AEs was observed on review of the safety data generated from this study.

Study Summary and Conclusions:

The overall safety profile of a mean low dose of 5 mg/day of NP01 (Lodotra) administered for 3-9 months to 2,672 RA patients was consistent with what has been observed in the Phase 3 clinical development studies for this drug as well as what has been reported historically in the literature for RA patients taking low dose immediate release prednisone. The low rates of AEs observed in this trial may be the result of reporting bias since the trial's observational non-interventional design required reporting of assessment parameters only if they were included as part of the subjects' routine medical visits.

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/s/

ROSEMARIE NEUNER
06/21/2012

SUSAN L LIMB
06/21/2012

support a morning stiffness claim, which would be a novel claim for a RA drug. Of note, prednisone is already approved for rheumatic disorders, including rheumatoid arthritis.

While the application is adequate for filing, preliminary review of the submission raises concerns about the clinical relevance of the data and whether the clinical data are essential to support the approval of a general treatment of RA indication. While the results from NP01-007 show statistically significant benefit for NP01 over placebo in terms of the primary endpoint, the ACR20, this result is expected since prednisone is already approved for RA. A general RA treatment indication could be supported by the pharmacokinetic-dissolution data alone. Alternatively, a novel indication such as the morning stiffness claim would require robust replicate results using a validated instrument for assessment. Whether the submitted data meet these latter requirements will be a review issue.

Comments for Sponsor

The following comment is to be conveyed to the Applicant in the 74-day Letter:

We have concerns regarding the validity of the assessment of morning stiffness and question the clinical relevance of the results. The inclusion of information on morning stiffness in the label will be a review issue.

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/s/

SUSAN L LIMB
12/08/2011