Effectiveness of Zometa® treatment for the prevention of bone metastases in high risk prostate cancer patients. A randomized, open-label, multicenter study of the European Association of Urology (EAU) in Cooperation with the Scandinavian Prostate Cancer Group (SPCG) and the Arbeitsgemeinschaft Urologische Onkologie (AUO).
Signature Page

**Compound name / number:** Zometa® (zoledronic acid, CGP42446)

**Protocol number:** CZOL446G DE08/SPCG Protocol No. 11

Approved by the following:

- **Prof. Dr. Manfred Wirth**
  - Signature
  - Date

- **Local Study Chairman**
  - Signature
  - Date

- **Dr. Giovanni. Pappagallo**
  - Signature
  - Date
Signature page for Investigators

Compound name / number: Zometa® (zoledronic acid, CGP42446)
Protocol number: CZOL446G DE08/SPCG Protocol No. 11
Country:

I understand that this amendment contains confidential information property of the EAU. I have received and read this amendment and I agree that it contains all the necessary details for carrying out the study described herein. I shall direct this amendment in the manner described herein and I shall make all reasonable efforts to complete the study within the designated time.

I will provide copies of this amendment and access to all information furnished by the EAU to the staff participating in the study and who are under my supervision. I will discuss this material with them to ensure that they have all the information for carrying out the study.

I agree to conduct this trial in accordance with all stipulations of the protocol and amendment; and in accordance with the Declaration of Helsinki.

Name of Investigator ___________________________ Signature ___________________________ Date ___________

**Table of contents**

- Signature Page ............................................................................................................................ 2
- Signature page for Investigators ................................................................................................3
- Rationale for amendment ............................................................................................................ 5
- Changes to Protocol including Amendment 1 ................................................................. 6
- 1. Introduction ......................................................................................................................... 6
- 2. Study objectives .............................................................................................................6
- 3.2. Discussion of design ........................................................................................................... 6
  - 3.3.2. INCLUSION AND EXCLUSION CRITERIA ............................................................ 7
  - 3.3.3 RANDOMIZATION ................................................................................................. 8
  - 3.3.4. INTERRUPTION OR DISCONTINUATION OF TREATMENT ............................. 8
- 3.4. Treatments ....................................................................................................................... 9
  - 3.4.1. INVESTIGATIONAL THERAPY AND REFERENCE THERAPY .......................... 9
- 3.5. Visit schedule and assessments ...................................................................................... 12
  - 3.5.1. VISIT SCHEDULE ............................................................................................... 12
  - 3.5.2. Efficacy assessments ............................................................................................... 13
  - 3.5.3. SAFETY ASSESSMENTS .................................................................................... 14
  - 6.1.5.2. Secondary efficacy variables ............................................................................ 14
- 9.1.1. INSTRUCTIONS FOR RAPID NOTIFICATION OF SERIOUS ADVERSE EVENTS 14
- 9.2.5. RECORDING OF DATA AND RETENTION OF DOCUMENTS ......................... 15
- 9.2.7. PUBLICATION OF RESULTS .................................................................................... 15
- Appendix 3: Staging of Prostate Cancer TNM Classification ................................................. 16
- Appendix 6: Local delegates of the Sponsor for SAE reporting ............................................ 18
Rationale for amendment

During the Steering Committee that took place in Munich on March 31st 2004 it was decided to re-introduce the sub-study on bone mineral density, that was erroneously cancelled with the Amendment 1. Therefore, the present Amendment re-introduces all the parts that were deleted with Amendment 1 as far as the sub-study on bone mineral density is concerned.

Since in the original protocol no limitation of the time-window between two infusions of the experimental drug was reported, it has been decided that the maximum time for Zometa discontinuation should be 16 weeks. Administration of the drug beyond 16 weeks after the last Zomata infusion will be considered as a major protocol deviation.

Due to recent changes made to Zometa prescribing information, an amendment to clinical study protocols with Zometa is required. These changes involve two areas:

- **Dose reduction for patients with renal impairment**: patients with advanced cancer frequently experience impaired renal function as a consequence of their disease and/or their treatment. To mitigate the risk of further renal deterioration, a new dosing schedule for Zometa has been developed for patients with renal impairment and is now being incorporated into prescribing information in most countries world wide. The dose of Zometa will be determined by patient’s renal creatinine clearance (CrCl) calculated by the Cockcroft-Gault formula. A Zometa dose of lower than 4 mg will be administered to patients with CrCl of ≤60 mL/min. The specific dose chosen is based on the principle of maintaining an area under the curve (AUC) of Zometa similar to that observed in patients with normal renal function receiving 4 mg Zometa, thereby preserving the efficacy of Zometa.

