# Clinical Study Report Synopsis

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## An open label, multiple dose Phase III clinical study in patients with prostate cancer to investigate the clinical efficacy and safety of a new GnRH implant (AMW Leuprorelin 10.72 mg implant) applied twice every 84 days

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| **Project No.:** | AMW/003/C |
| **EudraCT No.:** | 2011-006014-14 |
| **Investigational drug:** | AMW Leuprorelin 10.72 mg implant (subcutaneous application of the implant by means of a special applicator on day 0 and day 84) |
| **Reference drug:** | none |
| **Indication:** | Prostate cancer |
| **Phase of study:** | III |
| **First patient enrolled:** | 21 May 2012 |
| **Last patient completed:** | 19 Feb 2013 |

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# SYNOPSIS

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| *Name of Finished Product:* | *Volume:* | |
| *Name of Active Ingredient:*<br>**Leuprorelin** | *Page:* | |

**Title of Study:**
An open label, multiple dose Phase III clinical study in patients with prostate cancer to investigate the clinical efficacy and safety of a new GnRH implant (AMW Leuprorelin 10.72 mg implant) applied twice every 84 days

**Investigators:**

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Dr. med. Arman Amiri-Sani, Joint Practice Urology, Borken, Germany

**Study Centres:**
Three centres in Germany enrolled patients.

**Publication:**
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| **Study Period:** | **Phase of Development:** |
|---|---|
| First patient enrolled: 21 May 2012<br>Last patient completed: 19 Feb 2013 | III |

**Objectives:**
Overall objective:
- To investigate the clinical efficacy and safety of the new gonadotropin releasing hormone (GnRH) implant (AMW Leuprorelin 10.72 mg implant) applied twice every 84 days.

Primary objective:
- To demonstrate that AMW Leuprorelin 10.72 mg implant leads to a consistent suppression of testosterone levels below castrate level (0.5 ng/mL).

**Methodology:**
This was an open-label non-comparative, multiple dose Phase III study in patients with advanced prostate cancer suitable for hormonal manipulation. After a screening phase of up to 2 weeks, all eligible patients received active treatment with a new GnRH implant (AMW Leuprorelin 10.72 mg implant), applied twice, on Day 0 and Day 84. After each implant application, the patients were closely controlled for 84 days by several control visits.

**Number of Patients (Planned and Analysed):**
It was planned to screen patients until 50 eligible patients (i.e. patients compliant with all in- and exclusion criteria) were enrolled.

Overall, 54 patients were screened for the study. Three patients were screening failures and one patient withdrew his consent before baseline visit (Day 0). 50 patients were considered eligible at baseline and received study medication. These 50 patients were analysed in the safety analysis set as well as in the full analysis set (FAS). Additionally, a subset of the full analysis set ('FAS, treated patients') was analysed, comprising all FAS patients except those who are supposed to have failed applications of the study drug. This subset of the FAS comprised 49 patients.

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Two FAS patients were excluded from the per-protocol (PP) analysis set which comprised a total of 48 patients. The reasons for exclusion from the PP set were major protocol violations.

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

Main Inclusion Criteria:

- Males aged 18 years or older,
- Diagnosis of locally advanced, recidivated or metastatic carcinoma of the prostate suitable for hormonal manipulation including patients with rising PSA after having undergone surgery or radiotherapy with curative intention,
- Normal testosterone values (> 8 nmol/L or > 2.3 ng/mL) at screening according to immunoassay,
- Life expectancy of at least six months,
- The patient was capable of giving informed consent, which included compliance with the requirements and restrictions listed in the Consent Form,
- The patient was able to understand and follow instructions and was able to participate in the study for the entire study period,
- Patient has given his written informed consent to participate in the study after receiving adequate previous information and prior to any study-specific procedures.

Main Exclusion Criteria:

- Hypersensitivity to leuprorelin or to other GnRH analogues,
- Treatment with GnRH analogues completed less than 6 months prior to the baseline visit,
- Patients considered being candidates for curative therapy i.e. radical prostatectomy or radiotherapy within 6 months from inclusion,
- Cancer disease within the last 5 years except prostate cancer, and except surgically removed basocellular or squamous cell carcinoma of the skin,
- Patients with clinically significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, haematological, dermatological or any infectious disorder or any other condition including alcohol or drug abuse, which may have interfered with trial participation or which may have affected the conclusion of the study as judged by the investigator,
- Mental incapacity or language barriers precluding adequate understanding or co-operation,
- Previous participation in this study,
- Simultaneous or less than 12 weeks earlier participation in another clinical trial,
- Known allergy against one of the ingredients in the test preparation.

