



## CLINICAL STUDY PROTOCOL ADDENDUM 1

### GERMANY

**A Randomized Multi-Center, Double-Blind, Placebo-Controlled Study of a New Modified-Release Tablet Formulation of Prednisone (Lodotra®) in Patients with Rheumatoid Arthritis**

#### Circadian Administration of Prednisone in RA

#### The CAPRA-2 Study

<b>Development Phase:</b>	Phase III
<b>Protocol No.:</b>	NP01-007
<b>IND Number:</b>	72,569
<b>EudraCT Number:</b>	2007-003508-36
<b>Sponsor:</b>	Nitec Pharma AG Kägenstrasse 17 4153 Reinach, Switzerland <a href="http://www.nitecpharma.com">www.nitecpharma.com</a>
<b>Date of Protocol:</b>	17 January 2008
<b>Date of Protocol Addendum:</b>	17 April 2008

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**SIGNATURE PAGES**

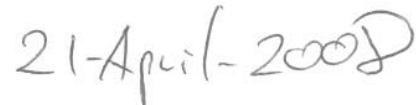
**SPONSORS APPROVAL OF STUDY PROTOCOL ADDENDUM**

This clinical study protocol addendum was subject to critical review and has been approved by the Sponsor.



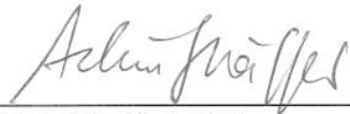
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Stephan Witte, PhD  
Chief Medical Officer



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Date



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Achim Schäffler, PhD  
EVP R&D and Technical Operations



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Date

## DECLARATION OF INVESTIGATOR

I agree to conduct this study in accordance with the requirements of this clinical study protocol addendum and also in accordance with the following:

- The principles of the “Declaration of Helsinki” (as amended in Tokyo, Venice, Hong Kong and South Africa)
- Good Clinical Practice, Respective local laws, and regulations

### Signature of Coordinating Investigator



\_\_\_\_\_  
Prof. Dr. Frank Buttgereit

22 - April 2008

\_\_\_\_\_  
Date

### Signature of Investigator at site

\_\_\_\_\_  
Investigator

\_\_\_\_\_  
Date

### **Rationale for this addendum**

The purpose of this addendum was to include an additional exclusion criterion for Germany, since it was advised that the administration of glucocorticoids can lead to an increase of internal eye pressure.

### **Summary of changes**

One additional exclusion criterion was added to the clinical study protocol.

To clearly highlight the changes made, the new text has been bolded (**new text**).

### **Protocol Synopsis, Page 8**

#### **Original text**

#### **Exclusion criteria:**

The presence of any of the following will exclude a patient from study enrolment:

- Suffering from another disease, which requires glucocorticoid treatment, e.g. asthma or neurodermatitis
- Synovectomy within 4 months prior to study start
- Use of glucocorticoids (by any route) within 6 weeks prior to screening visit (Visit 0)
- Use of biologicals: tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibitors within 3 months prior to screening visit (Visit 0) or other compounds within 1 year prior to screening Visit 0
- Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation
- Pregnancy or nursing
- Participation in another clinical study (use of an investigational product) within 30 days preceding Visit 0
- Re-entry of patients previously enrolled in this trial
- Suspected inability or unwillingness to comply with study procedures
- Alcohol or drug abuse
- Requirement of nonpermitted concomitant medication
- Known hypersensitivity to predniso(lo)ne
- Any contraindication for low dose prednisone treatment
- Significant renal impairment (serum creatinine > 150  $\mu$ mol/L)

- Significant hepatic impairment (investigator's opinion)
- Any uncontrolled concomitant disease requiring further clinical evaluation (e.g. uncontrolled diabetes, uncontrolled hypertension etc.)

#### New text

#### Exclusion criteria:

The presence of any of the following will exclude a patient from study enrolment:

- **An existing family predisposition for glaucoma, except if a medical ophthalmological examination of intraocular eye pressure measurement reveals normal findings**
- Suffering from another disease, which requires glucocorticoid treatment, e.g. asthma or neurodermatitis
- Synovectomy within 4 months prior to study start
- Use of glucocorticoids (by any route) within 6 weeks prior to screening visit (Visit 0)
- Use of biologicals: tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibitors within 3 months prior to screening visit (Visit 0) or other compounds within 1 year prior to screening Visit 0
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- Significant renal impairment (serum creatinine > 150  $\mu\text{mol/L}$ )
- Significant hepatic impairment (investigator's opinion)
- Any uncontrolled concomitant disease requiring further clinical evaluation (e.g. uncontrolled diabetes, uncontrolled hypertension etc.)

## Section 4.5, Exclusion Criteria, Page 28

### Original text

#### 4.5 EXCLUSION CRITERIA

Patients presenting with any of the following will not be included in the study:

- Suffering from another disease, which requires glucocorticoid treatment, e.g. asthma, neurodermatitis
- Synovectomy within 4 months prior to study start
- Use of glucocorticoids (by any route) within 6 weeks prior to screening Visit 0
- Use of biologicals: TNF $\alpha$  inhibitor within 3 months prior to screening Visit 0, other compounds within 1 year prior to screening Visit 0
- Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation
- Pregnancy or nursing
- Participation in another clinical study (use of an investigational product) within 30 days preceding Visit 0
- Re-entry of patients previously enrolled in this trial
- Suspected inability or unwillingness to comply with study procedures
- Alcohol or drug abuse
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- Suffering from another disease, which requires glucocorticoid treatment, e.g. asthma, neurodermatitis
- Synovectomy within 4 months prior to study start
- Use of glucocorticoids (by any route) within 6 weeks prior to screening Visit 0
- Use of biologicals: TNF $\alpha$  inhibitor within 3 months prior to screening Visit 0, other compounds within 1 year prior to screening Visit 0
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