- **Osteonecrosis of the jaw (ONJ)**: osteonecrosis of the jaw has been reported in cancer patients receiving bisphosphonates as a component of their therapy. The etiology and pathogenesis of ONJ are not clear, but multiple risk factors are involved, including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids), and co-morbid conditions (e.g. anemia, coagulopathies, infection, pre-existing oral disease). Therefore, a causal relationship between bisphosphonate therapy and ONJ has not been established. Since the majority of reported cases have been associated with dental procedures such as tooth extraction, and many had signs of local infection including osteomyelitis, it is prudent to amend Zometa clinical study protocols to introduce measures that should help reduce the incidence of ONJ and to improve its recognition when it occurs.

The instructions for rapid notification of serious adverse events has been revised according to local internal procedure of Novartis subsidiaries of the countries involved in the trial. What changes from country to country is the information flow of SAEs between the Sponsor of the study and Novartis country subsidiaries. Consequently Appendix 6 (previously appendix 5) has been updated.

It has been specified that the FDA form 1572 is not needed as one of the essential documents of the study. Therefore, the document should not be collected anymore.

Staging of Prostate Cancer in Appendix 3 was replaced by the latest TNM Classification (American Joint Committee on Cancer, 2002).
Revisions to the protocol and to the amendment 1 are presented in bold text and deletions in strike out through the text.

**Changes to Protocol and the Amendments no. 1 and 2**

Revisions to the protocol or amendments are presented in bold text and deletions in strike out through the text.

The following sections have been modified:

1. Introduction

This protocol contains a substudy measuring bone mineral density in men with high risk prostate cancer starting with hormone therapy. In a recently completed trial (Zometa Protocol 705), Zometa® 4 mg given as a 15-minute intravenous infusion every 12 weeks for one year (5 treatments) significantly increased lumbar spine and hip bone mineral density compared to placebo in 106 men with prostate cancer who were beginning androgen deprivation therapy.44 Men who received the Zometa® infusions had an increase in lumbar spine bone mineral density (BMD) of 5.16% (p<0.001 vs. placebo). BMD increased by 1.08% in the total hip, 1.64% at the femoral neck, 2.37% at the trochanteric region, and 3.39% at Ward’s triangle, and decreased by 2.62%, 1.85%, 2.45%, and 0.58%, respectively, at these sites in the placebo group (p<0.001 for difference between zoledronic acid and placebo at the total hip, femoral neck, and trochanteric regions, respectively).

It is expected that in the present study Zometa® in addition to the prevention of bone metastases will show its potential in preventing hormone therapy induced bone loss.

2. Study objectives

It is the aim of this prospective, randomized, open label, two-arm, parallel group clinical study to assess the efficacy and tolerability of 4 mg zoledronic acid every 3 months in high risk prostate cancer patients as compared to control in preventing bone metastases.

**Secondary study objectives** are

- to evaluate the effect of zoledronic acid on bone mineral density at two and four years after randomization in patients receiving hormonal therapy at study entry (substudy in selected centers)

3.2. Discussion of design

Patients will receive intravenous study treatment (zoledronic acid) for a total duration of 48 months or no treatment (control group). After the development of bone metastases in the control group, it is recommended to treat all patients with 4-mg zoledronic acid.
The following scheme illustrates this design:

3.3.2. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- At least one of the following conditions must be present:
  - Gleason Score 8-10
  - pN+
  - PSA $\geq$ 20 at diagnosis (PSA measurement within one month before prostate biopsy)

Exclusion criteria

- Serum creatinine $>3$ mg/dl (265 µmol/L)
- Abnormal renal function as evidenced by a calculated creatinine clearance $<30$ ml/minute. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula:

  \[
  \text{CrCl} = \frac{[140-\text{age (years)}] \times \text{weight (kg)} \times 0.85 \text{ for female patients}}{[72 \times \text{serum creatinine (mg/dL)}]}
  \]

  * Conversion creatinine values from micromol/l to mg/dL.

  If serum creatinine is measured in micromol/l, the creatinine value in micromol/l should be multiplied with factor 0.0113 in order to obtain the creatinine value in mg/dL.

