



## CLINICAL STUDY PROTOCOL AMENDMENT 1

**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 Amendment:</b>	04 August 2008

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**SIGNATURE PAGES**

**SPONSORS APPROVAL OF STUDY PROTOCOL AMENDMENT**

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



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Stephan Witte, PhD  
Chief Medical Officer

05 AUG 2008

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Date



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Achim Schäffler, PhD  
EVP R&D and Technical Operations

05 Aug 2008

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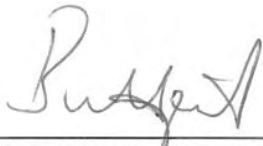
Date

**DECLARATION OF INVESTIGATOR**

I agree to conduct this study in accordance with the requirements of this clinical study protocol amendment 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



\_\_\_\_\_  
Date

**Signature of Investigator at site**

\_\_\_\_\_  
Investigator

\_\_\_\_\_  
Date

### **Rationale for this amendment**

The purpose of this amendment was to make clarifications and changes to sections of text in order to make them consistent throughout the protocol, to better reflect current clinical practice, and to make some necessary administrative changes.

### **Summary of changes**

Number of sites to be utilized changed from 40 to 45 to 50 to 55.

Changes to three exclusion criterion for clarification of the text and to better reflect current clinical practice.

Additional text regarding ongoing AEs at final visit included for consistency.

Collection and development of Hemocult/guaiac test moved from Visit 0 to Visit 1 in study schedule.

Hemocult/guaiac tests to be performed for safety reasons only and no longer for efficacy evaluation.

Additional text added regarding destruction of study materials for clarification.

Address of Coordinating Investigator added.

To clearly highlight the changes made, the new text has been bolded and italicized (*new text*) and any text removed is shown with strikethrough (~~old text~~).

### **Protocol Synopsis, Page 7**

#### **Original text**

##### **Study Sites:**

Approximately 40 to 45 in North America and Europe

#### **New text**

##### **Study Sites:**

Approximately ~~40 to 45~~ ***50 to 55*** in North America and Europe

## Protocol Synopsis Exclusion Criteria, Page 8

### Original text

- 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 (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

### New text

- Suffering from another disease, which requires glucocorticoid treatment *during the study period*, 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:~~
  - *Continued use of systemic glucocorticoids within 4 weeks prior to screening visit (Visit 0)*
  - *Intermittent use of glucocorticoids within 2 weeks prior to screening visit (Visit 0). (Intermittent is defined as a maximum of 7 days treatment with a cumulative dose of  $\leq 100$ mg prednisone or equivalent within 6 weeks prior to Visit 0)*
  - *Joint injections within 6 weeks prior to screening visit (Visit 0)*
  - *Topical glucocorticoids, e.g. intra-nasal or inhaled glucocorticoids must be stopped at screening visit (Visit 0)*
- Use of biologicals *such as: tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibitors and other compounds* within *5 serum half lives*~~3 months~~ prior to screening visit (Visit 0), ~~other compounds within 1 year prior to screening Visit 0~~

## Study Schedule, Page 12

### Original text

		Randomization				
		Double-blind phase				
Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	
Week	-1	0	2	6	12	
Collect and develop Hemocult/guaiaac Test	✓				✓	

### New text

		Randomization				
		Double-blind phase				
Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	
Week	-1	0	2	6	12	
Collect and develop Hemocult/guaiaac Test	✗	✓			✓	

## Study Schedule Footnotes, Page 13

### Original text

- f: If an AE is reported as 'ongoing' at Week 12, an additional follow-up will be performed at Week 16. If the ongoing AE at Week 12 involves a laboratory abnormality, an extra visit will occur at Week 16 for assessment of laboratory safety. If the ongoing AE at Week 12 does not involve a laboratory abnormality the patient will be followed up by telephone at Week 16.

### New text

- f: ~~If an AE is reported as 'ongoing' at Week 12, an additional follow-up will be performed at Week 16. If the ongoing AE at Week 12 involves a laboratory abnormality, an extra visit will occur at Week 16 for assessment of laboratory safety. If the ongoing AE at Week 12 does not involve a laboratory abnormality the patient will be followed up by telephone at Week 16.~~ **For ongoing AEs at final visit the clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up.**

### Section 3.1 Study Design, Page 25

#### Original text

This is a randomized multi-center, double-blind, parallel-group, placebo-controlled 13 week study comparing evening administration of 5 mg Lodotra® to placebo in patients with RA. It is planned to randomize a total of 294 patients in 40 to 45 centers in North America and Europe. Approximately 350 patients will be enrolled (at Visit 0), with a minimum of 6 and a maximum of 28 patients at each center.

