THE ASSESSMENT OF SAFETY PROFILE AND TOLERANCE OF ZOLEDRONIC ACID ACTAVIS® FORMULATION IN POLISH PATIENTS POPULATION

PROTOCOL OF NON-INTERVENTIONAL, POST-MARKETING STUDY

STUDY NUMBER: EPH/ACID/2014/023/001

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LEGAL NOTICE:

This Protocol does not in any way constitute a basis for a decision on any diagnostic or therapeutic methods with respect to any participant of the study.

In accordance with Art. 36u paragraph. 2 of the Act of 6 September 2001 - Pharmaceutical Law (Journal of Laws 2001 No. 126, item. 1381), Study Protocol requires approval by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocides and obtain consent for its conducting

SIGNATURES ON A PROTOCOL

Investigator Signature:

I confirm that I have read the protocol of non-interventional, post-marketing study entitled:

THE ASSESSMENT OF SAFETY PROFILE AND TOLERANCE OF ZOLEDRONIC ACID ACTAVIS® FORMULATION IN POLISH PATIENTS POPULATION

I am aware of investigator responsibilities imposed on me resulting from binding regulations and Study Protocol. I agree to conduct of this study in accordance with these guidelines.

NAME AND LAST NAME: _____ SIGNATURE: _____

POSITION: *Investigator*

ADDRESS THE MEDICAL CENTER: _____ DATE: _____

_____

_____

PROTOCOL SUMMARY

PROJECT TITLE :	**THE ASSESSMENT OF SAFETY PROFILE AND TOLERANCE OF ZOLEDRONIC ACID ACTAVIS® FORMULATION IN POLISH PATIENTS POPULATION**
THE AIMS	**The main aim of the study:** The assessment of safety profile of ZOLEDRONIC ACID ACTAVIS formulation in patients with advanced malignancies involving bone. **Additional aim of the study:** The assessment of the treatment tolerance.
PHASE OF THE STUDY:	Non -interventional, post-marketing study, hereinafter referred to as 'Observing Program'
DESIGN OF THE STUDY:	In the study will participated Oncologist and Urologist proving treatment of patients with advanced malignancies involving bone using ZOLEDRONIC ACID ACTAVIS formulation not less than 30 days prior to enrollment. Observing program will be implemented about 4 months. Data on the safety profile of ZOLEDRONIC ACID ACTAVIS formulation will be recorded in individual observation form (CRF) over two consecutive visits: the starting visit (first -1) and control visit (second -2) at least two months from the date of 1st visit. According to the date of the planned visit arising from clinical needs of the patient.
STUDY POPULATION:	Adults patients diagnosed with advanced malignancies involving bone (diagnosis according to ICD-10) in which by clinical indications at least 30 days prior to enrollment started therapy with ZOLEDRONIC ACID ACTAVIS formulation.
DRUG ASSESSED IN THE NON-INTERVENTIONAL STUDY:	*ZOLEDRONIC ACID ACTAVIS* 4 mg/5mL concentrate for solution for infusion contains in 1 mL concentrate 0.8 mg zoledronic acid (as monohydrate). It is sterile, clear and colorless concentration for solution for infusion. ZOLEDRONIC ACID ACTAVIS formulation indicated in prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcaemia) in adults patients with advanced malignancies involving bone as well as in treatment of adults patients with tumor-induced hypercalcaemia (TIH).
ENDPOINTS:	**Safety endpoints and methods its evaluation:** Collection of information on adverse events related to ZOLEDRONIC ACID ACTAVIS formulation treatment. Serious adverse events should be reported to EUROPHARMA immediately, not later than 24 hours after being informed of the SAE. This report does not relieve the doctor from the notification of adverse events in accordance with Art. 45a of the Act on the profession of doctor and dentist.
STATISTICAL METHODS:	A sample size of approximately 3,500 patients was based on the feasibility study. The data analysis obtained in the study will be descriptive: data sets will consist of summary statistics, such as numbers, mean values, standard deviation, median, minimum and maximum values observed frequency/ percentage. The safety analysis will be conducted on the safety population.

Procedures for particular visits	**Visit 1**	**Visit 2***
Demographic data	X	
Data on the primary disease	X	
Qualification of patient to the observational study (inclusion criteria)	X	
History concerning the treatment of the primary disease before the administration *ZOLEDRONIC ACID ACTAVIS* formulation	X	
History concerning comorbidities and its treatment	X	X
History concerning course of treatment and the occurrence of possible adverse events of *ZOLEDRONIC ACID ACTAVIS* formulation	X	X
History concerning tolerance of *ZOLEDRONIC ACID ACTAVIS* formulation in patient opinion	X	X
Recording of any changes in the drugs used in comorbidities therapy during treatment with *ZOLEDRONIC ACID ACTAVIS* formulation	X	**X**

* This visit will take place only if it is planned as a part of routine observation of the patient.

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1. INTRODUCTION

1.1. Basic information about the disease that is the subject of the study

The bone metastases occurs in approximately 50% of patients with advanced malignancy. The bone lesions are most common in multiple myeloma (80-100%). However, in the solid tumors epidemiological data indicate that 75% of advanced cancer with bone metastases occur in patients diagnosed with breast, prostate and lung cancers. Only 10% of bone metastases is isolated, in other cases, the changes are most often multiple, where the metastases are located outside of the bone. One of the factors that determine the risk of the cancer dissemination to the bone is the location of a primary outbreak. It is estimated that the prevalence of bone metastases in breast cancer patients is 65-75%, in prostate cancer 65-75%, in lung cancer 30-40%, 20-25% in kidney cancer, 30-40% in bladder cancer and 15-45% in melanoma. High risk of metastatic foci formation in the bone occurs also in the course of thyroid cancer (50-60%). In 80% of cases of neoplastic lesions localized in circles, pelvis and proximal femurs sections [1-4].

In the case of solid tumors process dissemination to bone occurs mainly through blood vessels, both arteries and veins. Initially metastatic locate and develop in the spongy part of the bone, then gradually also take part compacted bone. Less frequently in this type of cancer process may spread to the bone by continuity. In turn, multiple myeloma bone infiltrate primarily by continuity.

Bone tumor foci depending on their radiographic image can be of osteolytic and osteosclerotic, but mostly are mixed, due to the interaction of osteoclasts and osteoblasts.