  For example: serum creatinine is 265 micromol/l x 0.0113 = 3 mg/dL.
• Current active dental problems including infection of the teeth or jawbone (maxilla or mandibular); dental or fixture trauma, or a current or prior diagnosis of osteonecrosis of the jaw (ONJ), of exposed bone in the mouth, or of slow healing after dental procedures

• Recent (within 6 weeks) or planned dental or jaw surgery (e.g., extraction, implants)

3.3.3 RANDOMIZATION

All patients meeting the study entry criteria will be randomly assigned in a ratio of 1:1 to receive either:

• Zometa® 4 mg in 100 ml of calcium-free solution (e.g., 0.9% sodium chloride or 5% glucose) administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months and a supplement of calcium 500 mg and 400-500 I.U. vitamin D

or

• a supplement of calcium 500 mg and 400-500 I.U. vitamin D alone

3.3.4 INTERRUPTION OR DISCONTINUATION OF TREATMENT

Patients who fail to receive an infusion of trial medication (e.g., in case of an intercurrent illness) for a period exceeding 12 weeks do not have to be permanently discontinued from study medication. These patients may be restarted on study medication as soon as clinically advisable at the discretion of the investigator. The reason for postponement, and the date when the postponed infusion of Zometa® was administered, will be recorded in the CRF. The maximum time for Zometa® discontinuation i.e. the maximum time between two Zometa® infusions should be 16 weeks. Administration of study drug beyond 16 weeks will be considered as a major protocol deviation.

The local serum creatinine result must be evaluated according to the following criteria:

• If the patient’s baseline serum creatinine was < 1.4 mg/dl at the time of study entry, an increase of 0.5 mg/dl or more will require the delaying of the dose of study drug until the patient’s serum creatinine returns to no higher than 10% above the baseline value.

• If the patient’s baseline serum creatinine was ≥ 1.4 mg/dl, then any increase in the serum creatinine of 1.0 mg/dl or more will require that the study drug be delayed until the patient’s serum creatinine returns to no higher than 10% above the baseline value.

• Any doubling of the baseline serum creatinine value will require that the study drug be delayed until the patient’s serum creatinine returns to no higher than 10% above the baseline value.

• Should the study drug need to be delayed, the patient’s serum creatinine will continue to be followed at intervals according to the Investigator’s clinical judgement, but at least at the regularly scheduled study visits until full recovery (i.e., return to no higher than 10% above the baseline value). Other study procedures should be followed according to the protocol schedule even if study drug continues to be held.

Should Zometa® need to be delayed according to serum creatinine value during the study, Zometa® should be re-initiated at the same dose as that prior to treatment interruption.
3.4. Treatments

3.4.1. INVESTIGATIONAL THERAPY AND REFERENCE THERAPY

According to randomization, patients will receive:

**Group A:** Zometa® 4 mg in 100 mL of calcium-free solution (e.g. 0.9% sodium chloride or 5% glucose) administered intravenously as a 15-minute infusion every 3 months for a treatment period of 48 months

or

**Group B:** No investigational treatment

Patients assigned to group A will be treated with Zometa 4 mg if at baseline the creatinine clearance is > 60 mL/min.

For patients with mild to moderate renal impairment (30 mL/min ≤ creatinine clearance ≤ 60 mL/min) at baseline the dose of Zometa must be adjusted in accordance with the following schema:

<table>
<thead>
<tr>
<th>Baseline Creatinine Clearance (mL/min)</th>
<th>Zometa Recommended Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>50 - 60</td>
<td>3.5 mg</td>
</tr>
<tr>
<td>40 - 49</td>
<td>3.3 mg</td>
</tr>
<tr>
<td>30 - 39</td>
<td>3.0 mg</td>
</tr>
</tbody>
</table>

*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl=75mL/min)

These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula:

\[ \text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for female patients} \]

Patients receive study drug (group A) or observation (group B) until month 48 or until first documented evidence of bone metastases, whichever is shorter. After the development of bone metastases, patients should receive bisphosphonates according to local treatment guidelines (e.g. Zometa every 4 weeks).

Zometa® (zoledronic acid) will be provided in plastic vials containing 4 mg zoledronic acid in 5 mL concentrate solution for infusion. Each zoledronic acid plastic vial contains 4 mg zoledronic acid (anhydrous).

