20 January 2011
EMA/CHMP/10929/2011
Human Medicines Development and Evaluation

WITHDRAWAL ASSESSMENT REPORT

FOR

ZOMETA

International Nonproprietary Name:

zoledronic acid

Procedure No. EMEA/H/C/000336/II/0034

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABCSG	Austrian Breast and Colorectal Cancer Study Group
AE	Adverse Event
AI	Aromatase inhibitor
AIBL	Aromatase inhibitor-associated bone loss
APR	Acute phase reactions
BMD	Bone mineral density
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate, 5-fluorouracil
CRF	Case Report Form
DFS	Disease free survival
ER+	Estrogen receptor positive
GCP	Good Clinical Practice
GnRH	Gonadotropin releasing hormone
HCM	Hypercalcaemia of malignancy
HR+	Hormone receptor positive
IAB	International Advisory Board
IDMC	Independent Data Monitoring Committee
L1-L4	Lumbar spine vertebrae 1 through 4
L2-L4	Lumbar spine vertebrae 2 through 4
LHRH	Luteinizing hormone-releasing hormone
o.d.	omnie die/once a day
OFS	Ovarian function suppression
OS	Overall survival
PgR+	progesterone receptor-positive
p.o.	per os/oral(ly)
PSUR	Periodic Safety Update Report
RFS	Recurrence free survival
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	standard deviation
SRE(s)	Skeletal-related event(s)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the CHMP considers that the application for Zometa, in the treatment of:

Formerly proposed indication:
Adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women, in conjunction with hormonal therapy

Currently proposed indication:

Adjuvant treatment of hormone receptor positive early breast cancer in premenopausal women for whom hormonal therapy is recommended.

is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- Lack of clinical confirmatory evidence of an anti-tumor activity of Zometa when used as add-on to an adjuvant regimen in patients with EBC
- The adjuvant control treatments that were used in the pivotal trial are not considered representative of current European standards in pre-menopausal women with EBC. An extrapolation to combine zoledronic acid with "standard hormonal therapy" has not been justified based on the submitted data.
- The quality of the source data and the overall integrity of the results of the single pivotal trial ABCSG-12 has been put into question

Proposal for questions to be posed to additional experts
N/A

Inspection issues

Should this application be considered approvable during the review process, the CHMP will find it relevant to ask for a GCP inspection of the pivotal trial data because of its history as an independently run trial not designed for regulatory purposes. The original database used by ABCSG was not validated, and Novartis has only begun collaborating with the ABCSG after the results of the ABCSG-12 trial were presented at the ASCO 2008. Following this, the MAH of Zometa has tried to improve the quality of the trial data by creating an entirely new updated and validated MACRO database. A confirmation of the data quality in this single pivotal trial by an independent inspection by regulatory authorities would therefore seem appropriate.

II. EXECUTIVE SUMMARY

II.1 Problem statement

With an estimated worldwide incidence of 1 million patients annually, **breast cancer** is a global public health problem. In developed countries, the lifetime risk of breast cancer in women is 1 in 8, or about 12% (Jemal et al. 2009). Breast cancer is the most commonly diagnosed cancer (excluding skin cancer) and the second leading cause of cancer-related mortality among women in the United States and European Union (40,170 estimated deaths in 2009 and 131,900 estimated deaths in 2006, respectively) (Jemal et al. 2009, Ferlay et al. 2007). Approximately 40% of women are premenopausal when they are diagnosed with breast cancer (Jemal et al. 2009), and over 60% of these patients are hormone receptor–positive (HR+) (Li et al. 2003). In recent years, the incidence of early breast cancer has increased as a result of the implementation of screening programs. Despite the advances in adjuvant systemic therapy, 30% of patients treated for early breast cancer will eventually die of the disease (Sharma et al. 2008).

The unmet medical need is to reduce the number of premenopausal women with early breast cancer experiencing disease recurrence and death from breast cancer. The challenge in the adjuvant setting is to develop innovative systemic treatments that are safe and effective in reducing the rates of disease recurrence and mortality beyond what is achievable with currently available therapies.

II.2 About the product

Zometa (zoledronic acid 4 mg for intravenous injection) is a potent third-generation bisphosphonate. The primary action of zoledronic acid on bone is to *inhibit bone resorption*. The molecular mechanism of action of zoledronic acid in osteoclasts, as well as other cells that internalize the compound, is inhibition of farnesyl diphosphate synthase (FPPS). This is a key enzyme in the arm of the mevalonate pathway that leads to protein prenylation of small intracellular GTPase signaling molecules which are involved in essential functions such as vesicular trafficking and cytoskeletal transformation. Without post-translational prenylation, the function of these molecules is disrupted, affected cells become quiescent, and premature apoptosis ensues.