The location tumor cells in bone leads to an imbalance between the process of osteogenesis and osteolysis. The severity of osteolysis process is the result of the direct tumor cell adhesion to the bone, and release of compounds activating osteoclasts. Tumor cells secrete substances that stimulate osteoclast activity indirectly affecting mainly the activity of osteoblasts and stromal cells. These include parathyroid hormone related protein (PTHrP) and interleukin -1, 6 and 11 [5-7]. These factors increase the expression of RANKL (RANK ligand) in the cell membrane of osteoblasts and stromal cells. RANKL binds to its receptor - receptor activator of nuclear transcription factor kappaB (RANK), which is frequently situated in the cell membrane of osteoclast progenitor cells and mature osteoclasts. Activation of the nuclear transcription factor-kappaB results in elevated expression of many genes known to accelerate differentiation and growth of osteoclasts and osteolytic and increasing the mature forms activity [7,8]. It is suggested that an important role in the excessive activation of osteoclasts by RANKL plays a deficiency of osteoprotegerin, that under physiological conditions binds to RANKL and reduces the possibility of its activation by RANK [9].

Osteoclast activation and associated bone destruction associated with the release of large amounts of growth factors, particularly TGF-β and IGF-1. This is the contraregulatory mechanism becouse TGF-β inhibits osteolysis, and IGF-1 stimulates osteogenesis. However, the growth factors are also potent stimulators of growth of cancer cells [10-12]. All the mechanisms described above are mutually driving lead to a “vicious circle” in that there is a positive feedback loop between tumor cells, osteoblasts, osteoclasts and bone marrow stromal cells [7,8]. This pathogenesis is characterized primarily for osteolitic metastases. Much less known are the pathways of pathogenesis of osteosclerotic metastasis. In patients with prostate cancer with metastatic foci in bone were observed significantly increased levels of circulating endothelin-1, that is a potent stimulator of bone formation [13]. However, it seems, that in the initial period of metastasis formation osteoclast activation plays an important role [14,15].In experimental studies performed in the metastasis model of human breast cancer was observed that in osteoblastic bone formation process is preceded by a massive osteolysis [16].

The most common symptoms bone metastases of cancer are pain, pathological fractures, hypercalcemia, neurological disturbances as a result of spinal cord compression or peripheral nerve fibers, and impaired bone marrow function.

Pain associated with bone metastases is the most common symptom locate there neoplastic process (70-95% of patients) and relatively often precedes the appearance of destructive changes in bone tissue. In the previously published studies was observed that the pain reported 49% of patients with bone metastases and 31% non-metastatic foci at this location [17]. Pain in patients with metastases in bone tissue usually have localized nature, although in 40% of patients with prostate cancer and 10% of patients with breast cancer or lung pain is a generalized. Bone pain may also radiate or change their locations [18]. Furthermore, in 80% of patients suffer puncturing or incidental pain, that may occur in various situations, such as during coughing or change the position.

The most serious complication of the cancer dissemination to the bone tissue are pathological fractures, which affects 5 to 15% of patients. Most often it is a fracture of the femur (50%) and humerus (15%). The main risk factors for these fractures are an osteolytic metastasis or with a significant advantage of this process, severe radicular pain, infiltration of cortical bone covering> 2/3 and location of infiltration place exposed to high loads [19].The occurrence of pathological fractures increase the risk of death in patients with breast cancer by 32% and prostate cancer by 20% [20].

A serious and may be life-threatening complication of cancer is hypercalcemia. This disturbances is observed in 10-20% of patients with malignant tumors, and its incidence increases 2-fold in patients with an advanced cancer. Hypercalcemia is diagnosed mainly in patients with multiple myeloma, breast cancer and lung cancer. The mechanism of the development of hypercalcemia in patients with cancer include: increased bone osteolysis, decreased secretion of calcium into the lumen of the distal tubule and an increase resorption of calcium feedback in the proximal parts of the renal tubule. The clinical manifestations of hypercalcemia include nausea, vomiting, abdominal pain, confusion, arrhythmias and kidney dysfunction. It should be emphasized that the severity of these not characteristic clinical signs does not always correlate with serum ionized calcium concentration [1,21,22].

Neurological disturbances in patients with metastatic foci in the bone may be a result of pressure spinal by splinters of bone infiltration into the spinal canal or blood circulation impaired. Paresis or paralysis occur in over 60% of patients, and sensory disturbances in more than 70%. Associated with pathological vertebral fractures spinal cord injury on the border of the lumbar and sacral can cause abnormal urination and / or defecation [20].

The impairment of bone marrow function in patients with advanced cancer may be due to treatment - chemotherapy and radiotherapy, but also may be increased or caused by direct destruction of the bone marrow by infiltrating bone by tumor cells.

All of the above complications of the cancer spreading to bone tissue can greatly reduce the efficiency of the patient in terms of physical activity. As a result, increased risk of infections of the respiratory and urinary tract, thrombosis, muscle atrophy and formation of bedsores. This not only causes an even greater reduction in the quality of life of patients, but also shortens their survival.

Understanding the pathomechanisms of bone metastases and understand the role plays in this process osteoclast enabled the invention of the group preparations, that binding to exposed bone mineral substance in the process of osteolysis. These are the bisphosphonates [23]. Currently in clinical practice, three generations of bisphosphonates are used: first generation - do not contain a nitrogen atom in the molecule (etidronate and clodronate), the second generation - including the nitrogen atom incorporated in the aliphatic side chain (pamidronate, alendronate and ibandronate), third generation - comprise one or two nitrogen atoms located in a heterocyclic ring side (risedronate, and zoledronic acid).Strength activity of bone resorption inhibiting subsequent generations bisphosphonates increases by a multiple in relation to the I generation (for example, if the potency of etidronate adopted for one, the force of action of pamidronate is greater than 100 times and risedronate is 10,000 times higher [24,25]. Generations of bisphosphonates are also different mechanisms of action at the cellular level, that is dependent on the absence of nitrogen in the compounds I generation and its contents in molecules of compounds II and III generation.

The strongest acting bisphosphonates is zoledronic acid. Its potency is 10-10000 times higher than etidronate and 100-1000 times greater than pamidronate [24,25]. Zoledronic acid binds strongly to bone mineral substance and is released during bone resorption, and then absorbed by osteoclasts. However, in contrast to the non-nitrogen containing bisphosphonates, zoledronic acid is not metabolized by osteoclasts to cytotoxic compounds [26]. Zoledronic acid is primarily an inhibitor of enzymes in the cholesterol biosynthetic pathway [27]. Arising in the course the reaction of the two metabolites - farnesyl diphosphate and geranylgeranylu diphosphate play an important role in maintaining the proliferative potential of cells, as they are necessary for the prenylation (post-translational modification) protein binding guanosine triphosphate (GTP), such as Ras, Rho and Rac [28]. This process is necessary for the proper fixation of the proteins on the internal side of the cell membrane, which in turn causes their activation. After activation, these proteins are potent activators of kinase phosphorylation, transmitting proliferation signal with the membrane receptors of proliferative growth factors to the cell nucleus. Where mediates of transcription factors initiating the expression of genes encoding proteins involved in the growth and proliferation of the cells [29].