The zoledronic acid 4 mg/5 mL concentrate solution is not for direct infusion and has to be further diluted prior to the use. Prior to administration, the 5mL of the concentrate solution must be diluted with 100 mL calcium-free infusion solution (0.9% sodium chloride solution or 5% glucose solution). The appropriate volume of the reconstituted zoledronic acid solution is 105 mL. The necessary infusion bags/bottles containing either 100mL calcium free 0.9% sodium chloride or 5% dextrose solution have to be used for the set up of the infusion and will be provided by the study center.

According to the Zometa® recommended dose based on the calculated creatinine clearance, an appropriate volume of Zometa® concentrate/5 mL is as follows:
5.0 mL for 4.0 mg dose  
4.4 mL for 3.5 mg dose  
4.1 mL for 3.3 mg dose  
3.8 mL for 3.0 mg dose

The withdrawn concentrate solution must be diluted in 100 mL of sterile 0.9% sodium chloride or 5% dextrose injection. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Zometa® (zoledronic acid) 4 mg/5 mL concentrate solution must not be mixed with calcium-containing solutions such as Ringer’s solution.

If not used immediately after dilution with infusion media, for microbiological integrity, the final solution must be placed in a refrigerator with a temperature between 2-8 °C. The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in a refrigerator and end of administration of the infusion must not exceed 24 hours. Reconstituted zoledronic acid solutions must be administered in no less than a 15-minute intravenous infusion in a line separate from all other drugs.

Patients must be evaluated prior to and following the administration of the zoledronic acid infusion to ensure that they are adequately hydrated.

Since no data are available on the compatibility of zoledronic acid with other intravenously administered substances, zoledronic acid must not be mixed with other medications or substances and should always be given through a separate infusion line.

Stability studies using diluted zoledronic acid 4 mg/5 mL concentrate solutions in glass bottles and infusion bags made from polyvinylchloride (PVC), polypropylene (PP) and polyethylene (PE) prefilled with 0.9% sodium chloride solution or 5% dextrose solution and with infusion lines made from PVC and PE showed no incompatibility.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total # Vials</th>
<th>Calcium-free Infusion solution</th>
<th>Total Volume Infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid 4 mg I.V. every 3 months</td>
<td>1 vial of 4.0 mg/vial in 5 ml concentrate solution</td>
<td>100 mL</td>
<td>105 mL</td>
</tr>
</tbody>
</table>

Serum creatinine is to be measured prior to each dose of study drug. The local laboratory serum creatinine result must be available prior to administration of the dose of study drug but a two weeks window for checking creatinine is allowed prior to the next dose (see section 3.3.4 of this protocol).

Study drug supplies will be shipped to each study center. Drug will be packaged in an open-label fashion. Medication labels will comply with the local legal requirements in each country. Medication labels will supply no information about the subject. The storage conditions for study drug will be described on the medication label and will be maintained at all times and expiration periods will be strictly complied with.

The clinical investigator will keep the clinical supplies in a secure place and protected against access by unauthorized persons. The study drug is to be used for the study outlined in this protocol, only. Any other usage is explicitly forbidden. The clinical investigator also undertakes to operate a complete system of drug accounting to record dispensing and return of study drugs. The per-patient consumption must be recorded on the study drug administration CRF and on a drug dispensing log.
Clinical supplies that are not required must be stored at the study center, recorded and returned at study closure.

The study center will confirm the receipt and complete return of clinical supplies.

Invasive dental procedures should be avoided if possible during the study. However for patients who develop osteonecrosis of the jaw (ONJ) or require dental procedures during the study, the patient may choose to continue or discontinue the study based on the individual risk benefit discussion with their physician. There is currently limited data to define whether discontinuation of bisphosphonate in these situations impact the outcome of ONJ or reduces the risk of developing ONJ after dental procedures.
### 3.5. Visit schedule and assessments

#### 3.5.1. VISIT SCHEDULE

Table 1: Evaluation schedule

<table>
<thead>
<tr>
<th>Study period</th>
<th>Screening</th>
<th>Infusions with zoledronic acid every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week</td>
<td>Months</td>
</tr>
<tr>
<td>-4/-0</td>
<td>1</td>
<td>2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18</td>
</tr>
<tr>
<td>Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion / exclusion criteria, informed consent</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Study drug administration</td>
<td>x x x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Medical history, pretreatment</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>x</td>
<td>In case of PSA &gt; 10ng/ml&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- **Infusions with zoledronic acid every 3 months**