**Test Drug, Dose and Mode of Administration, Batch Number:**

AMW Leuprorelin 10.72 mg implant
Active substance: leuprorelin base 10.72 mg
Implant to be injected subcutaneously. Study medication was applied at study site by investigator.
Batch number: C0009AM0801IMP
Expiry Date: 02/2013
All treated patients received study medication with the same batch number.

**Duration of Treatment:**

The duration of treatment was 168 days with two applications of AMW Leuprorelin 10.72 mg implant, on Day 0 and on Day 84.

**Reference Therapy, Dose and Mode of Administration, Batch Number:**

Not applicable

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**Criteria for Evaluation:**

Primary Efficacy Variables:

- Testosterone plasma levels measured by LC-MS/MS at each visit from Day 28 until the end of the study.

Efficacy Endpoints derived from primary efficacy variables:

- Percentage of patients with plasma testosterone below castrate level (i.e. below 0.5 ng/mL) 4 weeks after treatment initiation (at Day 28) and at the end of the first treatment cycle (Day 84),
- Percentage of patients with plasma testosterone below castrate level (i.e. below 0.5 ng/mL) at the end of the study (Day 168),
- Percentage of patients with testosterone levels above castrate level (i.e. above 0.5 ng/mL) at the beginning of the second treatment cycle (i.e. on Day 87),
- Percentage of patients with consistent suppression of testosterone levels below castrate level (i.e. below 0.5 ng/mL) at all visits from Day 28 until the end of the study
- Percentage of patients with 0, 1, 2, and more than 2 of their testosterone levels measured from Day 28 until the end of the study above or equal castrate level (i.e. above or equal 0.5 ng/mL)

Secondary Efficacy Variables:

- Testosterone plasma levels measured by LC-MS/MS at each visit before Day 28
- Leuprorelin levels at each visit from Day 0 until the end of the study
- LH levels at each visit from Day 0 until the end of the study
- FSH levels at each visit from Day 0 until the end of the study
- PSA levels at baseline (Day 0) and at the end of each treatment cycle

Secondary Efficacy Endpoints:

- Mean values of testosterone, leuprorelin, LH, FSH and PSA levels by visit
- Time to achieving testosterone plasma levels below castrate level, i.e. first visit with a testosterone plasma level below castrate level (i.e. below 0.5 ng/mL)

Safety Variables:

- Adverse Events (AEs),
- Vital signs (blood pressure, heart rate), body weight and temperature
- Safety laboratory parameters,
- Changes between baseline and end of study in findings from the examination of the prostate,
- Assessment of local tolerability of the impant.

**Statistical Methods:**

Three analysis sets were used for the statistical analysis of primary efficacy variables: the full analysis set (FAS) (primary analysis set for efficacy analyses; all patients who were considered by the investigator to be eligible for treatment at the Day 0 visit), the 'full analysis set, treated patients' (TRT) (all patients of the full analysis set except patients with failed applications of the study drug), and the per-protocol (PP) set (per-protocol analysis; all patients of the FAS, except for patients with major protocol violations).

The safety set included patients who received at least one application of study medication.

The primary objective of this phase III study was to demonstrate that AMW Leuprorelin 10.72 mg implant leads to a consistent suppression of testosterone levels below castrate level (0.5 ng/mL). Primary efficacy variables were the testosterone plasma levels measured by LC-MS/MS at each visit from Day 28 until the end of the study. The first four efficacy endpoints derived from the primary

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efficacy variables were analysed using absolute and relative frequencies. The denominator was the number of patients for whom each endpoint was assessable (number of patients with 'yes' or 'no'). Two-sided exact 95% confidence intervals (Clopper-Pearson CIs) were calculated for these endpoints.

The denominator for the last efficacy endpoint derived from the primary efficacy variables was the number of patients with at least two testosterone levels available from Day 28 onwards.

Subgroup analyses were performed as planned in the protocol and in the Statistical Analysis Plan.

Descriptive statistical methods were used to analyse all variables. Continuous variables are summarised using the following standard descriptive summary statistics: Number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data are described using absolute and relative frequencies.