Cancer cells are often mutated genes coding the above-mentioned proteins, in particular Ras. Through the mutations activity of the proteins of these is kept constant, independently of the effect of extracellular growth factors. What gives the cell unlimited proliferative potential [30]. Zoledronic acid dose-dependently inhibited farnesyl diphosphate synthase activity, which inhibits the prenylation of Ras, Rac, and Rho proteins, which in turn causes inhibition of proliferation signal transduction to the nucleus [31]. This action of zoledronic acid causes considerable phenotypic changes of cells that absorbed it, especially osteoclasts but also tumor cells from bone metastases. These changes include:

» inhibition of osteoclast activity and induction of apoptosis,
» inhibition of tumor cell growth and induction of apoptosis,
» inhibition of cell adhesion breast and prostate cancer to bone,
» synergistic action with the preparations used in chemotherapy and hormonal therapy,
» inhibition of angiogenesis.

It should be emphasized that due to the high affinity of zoledronic acid, the bone, the concentration and the effect on other tissues of the body is low [24].

Changes in osteoclast function resulted from the inhibition of protein prenylation by zoledronic acid mainly include:

» molecular organization of cytoskeletal proteins, resulting in abnormal cytoplasm compartment and launch mechanisms initiating the process of apoptosis,
» fluidity of cell membranes, including mitochondrial membrane potential changes which are associated with activation of the proteases responsible for the effector phase of apoptosis,
» the disappearance of the creation of the brush border, which inhibits the resorbing activity of osteoclasts [26,32].

Zoledronic acid inhibits also the differentiation of osteoclast precursor cells and reduces the influx of mature osteoclasts to sites of bone resorption [24].

The results of in vitro studies showed that zoledronic acid also inhibits proliferation of osteoblasts. Simultaneously it was observed that it induces the differentiation of osteoblasts, increasing their osteogenic activity [33].

Number of studies mainly experimental inhibitory effect of zoledronic acid on growth of several tumor cells was found. However, this action of zoledronic acid seems to be restricted to the bone metastasis, because the concentration of the drug outside of the bone is too small. In addition, synergism in the range of cytotoxic or cytostatic between zoledronic acid and other drugs with these mechanisms of action was found. It was observed that zoledronic acid induces apoptosis in multiple myeloma cells, and inhibits IL-6 production by marrow stromal cells, that is the main growth factor of plasmocytes and strong inducer of osteolysis. Additionally, inhibits the production of metalloproteinase-1 by stromal cells (inhibition of tumor cell growth and bone resorption) but increases the synthesis of metalloproteinase-2 (which may be adversely affected in terms of antitumor and antiresorptive effects) [34]. Proapoptotic effect of zoledronic acid on neoplastic plasmocytes enhances co-administration of dexamethasone [35], and this effect is even enhanced by the addition of antagonist of IL-6 receptor [36].

Inhibition of the adhesion of breast and prostate cancer to bone is associated with the fact that zoledronic acid acts as a zinc ion chelator - a cofactor of metalloproteinase activity [37]. The result of experimental studies have shown that the drug induces apoptosis of breast cancer cells via an increased release of mitochondrial cytochrome c into the cytosol and activation of caspases [38]. Additionally, zoledronic acid in breast cancer cell culture with very high metastatic potential (MDA--MB-231) inhibited the expression of cyclooxygenase-2 (COX-2), resulting in the decrease synthesis of prostaglandin E2 (PGE2) a potent osteoclastic stimulator [39]. Zoledronic acid demonstrates also dose- dependent synergistic activity with paclitaxel proapoptotic cells MDA-MB-231, and short exposure this cells to zoledronic acid was sufficient to occurs the effect [40]. However, in the study, which evaluated the effect of co-administration of zoledronic acid, docetaxel and COX-2 inhibitor (SC236) on the growth of breast cancer cells overexpressing the HER-2/neu receptor, showed that the effect of zoledronic acid be less pronounced in the case of overexpression of the receptor [41].

In studies assessing the effect of zoledronic acid on prostate cancer cells the action of this drug stopping their proliferation with a very large increase in the percentage of cells in the G0 and G1 cell cycle was observed, while pamidronate induce their apoptosis [42]. The results of another study revealed that zoledronic acid induces also apoptosis in prostate cancer cells and the mechanisms causing this effect are the same as for the impact of the drug on osteoclast [43,44].

It has also been suggested that the zoledronic acid may also find use in the treatment of early stages of cancer as it inhibits proliferation and induces apoptosis of endothelial cells in vitro. Additionally, in animal studies inhibition of angiogenesis was found [45,46]. This zoledronic acid action was also confirmed by the results of studies conducted in patients with bone metastases after its first dose before starting chemotherapy [47].

Zoledronic acid has a direct cytotoxic action against human osteosarcomas cells, resulting in cell cycle arrest in the S phase, and the induction of apoptosis [48].

The unique properties zoledronic acid compared to other bisphosphonates include:

» the maximal effect in the treatment hypercalcemia induced by cancer cells,
» clinical efficacy in all types of bone metastatic
» treatment efficacy of bone metastases of prostate cancer, kidney cancer and non-small cell lung cancer confirmed in a prospective randomized clinical trials,
» ease of administration of the drug in the form of a 15 minute infusion.

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1.2. 1.1 Basic information about the study drug

ZOLEDRONIC ACID ACTAVIS (active substance zoledronic acid monohydrate)

Zoledronic acid belongs to the class of bisphosphonates. It is an inhibitor of osteoclastic bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. The results of long-term experimental studies revealed that zoledronic acid inhibit bone resorption without adversely affecting the bone formation, mineralization or mechanical properties. The detailed molecular mechanism action of zoledronic acid was described above.

Treatment with zoledronic acid patients diagnosed with advances malignances involving bone in addition to bone resorption inhibition, may improve the overall effectiveness of the treatment of bone metastases. The results of in vivo studies shown that inhibition of osteoclastic activity by zoledronic acid alters the bone marrow microenvironment, making it less conductive to tumor cell growth, anti-angiogenic activity and anti-pain activity. In turn the results of in vitro studies revealed that zoledronic acid inhibits osteoblast proliferation, stimulates directly cystostatic and pro-apoptopic activity in tumor cells, in addition has synergistic cytostatic effect with other anti-cancer drugs and anti-adhesion/invasion properties.