- **Screening**

- **Inclusion / exclusion criteria, informed consent**

- **Study drug administration**

- **Medical history, pretreatment**

- **Bone Scan**

- **X-ray/CT/MRI**

  - In case of symptoms (e.g. bone pain) or bone metastases in bone scan appropriate radiologic confirmation of bone metastases (X-rays, MRI or CT) are to be done

- **Bone metastases**

- **Serum testosterone**

- **Serum PSA**

- **Serum Creatinine**

- **Creatinine Clearance**

- **Biochemistry**

- **Hematology**

- **Physical examination**

- **Adverse events**

- **Concomitant medication**

- **DXA Scan**

- **Markers of bone turnover**

- **Survival**

- **Study phase completion**

<table>
<thead>
<tr>
<th>Study period</th>
<th>Screening</th>
<th>Infusions with zoledronic acid every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Adverse events**

- **Concomitant medication**

- **DXA Scan**

- **Markers of bone turnover**

- **Survival**

- **Study phase completion**

---

<sup>a</sup> Includes prior treatment, staging etc.

<sup>b</sup> if no bone metastases are diagnosed bone scan will be repeated after 12 months or when symptoms (i.e. bone pain) occur

<sup>c</sup> More frequently if chemotherapy is used

<sup>d</sup> Includes questioning patient regarding symptoms of their prostate cancer and ECOG Performance Status.

<sup>e</sup> Selected patients/centers only

<sup>f</sup> Selected patients/centers only

<sup>g</sup> Until last patient finished visit 18. Patient must be contacted every 6 months and at study end.

<sup>h</sup> samples are to be taken before administration of study drug

<sup>i</sup> calculated through Cockcroft-Cault formula

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Visit 1 (-4/-0 weeks) Screening
10. Venous blood serum for bone TRAP, skeletal alkaline phosphatase, osteoprotegerin, N-telopeptide and creatinine will be collected and frozen at –20°C (selected centers only).

11. Bone mineral density measurements (by DXA scan) will be performed at selected centers.

Additional examinations:

Visit 10
Bone mineral density (by DXA scan) will be performed at selected sites.

Visit 18 (final visit or premature discontinuation)
9. Bone mineral density (by DXA scan) will be performed at selected sites.

3.5.2. Efficacy assessments

Secondary efficacy variables:

- Bone mineral density

A Bone Mineral Density (BMD) measurement by dual energy x-ray absorptiometry (DXA - Hologic, Lunar etc) will be performed at Visit 1 and repeated at Visit 10 as well as at last visit (Visit 18, month 48) in patients receiving hormone therapy at study entry. Primary scanning site is the lumbar spine (L1 to L4) and the secondary scanning site is the total hip (including femoral neck, trochanteric region and Ward’s triangle, femoral shaft). DXA will be assessed in selected centers in selected patients only.

A copy of DXA scan containing study name, hospital, patient ID, DOB and randomization number, with the calibration report of DXA will be collected by the Local CRO for a Central review performed by Prof. Andrea Tubaro.

Endpoint

The absolute difference of T-score at the lumbar spine and total hip as evaluated at visit 1 and at visit 10 and visit 18 is the outcome variable for this study.

Statistical design

The study is dimensioned to demonstrate an effect size (ES) of 0.8 between treatment arms. ES is obtained as the absolute value of the mean divided by the standard deviation of the difference. ES for t-test is interpreted as: 0.2 = small, 0.5 = medium, 0.8 = large [Cohen J (1988). Statistical power analysis for the behavioural sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates]. Thus, 26 patients per arm are to be enrolled, for alpha (2-sided) and beta errors of 0.05 and 0.20, respectively.

- Parameters of bone turnover (measured in treatment and control group)

Patients and samples

Patients in the treatment and the control group should be included.
Serum samples (10 ml) should be taken before administration of study drug from fasting patients before 8.30 in the morning (optimal but not obligatory: serum from fasting patients before 8.30 in the morning) by phlebotomy puncture at the following regimen:
- Zero serum sample before the first Zometa application (visit 2)
- Every three months, during the visits (3., 4., 5., … )

Blood samples should be collected in evacuated Monovette plastic tubes for serum and will be centrifuged at 2000g for 10 min at 4°C within 2 h after venipuncture. After incubation at room temperature (RT) for approximately 30-40 minutes samples will be centrifuged at 2000xg for 10 min. The supernatants will be frozen at –20 °C (or better but not obligatory at –80°C) and not thawed before analysis. Samples will be shipped on dry ice (provided by the courier) twice a year to PD Dr. Michael Lein. The samples should not be stored at –20 °C longer than 8 weeks, otherwise they should be transferred to a –80 °C refrigerator. Blood samples taken and date of sample taken have to be documented on the CRF.