Zometa is currently registered and marketed in the United States for the treatment of patients with hypercalcaemia of malignancy (HCM), multiple myeloma, or documented bone metastases from solid tumors in conjunction with antineoplastic therapy and in the European Union for tumor-induced hypercalcaemia and for the prevention of skeletal related events (SRE) in patients with advanced malignancies involving bone. It is approved in more than 100 countries worldwide.

A growing body of published *preclinical* evidence shows that **bisphosphonates** in general and **zoledronic acid** in particular exert *anticancer effects* by different mechanisms: direct anti-cancer action by induction of tumor cell apoptosis and synergistic action in combination with chemotherapy, anti-metastatic action by inhibition of tumor cell adhesion to both mineralized and non-mineralized matrices and inhibition of tumor cell invasion through extracellular matrix; and possibly both anti-cancer and anti-metastatic action by inhibition of angiogenesis and immunomodulatory effects through stimulation of γδ T cells.

The anti-tumor activity has also been seen in a number of small *clinical* pilot trials. For instance it has been observed that zoledronic acid reduces the prevalence and persistence of disseminated tumor cells (DTCs) that are predictive of disease recurrence in the bone marrow of women with EBC.

The concomitant use of the oral bisphophonate clodronate to standard adjuvant therapy has been examined in several trials in patients with stage I-III BC and overall, the results have been conflicting.

The pivotal trial of this application (ABCSG-12) represents currently the only large clinical trial of the anti-tumor activity outside bone of the more potent zoledronic acid in premenopausal patients with EBC.

However, a number of ongoing trials are also investigating the role of zoledronic acid in the (neo) adjuvant setting of BC (AZURE, SUCCESS, SWOG0307). Particularly, the pending results of the AZURE trial are expected to elucidate the anti-tumor activity of zoledronic acid further. This trial evaluates the efficacy of zoledronic acid in 3360 patients with stage I/III BC who are receiving standard adjuvant endocrine therapy and/or chemotherapy. In a retrospective analysis of a *neoadjuvant* subset of the study (N=205), the addition of zoledronic acid to chemotherapy significantly reduced the median residual invasive tumor size at surgery from 42.4 mm (chemotherapy) to 28.2 mm (chemotherapy plus zoledronic acid).

The **ABCSG-12** pivotal trial in this submission investigates new therapies aimed to improve disease free survival (DFS), specifically the adjuvant endocrine therapy (goserelin plus either tamoxifen or anastrozole) with or without zoledronic acid in premenopausal patients with HR+ early breast cancer.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

- *Legal basis*

This is a type II variation for Zometa through the centralised procedure (EMEA/H/C/336/II/34).

- *Proposed indication*

- Formerly proposed indication:
Adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in pre- menopausal women, in conjunction with hormonal therapy

- Currently proposed indication:

Zometa is indicated as adjuvant treatment of hormone receptor positive early breast cancer in pre-menopausal women for whom hormonal therapy is recommended.

- *CHMP Guidelines/SA*

Novartis has sought regulatory input from FDA and the CHMP Rapporteur for Zometa on the appropriateness of study ABCSG-12 to support the regulatory submission of zoledronic acid 4 mg for the adjuvant treatment of premenopausal women with HR+ early breast cancer in conjunction with hormonal therapy. No formal EMA Scientific Advice was sought.

The effort made by Novartis to construct a validated database to meet regulatory standards and the effort to increase quality by re-entering all data from CRF, as well as the cleaning of the data and seeking completeness was acknowledged. There were clinical questions regarding whether the adjuvant hormonal therapy (goserelin plus either tamoxifen or anastrozole for 3 years) was widely utilized and, therefore appropriate for the study population and for the intended target population. Additional discussion included the inconsistencies in the protocol regarding the goals and objectives of the study and their clarification in the ABCSG-12 final SAP.