The results of the first randomized, double-blind, placebo-controlled study compared zoledronic acid 4 mg to placebo for prevention of skeletal related events (SREs) in prostate cancer patients revealed that zoledronic acid 4 mg significantly reduced the proportion of patients experiencing at least one skeletal related event (SRE), delayed the median time to first SRE by >5 months, and reduced the annual incidence of events per patient – skeletal morbidity rate. Multiple event analysis showed a 36% risk reduction in developing SREs in the zoledronic acid 4 mg group compared with placebo. Patients receiving zoledronic acid 4 mg reported less increase in pain than those receiving placebo, and the difference reached significance at months 3,9,21 and 24. Fewer zoledronic acid 4 mg patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions.

The results of other study including solid tumors other than breast or prostate cancer, zoledronic acid 4 mg significantly reduced the number of patients with an SRE, delayed the median time to first SRE by >2 months, and reduced the skeletal morbidity rate. Multiple event analysis showed 30.7% risk reduction in developing SREs in the zoledronic acid 4 mg group compared to placebo.

In turn in a third phase randomised, double-blind trial, 4 mg zoledronic acid or 90 mg pamidronate every 3 to 4 weeks were compared in patients with multiple myeloma or breast cancer with at least one bone lesion. The results shown that 4 mg zoledronic acid has comparable efficacy to 90 mg pamodronate in SREs prevention. The multiple event analysis revealed a significant risk reduction of 16% in patients treated with 4 mg zoledronic acid in comparison with patients receiving pamidronate.

Zoledronic acid 4 mg was also studied in a double-blind, randomized, placebo-controlled trial in 228 patients with documented bone metastases from breast cancer to evaluate the effect of 4 mg zoledronic acid on the skeletal related events (SER) rate ratio, calculated as the total number of SRE events (excluding hypercalcaemia and adjusted for prior fracture), divided by the total risk period. Patients received either 4 mg zoledronic acid or placebo every four weeks for one year. The SRE rate (events/person year) was 0.628 for zoledronic acid and 1.096 for placebo. The proportion of patients with at least one SRE (excluding hypercalcaemia) was 29.8% in the zoledronic acid – treated versus 49.6% in the placebo group (p=0.003). Median time to onset of the first SRE was not reached in the zoledronnic acid – treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid 4 mg reduced the risk of SREs by 41% in a multiple event analysis (risk ratio = 0.59, p=0.019) compared with placebo. In the zoledronic acid –treated group, statistically significant improvement in pain scores was seen at 4 weeks and at every subsequent time point during the study, when compared to placebo. The pain score for zoledronic acid was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score.

Clinical studies in tumor-induced hypercalcaemia (TIH) demonstrated that the effect of zoledronic acid is characterized by decrease in serum calcium and urinary calcium extraction. In Phase I dose finding studies in patients with mild to moderate tumor-induced hypercalcaemia (TIH), effective doses tested were in the range of approximately 1.2-2.5 mg.

To assess the effects of 4 mg zoledronic acid versus pamidronate 90 mg, the results of two pivotal multicentre studies in patients with TIH were combined in a pre-planned analysis. There was faster normalization of corrected serum calcium at day 4 for 8 mg zoledronic acid and at day 7 for 4 mg and 8 mg zoledronic acid. Median time to normocalcaemia was 4 days. Median time to relapse (re-increase of albumin-corrected serum calcium ≥2.9 mmol/l) was 30 to 40 days for patients treated with zoledronic acid versus 17 days for those treated with pamidronate 90 mg (p-values: 0.001 for 4 mg and 0.007 for 8 mg zoledronic acid). There were no statistically significant differences between the two zoledronic acid doses.

In clinical trials 69 patients who relapsed or were refractory to initial treatment (zoledronic acid 4 mg, 8 mg or pamidronate 90 mg) were retreated with 8 mg zoledronic acid. The response rate in these patients was about 52%.

In clinical trials performer in patients with tumor-induced hypercalcaemia (TIH), the overall safety profile amongst all tree treatment groups (zoledronic acid 4 and 8 mg and pamodronate 90 mg) was similar in types and severity.

Pharmacokinetic properties of Zoledronic acid

After intinitiating the infusion of zoledronic acid, the plasma concentrations of zoledronic acid rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to <10% of peak after 4 hours and <1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak period to the second infusion of zoledronic acid on day 28.

Intravenously administered zoledronic acid is eliminated by triphasic process: rapid biphasic disappearance from the systemic circulation, with half-life of t1/2 α 0.24 and t1/2β 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of t1/2γ 146 hours. There were no accumulation of zoledronic acid in plasma after multiple doses given every 28 days.

From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 l/h, independent of dose, and unaffected by gender, age, race and body mass. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

The interpatient variability in pharmacokinetic parameters for zoledronic acid was high, as seen with other bisphosphonates.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation and in animal studies <3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearence of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 cancer patients studied. Population analysis showed that for a patient with creatinine clearance of 20 ml/min (severe renal impairment), or 50 ml/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37% or 72%, respectively, of that of a patient showing creatinine clearance of 84 ml/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance <30 ml/min).

In an in vitro study, zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/ml to 5000 ng/ml. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/ml to 77% at 2000 ng/ml of zoledronic acid.

Therapeutic indications for ZOLEDRONIC ACID ACTAVIS formulation:

» prevention of skeletal related events (pathological fracture, spinal compression, radiation or surgery to bone, or tumor induced hypercalcaemia) in adults patients with advanced malignancies involving bone,
» treatment of adult patients with tumor induced hypercalcaemia (TIH)

ZOLEDRONIC ACID ACTAVIS formulation must only be prescribed and administered to patients by healthcare professional experienced in the administration of intravenous bisphosphonates.

Prepare and administer ZOLEDRONIC ACID ACTAVIS formulation:

To prepare an infusion solution concerning 4 mg Zoledronic acid Actavis further dilute the Zoledronic acid Actavis concentrate (5,0 ml) with 100 ml calcium-free or other divalent cation-free infusion solution. If a lower dose of Zoledronic acid Actavis is required, first withdraw the appropriate volume as indicated below and then dilute it further with 100 ml of infusion solution. To avoid potential incompatibilities, the infusion solution used for dilution must be either 0.9% w/v sodium chloride or 5% w/v glucose solution.

Introduction for preparing reduced dose of Zoledronic acid Actavis:

Withdraw the appropriate volume of the liquid concentrate, as follows:

» 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 solution containing zoledronic acid is given as a single 15-minute intravenous infusion in a separate infusion line, The hydration status of patients must be assessed prior to and following administration of Zoledronic acid Actavis to ensure that they are adequately hydrated.

Do not mix Zoledronic acid Actavis concentrate with calcium-containing or other divalent cation containing solution such as lactated Ringer's solution. Since no data are available on the compatibility of Zoledronic acid Actavis with other intravenously administered substances. Zoledronic acid Actavis must not be mixed with other medications/substances and should always be given through a separate infusion line.