During the screening phase informed consent to participate will be obtained (at Visit 0) and the eligibility of the patient for enrollment will be assessed and documented. The patient must meet all inclusion and exclusion criteria at Visit 0 before receiving screening medication, and must also meet all randomization criteria at Visit 1 before receiving Lodotra® or placebo. Patients not treated with a glucocorticoid for the 6 weeks prior to the screening visit (at Visit 0) will be eligible for inclusion. The single-blind screening phase will last for 1 week, and will include daily recording of duration of stiffness in the diaries prior to Visit 1 to calculate a robust baseline value (average of 7 daily values collected on days -7 to -1).

#### New text

This is a randomized multi-center, double-blind, parallel-group, placebo-controlled 13 week study comparing evening administration of 5 mg Lodotra® to placebo in patients with RA. It is planned to randomize a total of 294 patients in ~~40 to 45~~ **50 to 55** centers in North America and Europe. Approximately 350 patients will be enrolled (at Visit 0), with a minimum of 6 and a maximum of 28 patients at each center.

During the screening phase informed consent to participate will be obtained (at Visit 0) and the eligibility of the patient for enrollment will be assessed and documented. The patient must meet all inclusion and exclusion criteria at Visit 0 before receiving screening medication, and must also meet all randomization criteria at Visit 1 before receiving Lodotra® or placebo. Patients not **currently** treated with a glucocorticoids ~~for the 6 weeks prior to the screening visit (at Visit 0)~~ will be eligible for inclusion. The single-blind screening phase will last for 1 week, and will include daily recording of duration of stiffness in the diaries prior to Visit 1 to calculate a robust baseline value (average of 7 daily values collected on days -7 to -1).



## Section 4.1 Number of Patients, Page 26

### Original text

This sample will be obtained from approximately 40 to 45 centers in North America and Europe. It is expected that each study site will enroll between 6 and 28 patients.

### New text

This sample will be obtained from approximately ~~40 to 45~~ **50 to 55** centers in North America and Europe. It is expected that each study site will enroll between 6 and 28 patients.

## Section 4.5 Exclusion Criteria, Page 28

### Original text

- 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

### New text

- Suffering from another disease, which requires glucocorticoid treatment ***during the study period***, 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:~~
  - ***Continued use of systemic glucocorticoids within 4 weeks prior to screening visit (Visit 0)***
  - ***Intermittent use of glucocorticoids within 2 weeks prior to screening visit (Visit 0). (Intermittent is defined as a maximum of 7 days treatment with a cumulative dose of  $\leq 100$ mg prednisone or equivalent within 6 weeks prior to Visit 0)***
  - ***Joint injections within 6 weeks prior to screening visit (Visit 0)***
  - ***Topical glucocorticoids, e.g. intra-nasal or inhaled glucocorticoids must be stopped at screening visit (Visit 0)***

- Use of biologicals *such as*: TNF $\alpha$  inhibitors *and other compounds* within *5 serum half lives* ~~3 months~~ prior to screening visit (Visit 0); ~~other compounds within 1 year prior to screening Visit 0~~

## Section 5.5 Supplies and Accountability, Page 36

### Original text

The investigator or pharmacist will record and acknowledge receipt of all shipments of the investigational product and document the condition of each shipment. The investigational products must be kept in a locked area with restricted access. The investigational products must be stored and handled in accordance with the manufacturer's instructions. The investigator is responsible for maintaining documentation showing the amount of investigational product provided to the investigational site, and dispensed to and collected from each study patient. Discrepancies in investigational product accountability must be explained and documented. An inventory of investigational products will be maintained. The monitor is responsible for verifying the investigator's documentation on receipt, use and return of investigational products. The monitor will check drug accountability at sites on an ongoing basis from the start of the study. The monitor will prepare a final report of the accountability of the investigational product for filing in the investigator file. Thereafter, the medication may be destroyed.

### New text

The investigator or pharmacist will record and acknowledge receipt of all shipments of the investigational product and document the condition of each shipment. The investigational products must be kept in a locked area with restricted access. The investigational products must be stored and handled in accordance with the manufacturer's instructions. The investigator is responsible for maintaining documentation showing the amount of investigational product provided to the investigational site, and dispensed to and collected from each study patient. Discrepancies in investigational product accountability must be explained and documented. An inventory of investigational products will be maintained. The monitor is responsible for verifying the investigator's documentation on receipt, use and return of investigational products. The monitor will check drug accountability at sites on an ongoing basis from the start of the study. The monitor will prepare a final report of the accountability of the investigational product for filing in the investigator file. Thereafter, the medication may be destroyed. *Destruction of study medication should follow the local applicable standard procedures.*

### **Section 7.2.3 End of Treatment, Page 43**

#### **Original text**

- Document incidences and types of AEs in the CRF

#### **New text**

- Document incidences and types of AEs in the CRF
  - *For ongoing AEs at final visit the clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up*

### **Section 7.3.1.8 Hemocult/Guaiac Tests, Page 47**

This entire section will be removed and the text placed in Section 7.3.2.3 Hemocult/Guaiac Tests (see below). As a consequence, Section 7.3.1.9 Diary will now become Section 7.3.1.8.