II.4 GCP aspects

According to the MAH the pivotal study was performed in compliance with the protocol and with the study-specific standard operating procedures (SOPs) of the Austrian Breast and Colorectal Cancer Study Group (ABCSG). These documents were designed to ensure compliance with the following regulations:

- Good Clinical Practice for Clinical Trials of Medicinal Products in the European Community 1992, including the archiving of essential documents
- Austrian Medicinal Products Act (Arzneimittelgesetz) 1996, Bundesgesetzblatt (Federal Gazette) 185/83
- German Medicinal Products Act (Arzneimittelgesetz), the "Guidelines for the Proper Conduct of Clinical Testing of Medicinal Products," and the ICH GCP Note for Guidance on Good Clinical Practice
- SAE reporting requirements specified in European Union Directive 2001/20/EC, which entered into force in Austria on 01-May-2004 and in Germany on 01-Aug-2004.
- World Medical Association Declaration of Helsinki.

The supportive AIBL studies were conducted according to Good Clinical Practice, as described in Novartis standard operating procedures and:

- ICH Harmonized Tripartite Guidelines E6 for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

- United States 21 CFR Parts 50 and 56 (Protection of Human Subjects) and IRB regulations

- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).

The non-clinical data in this type II indication for Zometa predominantly consists of peer-reviewed published scientific literature performed by independent, academic institutions. Thus, the studies have not been conducted in compliance with GLP. This is acceptable as the studies only relate to pharmacodynamics and pharmacokinetics.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

Zoledronic acid concentration-dependently inhibits cell proliferation and induces apoptosis *in vitro*. Considering the proposed clinical dosing regime (every 6 months), it seems likely that the main anti-tumor effects of zoledronic acid will be on tumor cells situated in bones, since the drug accumulates in bone tissues and is confined there for a long duration. In all other tissues, the tissue concentration may nevertheless be sufficient to inhibit tumor cell adhesion and invasion although it will only transiently be above the effective cytostatic concentration.
Zoledronic acid disrupts tumor angiogenesis *in vivo*. However, the mechanism responsible for this effect is not fully elucidated. Furthermore, it is presently not known whether the anti-angiogenic effect is likely to occur at clinical relevant tissue concentrations as inhibition was mainly observed at concentrations > 1 µM *in vitro*.
Considering the pharmacokinetic profile of zoledronic acid treated with the proposed dosing regime, it seems likely that the main pharmacological effect of zoledronic acid on soft tissue tumors is due to its inhibitory effects on tumor cell adhesion and invasion. Although extrapolation from *in vitro* data is difficult, data obtained with cancer cell lines and endothelial cells indicates that there may theoretically be differences in the sensitivity to zoledronic acid depending on cell/tumor types. Thus, it cannot presently be excluded that the current dosing regime may be insufficient for the inhibition of tumor cell adhesion/invasion of certain cancer types.
In vitro and *in vivo* data indicates that zoledronic acid may cause immunomodulation at clinical relevant plasma concentrations.
Although it is not entirely obvious which mechanism of action is mainly responsible for the anti-tumor efficacy *in vivo*, the present non-clinical data suggest that zoledronic acid may be beneficial for the treatment of tumors, which is not only restricted to bone. Furthermore, data indicate that the anti-tumor effects of zoledronic acid are enhanced in combination with standard antineoplastic therapy, thus, making it suitable for adjuvant treatment.
The lack of secondary pharmacodynamic, safety pharmacology and pharmacodynamic drug interaction studies is acceptable in view of the extensive clinical knowledge.

The biodistribution studies in rat and dog demonstrate several orders of magnitude higher affinity of zoledronic acid for calcified compared with non-calcified tissue. As shown in rats, bone exhibits a large storage capacity for zoledronic acid, which was not saturated after 16 daily doses, representing the cumulative annual dose of zoledronic acid in patients with metastasis to bone. In the skeleton of mature dogs, the uptake of drug was higher in the axial skeleton compared with appendicular bones or the head. It was most pronounced in the dynamic parts of bone and in regions with a high surface area (cancellous bone) compared with compact bone or the non-calcified central cavity of bone.
Bisphosphonates are known to complex with hydroxyapatite, thereby leading to a high sequestration of the drug into bone (Cremers et al., 2005).
Bisphosphonates are generally not subject to hepatic metabolism (Lin, 1996; Cremers et al., 2005), which is in line with the observed relatively low concentrations of zoledronic acid in the liver compared with other nonosseous tissue in rats and dogs and negligible faecal excretion of drug following intravenous dosing. Zoledronic acid is predominately excreted via the kidneys.

The Applicant has not submitted any new toxicity data, which is acceptable in view of the proposed indication.