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used. Aseptic techniques must be followed during the preparation of the infusion.

Healthcare professionals are advised not to dispose of unused Zoledronic acid Actavis via the domestic sewage system. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks. Patients should also be administered on oral calcium supplement of 500 mg and 400 IU vitamin D daily. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

When initiating treatment with Zoledronic acid Actavis in patients with multiple myeloma or metastatic bone lesion from solid tumors, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using Cockcroft-Gault formula. Zoledronic acid Actavis is not recommended from patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30-60 ml/min, the following Zoledronic acid Actavis dose is recommended:

» baseline creatinine clearance > 60 ml/min Zoledronic acid Actavis recommended dose is 4.0 mg zoledronic acid,
» baseline creatinine clearance 50-60 ml/min Zoledronic acid Actavis recommended dose is 3.5 mg zoledronic acid,
» baseline creatinine clearance 40-49 ml/min Zoledronic acid Actavis recommended dose is 3.3 mg zoledronic acid,
» baseline creatinine clearance 30-39 ml/min Zoledronic acid Actavis recommended dose is 3.0 mg zoledronic acid.

Following initiation of therapy, serum creatinine should be measured prior to each dose of Zoledronic acid Actavis and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

» For patients with normal baseline serum creatinine (<1.4 mg/dl or <124 micromol/l), an increase of 0.5 mg/dl or 44 micromol/l;
» For patients with abnormal baseline creatinine (>1.4 mg/dl or >124 micromol/l), an increase of 1.0 mg/dl or 88 micromol/l.

In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value. Zoledronic acid Actavis treatment should be resumed at the same dose as that given prior to treatment interruption.

Patients must be assessed prior to administration of Zoledronic acid Actavis to ensure that they are adequately hydrated. Overhydration should be avoided in patients at risk of cardiac failure.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Zoledronic acid Actavis therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered. Case of severe hypocalcaemia requiring hospitalization have been reported. In some instances, life-threatening hypocalcaemia may be encountered.

Other products containing zoledronic acid as active substance are available for osteoporosis indications and treatment of Paget's disease of the bone. Patients being treated with Zoledronic acid Actavis should not be treated with such products or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

The recommended dose in hypercalcaemia induced by malignance proces (albumin – corrected serum calcium ≥12.0 mh/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Zoledronic acid Actavis treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risk and benefits of treatment. In the clinical studies, patients with serum creatinine >400 micromol/l or >4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 micromol/l or <4.5 mg/dl.

Interaction of ZOLEDRONIC ACID ACTAVIS formulation with other medication products

In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro, but no formal clinical interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics, since agents may have an additive effects, resulting in the lower serum calcium level longer periods than required.

Caution is indicated when Zoledronic acid Actavis is used with other potentially nephrotoxic medical products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid Actavis is used in combination with thalidomide.

Caution is advised when Zoledronic acid Actavis is administered with anti-angiogenic medicinal products, as an increase in the incidence of osteonecrosis of the jaw (ONJ) has been observed in patients treated concomitantly with these medicinal products.

The adverse events related to use of **ZOLEDRONIC ACID ACTAVIS** formulation, including: (Summary of Product Characteristics, Zoledronic acid Actavis 4 mg/5 ml concentrate for solution for infusion, dated 08-01-2015, EMEA/H/C/002488)

Very common (≥1/10): hypophosphataemia

Common (≥1/100 to <1/10): anaemia, headache, conjunctivitis, nausea, vomiting, decreased appetite, bone pain, myalgia, arthralgia, generalised pain, renal impairment, fever, flu-like syndrome (including fatigue, rigors, malaise and flushing), blood creatinine and blood urea increased, hypocalcaemia

Uncommon (≥1/1000 to <1/100): thrombocytopenia, leukopenia, hypersensitivity reaction, anxiety, sleep disturbance, dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence, blurred vision, scleritis, orbital inflammation, hypertension, hypotension, arterial fibrillation, hypotension leading to syncope and circulatory collapse, dyspnoea, cough, bronchoconstriction, diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth, pruritus, rash (including erythematous and macular rash), increased sweating, muscle spasms, osteonecrosis of the jaw, acute renal failure, haematuria, proteinuria, asthenia, peripheral oedema, injections site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria, hypomagnesaemia, hypokalaemia

Rare (≥ 10 000 to <1/1 000): pancytopenia, angioneurotic oedema, confusion, uveitis, bradycardia, cardiac arrhythmia (secondary to hypocalcaemia), interstitial lung disease, arthritis and joint swelling as a symptom of acute phase reaction, hyperkalaemia, hypernatraemia, atypical subtrochanteric and diaphyseal femoral fractures

Very rare (< 10 000): Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia) episcleritis

1.3. The clinical reason for conducting this non-interventional study

ZOLEDRONIC ACID ACTAVIS is a generic formulation containing the active substance zoledronic acid monohydrate the first time used in the Polish population. This formulation obtained the registration in January 2013 and is available in commercially pharmacy, and its indications include the treatment of:

- prevention of skeletal related events (patholological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcaemia) in adults patients with advanced malignancy involving bone,

- treatment of adult patients with tumor-induced hypercalcaemia (TIH).

It should be emphasized that the treatment with Zoledronic acid Actavis formulation in the prevention of skeletal complications in patients with advanced malignancies involving bone is a long process, therefore not only to minimize the symptoms of the disease, but also a good tolerance and acceptance of the therapy by the patient are important. Moreover, the use of zoledronic acid requires constant security monitoring.

2. THE AIM OF THE STUDY

2.1. The main aim of the study:

Assessment of safety profile of ZOLEDRONIC ACID ACTAVIS in patients with advanced malignancy involving bone.

2.2. The additional aim of the study:

Assessment of the tolerance of the treatment.

3. STUDY DESIGN

3.1. Basic information

This is a non-interventional, post-marketing study. This study collects data on the occurrence of any adverse events and tolerability of **ZOLEDRONIC ACID ACTAVIS f**ormulation during treatment of patients **WITH ADVANCED MALIGNANCY INVOLVING BONE**. Treatment with this preparation should follow the instructions specified in the Summary of Product Characteristics. Patient inclusion of the study is independent of the previous decision regarding the treatment of the patient with **ZOLEDRONIC ACID ACTAVIS** formulation.

3.1.1. Characteristics of the study population

Adult patients of both sexes, who, based on ICD-10 meet the criteria for diagnosis of advanced malignancy involving bone and do not meet the exclusion criteria, as well as treated with ZOLEDRONIC ACID ACTAVIS not less than 30 days prior to enrollment will be included to the study.

3.1.2. Study design

This project is post-marketing, non-interventional, open multicenter study.