### **Section 7.3.2.3 Hemocult/Guaiac Tests, Page 51/52**

#### **Original text**

Hemocult/guaiac tests will be performed to assess gastrointestinal safety. The test samples will be developed locally. The investigator will be responsible for evaluating and documenting the test results.

Hemocult/guaiac tests must be performed prior to randomization at Visit 0 and prior to the end of treatment at Visit 4. In the case of patients experiencing any gastrointestinal AEs, additional Hemocult/guaiac test must be performed.

The central laboratory will be responsible for providing the Hemocult/guaiac test kits and detailed handling instructions.

#### **New text**

~~Hemocult/guaiac tests will be performed to assess gastrointestinal safety. The test samples will be developed locally. The investigator will be responsible for evaluating and documenting the test results.~~

~~Hemocult/guaiac tests must be performed prior to randomization at Visit 0 and prior to the end of treatment at Visit 4. In the case of patients experiencing any gastrointestinal AEs, additional Hemocult/guaiac test must be performed.~~

~~The central laboratory will be responsible for providing the Hemocult/guaiac test kits and detailed handling instructions.~~

*Hemoccult/guaiac tests must be performed prior to randomization at Visit 0 and prior to the end of treatment at Visit 4. In the case patients experiencing any gastrointestinal adverse events, additional Hemoccult/guaiac tests must be performed.*

#### *Screening phase/Randomization*

*At Visit 0 the investigator will provide the Hemoccult/guaiac test kit to the patient with precise instructions on the correct handling of the test kit. In addition, patients will receive a test instruction sheet. Patients will be reminded to return the test kit at the next visit. Patients should perform the test during the screening phase within 5 days prior to the next scheduled visit.*

*At Visit 1, prior to randomization, the investigator will collect the test samples. The investigator will be responsible for developing the test samples according to the guidelines provided by the central laboratory. The results of the tests should be evaluated and documented by the investigator.*

*Patients with a positive test will be advised to contact a gastroenterologist. If gastrointestinal bleeding can be excluded by the gastroenterologist, the patient may repeat the screening phase. If the Hemoccult/guaiac test result is again positive, the patient must not be randomized.*

*At Visit 1, an extra test kit will be provided to the patient.*

#### *During treatment phase and end of study*

*Patients will be advised to contact the site when experiencing any gastrointestinal AE. Under direction of the investigator, the patient must be instructed to collect new samples with the extra test kit provided, and return it to the site.*

*At Visit 3, patients will receive a new Hemoccult/guaiac sample kit. Two weeks prior to Visit 4, the site should contact and remind the patient to collect samples and return the test kit at the next visit.*

*At Visit 4, the test samples will be collected and developed by the investigator. Results will be documented and evaluated by the investigator.*

*If, at the end or during the study, the Hemoccult/guaiac test is positive, the patient must consult a gastroenterologist, and if gastrointestinal bleeding cannot be excluded, a gastrointestinal endoscopy must be performed. Medical reports of the gastroenterologist will be blinded and forwarded to the Sponsor.*

*The central laboratory will be responsible for distributing Hemoccult/guaiac test kits to the site. Test results will be evaluated locally. Detailed instructions about the handling of the Hemoccult/guaiac test will be described in a special laboratory manual, provided by the central laboratory.*

## **Section 14.2, Declaration of Investigator, Page 72**

### **Original text**

#### **14.2 DECLARATION OF COORDINATING INVESTIGATOR**

I hereby agree that I will assume the responsibilities of the Coordinating Investigator in this study, including reviewing and signing the following: study protocol, amendments to the protocol if applicable, and final study report.

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Prof. Dr. Frank Buttgereit

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Date

### **New text**

#### **14.2 DECLARATION OF COORDINATING INVESTIGATOR**

I hereby agree that I will assume the responsibilities of the Coordinating Investigator in this study, including reviewing and signing the following: study protocol, amendments to the protocol if applicable, and final study report.

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Prof. Dr. Frank Buttgereit

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Date