III.3 Clinical aspects

- **Tabular overview of clinical studies**

For the purpose of this submission, the **ABCSG-12 study** is *pivotal* and provides both, efficacy and safety data. Three Novartis-sponsored trials **(FEM345D2405, FEM345D2406 and ZOL446EUS32)** are included to provide *supportive* safety data.

Table 1 Overview of trials or sources of data

Source	Details
Pivotal controlled trial (conducted by the Austrian Breast and Colorectal Cancer Study Group)	
Study ABCSG-12: 1 prospective, randomized, open-label, multicenter trial in *premenopausal* women with HR+ early breast cancer (ABCSG-12)	
Long-term data	Number of patients: 1803 Disease free survival (primary efficacy endpoint), recurrence free survival and overall survival On treatment: 3 years Post-treatment follow-up: 5 years Bone mineral density* (substudy conducted in 415 patients) On treatment: 3 years Post-treatment follow-up: 2 years for BMD, 5 years for DFS, RFS, OS
Controlled trials (Novartis sponsored trials) included as supportive for safety evaluation	
AIBL studies: 3 prospective, randomized, open-label, multicenter trials in *postmenopausal* women with HR+ early breast cancer (FEM345D2405, FEM345D2406 and ZOL446EUS32)	
Long-term data	Number of patients: total 2194 patients (1065 in FEM345D2405, 527 in FEM345D2406 and 602 in ZOL446EUS32) Bone mineral density† (primary endpoint) On treatment: 5 years from randomization, up to disease recurrence or early discontinuation for other reasons Disease free survival (secondary efficacy endpoint) On treatment: 5 years from randomization, up to disease recurrence or early discontinuation or death Post-treatment follow-up: 5 years (FEM345D2405 and FEM345D2406 only) Overall survival (secondary efficacy endpoint) 5 years (FEM345D2405 and FEM345D2406 only)

*Change from baseline in lumbar spine (L1-L4) and hip trochanter BMD at 12 months

†Change from baseline in lumbar spine (L2-L4; secondary analysis including L1-L4) BMD at 12 months: Primary safety endpoint in [Study FEM345D2405] and [Study FEM345D2406]; change from baseline in lumbar spine (L1-L4) BMD, primary efficacy endpoint in [Study ZOL446EUS32]

Pharmacokinetics/Pharmacodynamics

The Clinical Pharmacology for Zometa has been detailed in prior applications.

Despite the concentration of zoledronic acid in bone, preclinical data indicate persistence of low levels of drug in soft tissue throughout the dosing interval. As such, zoledronic acid accumulates not only in osteoclasts but also in monocytes, macrophages, endothelial cells and tumor cells where it inhibits FPPS, a key enzyme in the synthesis pathway of isoprenoids. These are essential components for intracellular signalling molecules that in case of dysfunction will lead to premature apoptosis of the cell. By extrapolation of the tissue distribution data from animals to humans, the working hypothesis for the anticancer efficacy of zoledronic acid is currently that the slow release of zoledronic acid from bone and its retention in soft tissues will result in anti-proliferation and apoptosis of tumor cells.

The Applicant has presented both *in vitro* and *in vivo* preclinical data demonstrating a synergistic anti-tumor activity of zoledronic acid when combined with a variety of different antineoplastic agents including tamoxifen, letrozol and doxorubicin. These data form the basis for ongoing investigations on of the synergistic effect of chemotherapy followed by zoledronic acid in women with EBC. Published data from at subgroup of patients in the AZURE trial has reported a synergistic anti-tumor action of zoledronic acid and neoadjuvant chemotherapies (anthracycles or taxanes). The ANZAC study is currently investigating the mechanism of action of the observed synergism in the neoadjuvant setting.

Clinical efficacy

Dose-response studies

The MAH recognizes that no dose-finding studies have been performed specifically with focus on the anti-tumor effect of zoledronic acid. The dosing regimen used in the pivotal trial ABCSG-12 was pragmatically selected based on the demonstrated activity at bone level. However, the 4 mg/6 m dosing schedule (or the equivalent dose in animals) has demonstrated relevant anti-tumor activities in a number of preclinical and clinical studies, and importantly, the results of the ABCSG-12 trial indicate that the chosen dosing regimen both leads to improvement in DFS as well as maintenance of BMD.