3.2. Endpoints

Endpoints of safety- data collection of related adverse events associated with therapy.

3.3. Substantiation of the study construction

Non-interventional, post-marketing study assessing the safety of treatment with **ZOLEDRONIC ACID ACTAVIS**. In study patients no additional diagnostic procedures or monitoring and analysis will be performed and in analysis of the collected data, epidemiological methods only, will be used.

The aim of the study is to collect data on any adverse events that may occur during the routine use of ZOLEDRONIC ACID ACTAVIS in the Polish population, according to the indications and other information contained in the Summary of Product Characteristics.

The study will be conducted in approximately 3,500 patients who were treated with a ZOLEDRONIC ACID ACTAVIS formulation as part of routine therapy. Observation of the safety using the study drug by one patient will last for four months due to the chronic nature of the therapy. During this time, centers will gather data on any adverse events of ZOLEDRONIC ACID ACTAVIS that will be recorded in Observation Form and reported to the company Europharma M. Rachtan Sp. z o.o. Please see section 9.

3.3.1. Duration of the study

Observation of patients during the study will take approximately four months from the date of first visit.

4. COMPLIANCE WITH TERMS OF GOOD CLINICAL PRACTICE, ETHICAL ISSUES AND INFORMED CONSENT TO PARTICIPATE IN THE STUDY

4.1 Compliance with terms of good clinical practice, and ethical issues

This is a non-interventional study, thus not subject to the provisions of Directive 2001/20/EC of the European Parliament and of the Council of Europe of 4 April 2001.

The study will be conducted in accordance with all applicable provisions of Polish law.

4.2 Informed consent to participate in the study

In accordance with the Polish law in the case of non-interventional studies the obtain patient written informed consent to participate in the study is not required.

5. STUDY POPULATION

5.1 Records of participants in the study

Each Investigator will be required to keep list of patients included in the study. The list shall include the Patient name, initials and date of birth and must be kept confidentially at the study center.

The study is planned to include approximately 3,500 patients by Polish Oncologists and Urologists. Each physician participating in the study should make at least one follow-up.

5.2 Inclusion criteria

All participants of the study must meet the following criteria:

» Adult patients with advanced malignancies with bone metastases
» Treatment with ZOLEDRONIC ACID ACTAVIS formulation at least 30 days prior to enrollment

The inclusion of each participant in the study must be separated from the decision on the treatment with ZOLEDRONIC ACID ACTAVIS formulation.

5.3 Exclusion criteria

Patients meeting the following criteria will not be included in the study:

» Patients treated with ZOLEDRONIC ACID ACTAVIS less than 30 days prior to inclusion in the study.
» Patients diagnosed with chronic kidney disease stage 5 (Creatinine clearance before treatment < 30 mL/min).
» Hypersensitivity to the active substance, other bisphosphonates or any of the medicinal formulation excipients (mannitol, sodium citrate).

5.4 Procedures associated with the treatment discontinuation or the patient withdrawal from the study

If the patient discontinue participation in the Study, the main reason for exclusion from the study will be recorded in the Observation Form (CRF). Exclusion from the study because of adverse effects will be adequately described.

If the patient discontinue participation in the Study due to an associated adverse event, an investigator should follow the procedures described in Section 9 in order to assess the safety of ZOLEDRONIC ACID ACTAVIS.

6. METHODOLOGY

6.1 Schedule of the study

Summary of observations and assessments in the implementation of this study are presented in the following table.

Table1. Schedule of the project

Procedures for particular visits	Visit 1	Visit 2*
Demographic data	X	
Data on the primary disease	X	
Qualification of patient to the non-interventional study (inclusion criteria)	X	
History concerning the treatment of the primary disease before the administration of ZOLEDRONIC ACID ACTAVIS formulation	X	
History concerning comorbidities and its treatment	X	X
History concerning course of treatment and the occurrence of possible adverse events of ZOLEDRONIC ACID ACTAVIS formulation	X	X
History concerning tolerance of ZOLEDRONIC ACID ACTAVIS formulation in patient opinion	X	X
Recording of any changes in the drugs used in comorbidities therapy during treatment with ZOLEDRONIC ACID ACTAVIS formulation	X	X

* This visit will take place only if it is planned as a part of routine observation of the patient.

6.2 Visits to a specialist clinic under the study

6.2.1 Screening visit (day 0, visit 1)

All patients will use ZOLEDRONIC ACID ACTAVIS in accordance with the decision of the treating physician and in accordance with the conditions contained in the Summary of Product Characteristics. In the Observation Form the following information will be recorded:

- - patient number
- - patient initials
- - demographic data
- - data on primary disease
- - data on treatment with **ZOLEDRONIC ACID ACTAVIS**
- - concomitant diseases on the basis of medical history
- - data on pharmacotherapy of concomitant diseases
- - determination of the inclusion and exclusion criteria
- - data on tolerance of treatment with **ZOLEDRONIC ACID ACTAVIS** in opinion of the patient
- - data on adverse events related to treatment with **ZOLEDRONIC ACID ACTAVIS**.

6.2.2 Control visit 2 at least two months from the date of 1st visit according to the date of the planned visit arising from clinical needs of the patient

Patients will be reported on visits to the center for a set period of time. These visits will be conducted in accordance with the plan as part of routine follow-up of the Patient and time set according to the individual clinical needs. During these visits, the Investigators will collect and recorded in the Observation Form (CRF) information on the current course of the primary disease, its current treatment, adverse events related to treatment with ZOLEDRONIC ACID ACTAVIS, potential changes of pharmacotherapy used in primary disease and concomitant disease treatment and assessment of tolerance treatment with ZOLEDRONIC ACID ACTAVIS in the opinion of the patient.

7. ASSESMENT PERFORMED IN THE STUDY

The study project is not an evaluation of the effectiveness of treatment with **ZOLEDRONIC ACID ACTAVIS**.

7.1 Safety endpoints and methods of its evaluation

7.1.2. Related adverse events

Data on adverse events related to treatment with **ZOLEDRONIC ACID ACTAVIS** will be collected during the observation period and will also include adverse events occurring before enrolment to the Study. Information on these events will be collected during visits to specialist clinics based on directly asked questions in the survey. Doctors are required to report observed related adverse events to europharma@europharma.edu.pl. For further description on reporting of adverse events please see Section 9.

7.2 Tolerance endpoints and methods of its evaluation

Data on adverse events and tolerability of treatment with **ZOLEDRONIC ACID ACTAVIS** in Patient opinion will be collected during the observation period as a response to the survey questions regarding these aspects during 1 single visit or 2 consecutive visits to specialist clinics.

8. STUDY DRUG

8.1 Administration of the drug

The drugs will be used based on a recommendation by the treating doctor, after realizing the prescription at the public pharmacy.