**Summary:**

**Patients disposition:**

A total of 50 patients considered as eligible at baseline were treated with study medication, i.e. 50 patients received two applications of AMW Leuprorelin 10.72 mg implant during the course of the study. Out of these 50 patients who were included in the FAS, one patient died during the study as this patient experienced an acute renal failure of severe severity. There were no other premature terminations.

As requested by the study design, all patients were male (100%). For FAS patients the mean age at baseline was 74.2 years, the mean weight at baseline was 84.1 kg, and the mean height was 175 cm.

**Efficacy Results:**

One patient (Patient 10-006) showed leuprorelin values below the limit of quantitation following the first implant. The patient had testosterone values above castrate level following the first implant and achieved testosterone values below castrate level following the second implant. This patient was included in the FAS but excluded from the 'FAS, treated patients' analysis set.

Two further individual samples taken at visit Day 28 or later showed testosterone values above castrate level:
The testosterone value of Patient 10-011 at visit Day 70 was 0.595 ng/mL, i.e., slightly above castrate level. Testosterone values at visit Day 56 and visit Day 84 of the same patient were below the limit of quantitation. The testosterone value of patient 20-009 at visit Day 168 was 0.564 ng/mL. The preceding value was below the limit of quantitation.

Overall, 47/50 FAS patients (94.0%) achieved testosterone values below castrate level from Day 28 until the end of the study. For one patient the first implant did not lead to detectable leuprorelin levels and did not result in a decrease in testosterone below castrate level, another patient showed a testosterone value slightly above castrate level on Day 70, and a third patient had an increase in testosterone to a value slightly above castrate level at the end of the second treatment cycle.

Mean testosterone levels showed a noticeable decrease by visit Day 14, the mean value remained low until the end of the study.

Mean leuprorelin values showed a peak at the visits 3 days after each implant as expected.

Mean LH and FSH levels decreased by visit Day 14 and remained on lower levels throughout the

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study.

Mean PSA values also clearly decreased between baseline and the end of the first treatment cycle. Similarly low mean values were still observed at the end of the second treatment cycle.

In summary, the study successfully shows that AMW Leuprorelin 10.72 mg implant leads to a consistent suppression of testosterone levels below castrate level (0.5 ng/mL). A consistent suppression was achieved by 47/50 patients in the FAS (94.0%, [83.45%; 98.75%]) and by 47/49 patients (95.92%, [86.02%; 99.50%]) in the 'FAS, treated patients' analysis set.

**Safety Results:**

In total, 135 AEs occurred in 42 patients (84.0%) with applied implants. The vast majority of AEs were of mild or moderate severity. No AEs leading to discontinuation of study drug were reported.

A total of 87 AEs in 36 patients (72.0%) were rated as adverse drug reactions (ADRs), as a causal relationship with AMW Leuprorelin 10.72 mg implant was considered at least possible. All of these 87 were treatment-emergent ADRs.

In this trial, a total of seven SAEs occurred in seven patients (14.0%). As causality was assessed as unrelated for each SAE, none of these SAEs were declared as an ADR.

One patient, aged 74 at baseline, died after experiencing acute renal failure, causal relationship with the investigational product was assessed as unrelated by the investigator.

Laboratory parameters in general did not raise safety concerns.

AMW Leuprorelin 10.72 mg implant seemed to be generally well tolerated both locally and systemically. Several reported adverse events reflect the intended pharmacological action, i.e., suppression of testosterone levels.

**Conclusions:**

The study successfully shows that AMW Leuprorelin 10.72 mg implant leads to a consistent suppression of testosterone levels below castrate level (0.5 ng/mL). A consistent suppression was achieved by 47/50 patients in the FAS (94.0%) and by 47/49 patients (95.92%) in the 'FAS, treated patients' analysis set.

AMW Leuprorelin 10.72 mg implant seemed to be generally well tolerated both locally and systemically. Several reported adverse events reflect the intended pharmacological action, i.e., suppression of testosterone levels after continuous treatment.

In all patients treated with the AMW Leuprorelin 10.72 mg implant testosterone levels below 0.5 ng/mL could be achieved. Based on the current data, the AMW Leuprorelin 10.72 mg implant can be considered as efficacious and safe.

The study supports a favourable benefit/risk profile of AMW Leuprorelin 10.72 mg implant in the treatment of locally advanced, recidivated or metastatic carcinoma of the prostate suitable for hormonal manipulation in men.

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| **Date of the report:** | 29 May 2015 |