### 3.5.3. SAFETY ASSESSMENTS

#### Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety, each serious adverse event must also be reported to the local delegate of the Sponsor (listed in Appendix 6). Novartis has to be informed of each serious adverse event within 24 hours of learning of its occurrence through the process described in section 9.1.1.

#### 6.1.5.2. Secondary efficacy variables

**Bone Mineral Density**

DXA will be assessed at baseline, at visit 10 and at visit 18 in selected centers only. For both visits an analysis of variance (ANCOVA) will be performed with factors treatment and type and of hormone therapy and including the covariate DXA at baseline. Adjusted (=LS-) means will be presented for the treatment contrast together with its confidence interval and p-value.

### 9.1.1. INSTRUCTIONS FOR RAPID NOTIFICATION OF SERIOUS ADVERSE EVENTS

#### Reporting responsibility

Each serious adverse event must be reported by the investigator to **Novartis to the local delegate of the Sponsor (listed in Appendix 6)** within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to **Novartis** within 24 hours of receiving after the investigator has received it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug, the Medical Safety Expert of the Novartis Clinical Safety & Epidemiology Department or the Sponsor or its local delegate may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug that this serious adverse event has been reported.

#### Reporting procedures
The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax within 24 hours to the local Novartis Clinical Safety and Epidemiology (CS&E) Department, the local delegate of the Sponsor (see appendix 6). The local delegate, after ensuring that the form is accurately and fully completed, must then fax it within 24 hours to the local Novartis Clinical Safety & Epidemiology Department and the EAU CRO central office. The original copy and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site. The monitor will collect a copy of the Serious Adverse Event Form and deliver it to Novartis. Each discordance from this procedure due to local guidelines provisions will have to be discussed case by case and has to be submitted to the Sponsor.

9.2.5. RECORDING OF DATA AND RETENTION OF DOCUMENTS

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC approvals for the study protocol and all amendments
2. all source documents and laboratory records
3. CRF copies
4. patients' informed consent forms
5. FDA form 1572
6. any other pertinent study document.

9.2.7. PUBLICATION OF RESULTS

The substudy on substudies on bone mineral density and parameters of bone turnover will be published separately. The first author of these publications will be the investigator leading the substudy.
Appendix 3: Staging of Prostate Cancer TNM Classification

American Joint Committee on Cancer, 2002

TNM Staging

Primary Tumor, Clinical (T)

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
T1  Clinically inapparent tumor not palpable nor visible by imaging
    T1a  Tumor incidental histologic finding in 5% or less of tissue resected
    T1b  Tumor incidental histologic finding in more than 5% of tissue resected
    T1c  Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2  Tumor confined within prostate*
    T2a  Tumor involves one-half of one lobe or less
    T2b  Tumor involves more than one-half of one lobe but not both lobes
    T2c  Tumor involves both lobes
T3  Tumor extends through the prostate capsule**
    T3a  Extraprostatic extension (unilateral or bilateral)
    T3b  Tumor invades seminal vesicles(s)
T4  Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified at T1c.

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

Primary Tumor, Pathologic (pT)

pT2***  Organ confined
pT2a  Unilateral, involving one-half of one lobe or less
pT2b  Bilateral, involving more than one-half of one lobe but not both lobes
pT2c  Bilateral disease
pT3  Extraprostatic extension
pT3a  Extraprostatic extension****
pT3b  Seminal vesicle invasion
pT4  Invasion of bladder, rectum
**Note:** There is no pathologic T1 classification.

**Note:** Positive surgical margin should be indicated as residual microscopic disease.

According to the AJCC manual, “In general, total prostatoseminal-vesiculectomy, including regional node specimen, and histologic confirmation are required for pathologic T classification. However, under certain circumstances, pathologic T classification can be determined with other means. For example, (1) positive biopsy of the rectum permits a pT4 classification without prostatoseminal-vesiculectomy, and (2) a biopsy revealing carcinoma in extraprostatic soft tissue permits a pT3 classification, as does a biopsy revealing adenocarcinoma infiltrating the seminal vesicles”.