Study drug

ZOLEDRONIC ACID ACTAVIS is a formulation containing the active substance having the chemical name zoledronic acid (as monohydrate)

Pharmaceutical form: sterile, clear and colourless concentrate for infusion.

Potency: one ml concentrate contains 0.8 mg zoledronic acid (as monohydrate)

List of experiences: mannitol, sodium citrate, water for injections

Name and address of the manufacturer responsible for batch release:

Actavis Group PTC ehf.
Reykjavíkurvegur 76-78
220 Hafnarfjörður
Iceland

Description: sterile, clear and colourless concentrate for infusion.

8.2. Drug delivery

Not applicable

8.3. Patients identification

During the conduct of the study, all patients participating in it must be identifiable. The Investigator will conduct the list of Patients numbers and their names, so that their identification will be possible according to this list in the future, if necessary. The list of patients enrolled in the study should be stored confidentially at the study center.

Patient number will be assigned at baseline according to the chronological order of inclusion in the study in the center. Patients in the course of this study will be identified by a unique identification number consisting of a number of the center and the number of the patient. Patient and center numbers will be recorded in the Observation Form.

8.3 Concomitant medication

Data on other drugs used concomitantly with **ZOLEDRONIC ACID ACTAVIS** will be recorded in the Observation Form on every visit.

9. REPORTING RELATED ADVERSE EVENT

9.1 The division of adverse events

The related adverse events occurring during the treatment with the study drug is each related adverse events that follows during the active phase of the study, if:

» it was not present prior to the first dose of study drug

or

» it was presented before the first dose of study drug administration but its intensity was increased during the non-interventional Study

or

» it was presented before the first dose of study drug administration, its intensity did not changed but during the non-interventional Study found an association between administration of the study drug and the onset of this effect.

9.1.1. The term Serious Adverse Event

Serious adverse events are adverse events occurring regardless of the dose, that:

1. Causes death.
2. Constitutes a threat to life, which means that the action is related to a direct threat to life of the patient. It does not include a reaction that, if it had occurred in a more serious form, could have resulted in death.
3. This leads to hospitalization or prolongation of a previous patient's hospitalization, with the exception of the admission of the Patient to the hospital for social or administrative reasons.
4. It causes permanent or significant health detriment.
5. This leads to congenital malformations or perinatal damage.
6. Other effects of the medicinal product, that physicians according to his knowledge, considers medically important.

Regardless of the above criteria each adverse events that investigator considers as serious, should immediately (within 24 hours) be reported by e-mail to Office of Study Organizer: europharma@europharme.edu.pl or by fax +48 32 750 57 23, see section 9.6. Office of Study Organizer will be trained in how to report ADRs from this study to Sponsors PV Drug Safety via the Person Locally Responsible for Pharmacovigilance (PLRP) in Actavis Poland, 15, Marynarska str., 02-674 Warszawa, Poland, +48 22 6122954; A.Pintara-Batogowska; e-mail: apintara@actavis.com. This training will be documented. The flow of the SAEs are visualized in a flow chart in the Safety Management plan.

Hospitalization is defined as each admission of the patient to the hospital (also a period of less than 24 hours). In the case of protracted or long-term hospitalization, the hospitalization is considered to be a transfer within the patient's hospital in intensive care.

Prolonged hospitalization is definied as each prolongation of hospitalization outside the required time for the initial reason for admission of the patient to the hospital in the opinion of the Investigator or Doctor from the hospital.

9.1.2 Classification by severity

The related adverse events will be classified as mild, moderate or severe according to the following criteria:

Mild: symptoms do not alter the normal functioning of the Patient

Moderate: symptoms cause some degree of dysfunction of the Patient, but are not dangerous, unpleasant or embarrassing to the Patient.

Severe: symptoms are clearly dangerous for the Patient, cause significant impairment functioning or disability.

9.1.3. Classification according to the a causal relationship between the use of the administered drug and the occurrence of an adverse event

In the Study only adverse events data showing a causal-and-effect relationship with the administration of the study medicinal product will be collected.

Submission of possible and probable (likely time sequence, dose-response relationship) and certain adverse events (good response to discontinuation of the drug or the severity of the adverse events after restarting the drug) related to study medicinal product use will be reported. This report should also include the correct reason and comprehensive information covering the likely time sequence, a good response to treatment withdrawal/reduction of the dose or the severity of the adverse event after restarting the drug/increase the dose; another used pharmacotherapy and procedures – dose decrease, drug withdrawal, optional treatment administered, the effect of used procedure.

9.1.4. Assessment of expectedness

Whether a particular adverse event can be defined as an expected adverse reaction should be determined in accordance with the information contained in the approved Summary of Product Characteristics (SPC) or the Patient leaflet accompanying the authorization of the drug. Reference document for evaluating whether a particular adverse reaction can be defined as expected is in this study the current approved Summary of Product Characteristics, Polish version.

9.1.5. Deviations in the results of laboratory tests

Liver enzymes, total blood count, serum creatinine, uric acid and electrolytes concentrations, if these tests were made.

9.1.6. Deviations in physical examination

Blood pressure, heart rate assessment.

9.1.7. Deviations in the results of other additional tests

Not applicable.

9.2. Recording and monitoring the further course-related of adverse events

During each visit patients well-being will be recorded.

Each related adverse events will be recorded on the relevant pages of the Observation Form. The related adverse event should be recorded, including drug reactions, disease beginning during the observation or exacerbation of pre-existing disease.

Previously reported related adverse event which is recognized as “ongoing” shall be checked during each subsequent assessment.

For each recorded related adverse events Investigator must seek to obtain adequate information to determine the course of the related adverse events and to assess whether it meets the criteria for the classification of a related serious adverse event, that requires immediate (within 24 hours) notification to the Study Organizer. The Investigator must assess the causal relationship between the study drug administration and the occurrence of related adverse events and record the results of the evaluation in the Observation Form. Discontinuation of treatment with the study drug is necessary if the related event or its consequences are still present the next day after the related adverse event was recorded. Further monitoring is needed to down grade the event or its consequences, or to stabilize them at a level acceptable by investigator or a designated representative from the Office Study Organizer.

9.3 Related serious adverse events

9.3.1. The requirements for reporting of adverse events

All serious adverse events related to the use of the study drugs must be reported immediately within 24 hours after obtaining information by the Investigator of the event to the Study Organizer (Europharma). If the first report will be made by telephone, a detailed written CRF should be send.

9.3.2. The mandatory information to be included in the notification of related serious adverse event

The following information are the minimum that should be reported within 24 hours of the occurrence to the Study Organizer representative for all related serious adverse events:

- number of non-interventional study,
- centre number,
- patient number,
- description of related adverse event,
- Investigator name and surname, and contact details.

Additional information on the CRF must be provided to the Study Organizer representative as soon as they become available. Upon receipt of the first report Study Organizer will ask the investigator to assess the causal relationship, if such an assessment is not included in the first application.

The Investigator should provide the diagnosis or the name of the disease and not the individual clinical symptoms. The Investigator should also attempt to separate the primary related adverse event (the main adverse event) from the secondary - adverse events that occurred as a complication.

9.4. Deaths

All related adverse events leading to death during the study must be reported as related serious adverse events within 24 hours from the time the investigator was informed about the event.

Death should be reported as follows:

- Determination of related adverse event: the main cause of death (eg, multi-organ failure, pneumonia, myocardial infarction).
- **The only exception** is the unknown cause of death (ie, sudden or unexplained death), when the term associated adverse event may be “death” or “sudden death”.

9.5. Discontinuation of the treatment with the study drug or withdrawal from the study due to related adverse event as well as related serious adverse event

Discontinuation of the treatment with study drug or discontinuation of patient participation in the study for any reason due to the associated related adverse events should be distinguished from the discontinuation of the study drug or discontinuation of Patient participation in the study for any reason due to lack of therapeutic effect (see section 6).

If the study drug will be discontinued due to a related serious adverse event, this fact must be immediately notified to the representative of the Study Organizer (see section 9.3).

In all cases, the Investigator must provide further appropriate medical care for the patient.

9.6. Reporting of the related adverse events to the relevant authorities

Reporting of related AEs will be in accordance with applicable legal regulations.

If AE is deemed to be serious according to definition, the CRF are completed and Europharma (CRO) are notified immediately, not later than 24 hours after being informed of the SAE. Europharma will report these AEs to PLRP the next working day. PLRP send this data to the global PV Drug Safety, who will then submit it to the authorities.

Non serious AEs will be reported by Investigator in CRFs to Europharma. Europharma will report these AEs to PLRP once a month. PLRP send this data to the global PV Drug Safety, who will then submit it to the authorities.

10. STATISTICAL CONSIDERATIONS ON ADVERSE EVENTS

10.1. Patient classification and definition

The patient treated: Patient who received at least one dose of study drug.

10.2. Analysis, population, definition

Safety population: All patients who received at least one dose of study drug.

The safety data analysis will be conducted on the safety population.

10.3. The method of determining the sample size

This is a non-interventional study in which the number of patients about 3,500 was determined taking into account the practical limitations, and not on the basis of statistical analysis. Therefore, this study does not make up the basis for the formulation of definitive conclusions about the safety of the study drug.

This is a descriptive study evaluating safety and tolerance of treatment with study drug, thus in this study basic statistical analysis will be performed.

10.4. Statistical methods

On the basis of reported adverse events, the frequency of their occurrence in study population will be assessed. For the most common adverse events the characteristics of subpopulation in which it was reported will be analyzed.

10.4.1. Demographic data and other basic characteristics

The descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency for demographic and basic characteristics data (medical history, co-morbidities, the primary disease diagnosis) will be presented.

10.4.2. Distribution of patients and cases of exclusion from the study

The number of patients treated, the number of patients who discontinued treatment with study drug, and the number of patients who participated in the next study visits will be presented in the form of tables. The main reasons for patient discontinuing the participation in the study will be presented in the form of tables.

10.4.3. The safety assessment

All safety data will be included in the summaries of data on individual patients. Analysis and summary tables are based on data from the safety population

The related adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA).

The prevalence of all reported related adverse events and serious adverse events occurring during the study drug administration will be presented in the form of tables. In addition, summary tables will be presented, that will include data on the maximum severity, relationship to the study drug administration and related data on adverse events, and patients who discontinued treatment with study drug for any reason.

The related adverse events occurring during the study will be noted in the tables related to adverse events. Medication usage due to concomitant disease will be summarized with the number and percentage of patients receiving them divided into a group of pharmacological and generic name of the drug.

11. MONITORING PROCEDURES

The Investigator is responsible for the validation of all data collected in the center.

In this study patients are not being subjected to any additional diagnostic procedures and monitoring.

Completeness of Observation Forms will be checked at the Office of Study Organizer and any missing or inconsistent data will be clarified with the Investigator by the people involved in data management.

12. MANAGEMENT OF THE STUDY

12.1. The scope of the data collected

The investigator is required to record all the data relating to the procedures of the Protocol, the use of the study drug and safety data in the Observation Forms provided for the purpose of this study.

The Investigator is required to sign the page of Observation Form relating to the completion of study and a certificate of study completion to prove that all entered data is accurate and complete.

Any corrections in Observation Forms and source documents must be placed in such a way that the original entries were still legible (strikethrough single thin line). If the reason for the change is not obvious, this should be entered.

12.2. Verification of data quality

Observation Forms transferred from the Study centres to **Office of Study Organizer** will be analyzed in terms of completeness, consistency, clarity and compliance with the Protocol.

At appropriate places of Observation Form a reason for missing data and other deviations from the Protocol should be specified. The **Office of Study Organizer** will communicate to the Investigator any questions regarding the processing of data and the points that have not been sufficiently explained, the purpose of clarification or improvement. The Investigator must ensure that requests for clarification of data are immediately filled. The Investigator has the obligation to keep copies of all data changes and clarifications to the Observation Form (CRF).

12.3. Data management

Data management will be conducted by the Office of Study Organizer.

All the procedures of data processing will be carried out in accordance with standard operating procedures of Office of Study Organizer.

Office of Study Organizer will have an obligation to ensure that appropriate input methods (eg double data entry) are applied, and that the appropriate inquiries on missing or inconsistent data are addressed.

13. ADMINISTRATIVE PROCEDURES

13.1. Consent of the relevant authorities to carry out this study

In accordance with Art. 36u paragraph. 2 of the Act of 6 September 2001 - Pharmaceutical Law (Journal of Laws 2001 No. 126, item. 1381), Study Protocol requires approval by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocides and obtain consent for its conducting.

The Ethics Committee approval is not need because it is non-interventional study. Due to same reason patient consent is not need. In addition, patient consent is not need because the collected data included patient initial, only do not make a possibility to identify of the patient.

13.2. Rules on publication

Specified separately.

13.3. The report on the study

The report on the study will be prepared by Office of Study Organizer.

13.4. Details concerning contracts and financing

Contracts with the Investigators will be concluded by the Office of Study Organizer.

13.5. The insurance, taking responsibility and compensation

In accordance with the provisions of applicable law.

14. AMENDMENTS TO THE PROTOCOL

Amendments can be made by Office of Study Organizer.