**Regional Lymph Nodes (N)**

**Clinical**
- NX: Regional lymph nodes were not assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in regional lymph node or nodes

**Pathological**
- pNX: Regional nodes not sampled
- pN0: No positive regional nodes
- pN1: Metastases in regional node(s)

**Distant Metastasis***** (M)**
- MX: Distant metastasis cannot be assessed (not evaluated by any modality)
- M0: No distant metastasis
- M1: Distant metastasis
  - M1a: Non-regional lymph node(s)
  - M1b: Bone(s)
  - M1c: Other site(s) with or without bone disease

*****Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.
Appendix 5.6: Novartis Contact Local delegates of the Sponsor for SAE reporting

Each serious adverse event must be reported by the investigator to the local delegate of the Sponsor listed below within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. The local delegate reports the SAE the same day to the local Novartis subsidiary and to the EAU central office. Follow-up information about a previously reported serious adverse event must also be reported in the same way within 24 hours of receiving it.

**SAE reporting must be sent to:**

<table>
<thead>
<tr>
<th>Germany</th>
<th>Italy</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis Pharma GmbH</td>
<td>Novartis Farma S.p.A.</td>
<td>Novartis Healthcare A/S</td>
</tr>
<tr>
<td>Abteilung Arzneimittelsicherheit</td>
<td>Largo Umberto Boccioni, 1</td>
<td>Risikningsrapportering</td>
</tr>
<tr>
<td>Roonstraße 25</td>
<td>21040 Origgio (VA)</td>
<td>Attn: Khiem Nhi Giang</td>
</tr>
<tr>
<td>90429 Nürnberg</td>
<td>Italy</td>
<td>Fax: 39.16.84.02</td>
</tr>
<tr>
<td>Fax: 0911-273.12.085 or</td>
<td>OPIs s.r.l.</td>
<td>Anders Bruunten Eriksen / Marianne Pedersen</td>
</tr>
<tr>
<td>Fax: 0911-273.12.703</td>
<td>Via Matteotti, 10</td>
<td>Trial Form Support</td>
</tr>
<tr>
<td>Kurt Witt</td>
<td>20033 Desio</td>
<td>Vedboek</td>
</tr>
<tr>
<td>CSG Clinische Studien Gesellschaft mbH</td>
<td>Italy</td>
<td>Denmark</td>
</tr>
<tr>
<td>Wichmannstr, 5</td>
<td>Tel: +39.0362-636-1</td>
<td>Tel: +45-4565-2050 / +45-2711-1453 / +45-2711-1455</td>
</tr>
<tr>
<td>10787 Berlin</td>
<td>Fax: +39 0362 633 633</td>
<td>Fax: +45-4565-2055</td>
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<tr>
<th>Belgium</th>
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<th>Finland</th>
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<tr>
<td>Novartis Pharma N.V.</td>
<td>Novartis Pharmaceuticals UK Ltd.</td>
<td>Novartis Finland Oy</td>
</tr>
<tr>
<td>Medislaan 40 bus-1 B-1800 Vilvoorde</td>
<td>Frimley Business Park</td>
<td>Lääketurvakysikkö</td>
</tr>
<tr>
<td>Fax: +32-2-246.17.00</td>
<td>Frimley, Cambs, Surrey GU16 7SR</td>
<td>Fax: 09-6133-2204</td>
</tr>
<tr>
<td>Liesbet Lemmens</td>
<td>United Kingdom</td>
<td>Anna-Leena Laurikkala / Seppo Varmavuo</td>
</tr>
<tr>
<td>MSOURCE</td>
<td>Fax: +44-1276-69.83.19</td>
<td>Trial Form Support</td>
</tr>
<tr>
<td>Mechelsesteenweg 455 B5</td>
<td></td>
<td>Upseerinkatu, 1</td>
</tr>
<tr>
<td>B-1950 Kraainem</td>
<td>Finland</td>
<td>FIN-02600 Espoo</td>
</tr>
<tr>
<td>Brussels-Belgium</td>
<td>Tel: +358-986-763-50 / +358-400-802-352 / +358-40-719-6000</td>
<td>Finland</td>
</tr>
<tr>
<td>Tel: +32-2-768.01.66</td>
<td>Fax: +358-986-763-550</td>
<td>Fax: +358-986-763-550</td>
</tr>
<tr>
<td>Fax: +32-2-767.81.55</td>
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<tr>
<th>France</th>
<th>The Netherlands</th>
<th>Norway</th>
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<tr>
<td>Novartis Pharma S.A.S.</td>
<td>Novartis Pharma B.V.</td>
<td>Novartis Norge AS</td>
</tr>
<tr>
<td>2-8-4, rue Lionel-Terray</td>
<td>Postbus 241</td>
<td>CS&amp;E</td>
</tr>
<tr>
<td>Boîte Postale 208</td>
<td>NL-6800 L.Z. Arnhem</td>
<td>Fax: 23.05.20.87</td>
</tr>
<tr>
<td>F-92506 Rueil-Malmaison Cedex</td>
<td></td>
<td>Anders Bruunten Eriksen / Marianne Pedersen</td>
</tr>
<tr>
<td>Phone: +33-1-554-765-84</td>
<td>CuraTrial</td>
<td>Trial Form Support</td>
</tr>
<tr>
<td>Biologie &amp; Industrie</td>
<td>Zeus SAE</td>
<td>Vedboek</td>
</tr>
<tr>
<td>Dr. Sylvie BROSSEL</td>
<td>PO Box 30016</td>
<td>Denmark</td>
</tr>
<tr>
<td>89-91 rue Robespierre</td>
<td>6803 AA Arnhem</td>
<td></td>
</tr>
<tr>
<td>93100 MONTREUIL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Contact Information</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Austria   | Novartis Pharma GmbH  
           | Brunnerstrasse 50  
           | A-10435 Wien  
           | Tel: +43-1-8665-77-94  
           | Fax: +43-1-8665-77-94  
           | Result CRO Data GmbH  
           | Zeus SAE  
           | Hietzinger Hauptstrasse 22/D/2  
           | A-1130 Vienna  
           | Tel: +43-1-877-1690-13  
           | Fax: +43-1-877-1690-17 |
| Turkey    | Novartis Urunleri  
           | Pharma Sector  
           | Barbaros Bulvar No: 83  
           | TR-06000 Besiktas Istanbul  
           | Tel: +90 212-227-52-89  
           | Fax: +90 212-227-52-89  
           | Cafer Bayramoolu  
           | Omega CRO  
           | Guniz Sokak 32/12  
           | 06700 Kavaklidere Ankara  
           | Tel: +90-312-426-7722  
           | Fax: +90-312-427-7456 |
| Sweden    | Novartis Sverige AB  
           | Biverkningsrapportering  
           | Fax: 08-732-56-62  
           | Anne-Charlotte Warheim / Bertil Davidsson  
           | Trial Form Support  
           | Järnvägsgratan 10A  
           | SE-252-25 Helsingborg Sweden  
           | Tel: +46(0)4218-9902 / +46(0)709-13-5106 / +46(0)709-13-5102  
           | Fax: +46(0)4218-9901 |
| Spain     | Novartis Farmaceutica S.A.  
           | Gran Via de Les Corts Catalanes, 764  
           | E-08013 Barcelona  
           | Fax: +34-93-306-4412  
           | SEIF-88 S.L.  
           | C/ Sicilia, 253 4°-1ª  
           | 08025 Barcelona  
           | Fax: +34 93 238 6642 |
| Greece    | 358-986-763-50) S.A.C.I.  
           | 12th km National Rd No: 1  
           | GR-14451 Metamorphosis Attikis, Greece  
           | Tel: +30 210 2597-149  
           | Fax: +30 210 2580-500  
           | Koutsopoulou Maria, Integrated Laboratory Services (ILS)  
           | Klisthenous 240, Gerakas 15344 Athens  
           | Fax: +30 210 6615929 |
| Switzerland | Novartis Pharma Schweiz AG  
           | Clinical Safety and Epidemiology  
           | Department  
           | Monbijoustrasse 118  
           | CH-3007 Bern Switzerland  
           | Simone Rey-Rick  
           | PFC Pharma Focus AG  
           | Chriesbaumstrasse 2  
           | 8604 Volketswil / Zürich Switzerland  
           | Tel: +41-(0)1-908-6681  
           | Fax: +41-(0)1-908-6677 |
| Portugal  | Sylvia Bianchi  
           | Regional-Senior CRA  
           | Avenida do Lago 470B R/CB  
           | 2765-420 Monte Estoril Portugal  
           | Tel/Fax: +351-21-466-86-70 |