Main clinical studies

ABCSG-12

The pivotal study ABCSG-12 was a phase III, randomized, controlled, open-label trial study enrolling *pre-menopausal* patients with hormone receptor positive, stage I-II, invasive, early breast cancer (EBC). The study was not double-blinded. A blinded placebo-controlled design would have been preferable in order to overcome potential bias, especially as only a single study has been performed. The MAH stated as justification that placebo infusions are prohibited by Austrian Drug Law. However, this is not the case in other EU Member States and this issue remains controversial.

According to the MAH, the pivotal trial was designed with two primary objectives that were to compare:
1) the treatment effect of goserelin-anastrozole to goserelin-tamoxifen and
2) +/- zoledronic acid.
A 2x2 factorial design has been applied which requires that the two treatment variables are not interrelated in any way. Furthermore,
3) a substudy investigated the change in BMD in lumbar spine (L1-4) and trochanter hip during the allocated treatments +/- zoledronic acid. The rapid bone loss associated with antiestrogen treatments, particularly with AIs and ovarian suppression, but also tamoxifen in premenopausal women, remains an issue of concern. However, there is so far no clear evidence for the use of bisphosphonates in the adjuvant setting.

The pivotal trial included patients with early stage invasive breast cancer (EBC) which includes the *Stages I* and *II*: *Stage I* represents tumor <2 cm in size, axillary node-negative. *Stage II*: positive but ipsilateral and mobile axillary nodes, or tumor size >2 cm; a tumor >5 cm must be node-negative to be considered early stage.
These patients represent a relatively heterogeneous study population that also includes patients with an *intermediate* or *high risk* of disease recurrence according to current risk stratification. With reference to European guidelines, these patients would not be candidates for adjuvant endocrine therapy only. Consequently, the investigational "backbone" treatment arms are not considered optimal adjuvant regimens from a European perspective which hampers the interpretation of the study results.

All patients received ovarian suppression with goserelin 3.6 mg s.c. q 28 d. They were randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups to consisting of goserelin PLUS either tamoxifen (20 mg/day p.o.) OR anastrozole 1 mg p.o.daily, and either with or without the addition of zoledronic acid (4 mg i.v. q 6 mo) for 3 years.

Standard doses of goserelin, tamoxifen and anastrozole have been used.

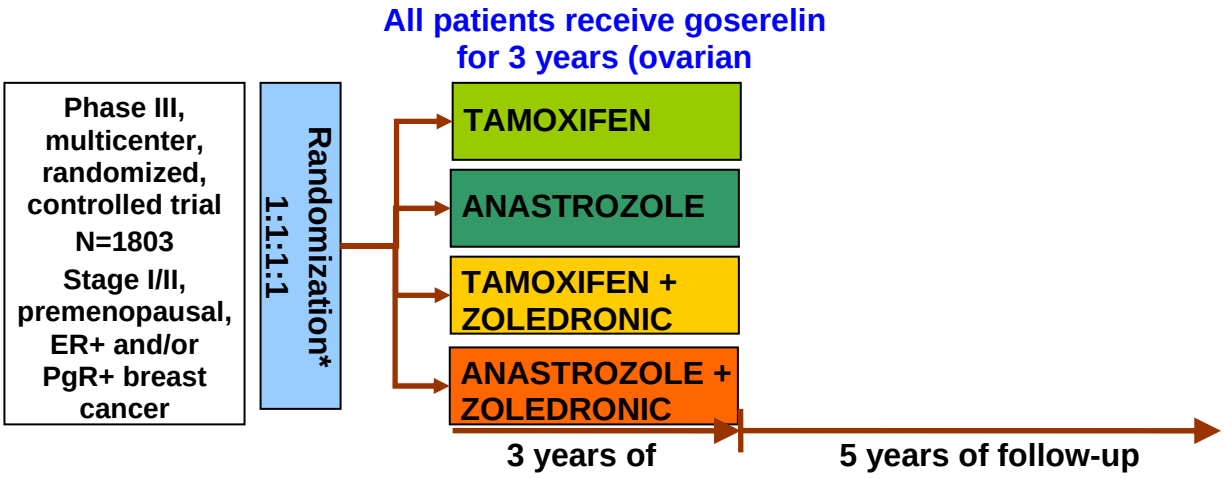
The type and duration of endocrine therapy used in ABSCG-12 were selected based on the outcome of a previous study (ABSCG-5) which had found the combination of goserelin for 3 years + tamoxifen for 5 years superior to CMF chemotherapy in terms of RFS. The combination of goserelin + anastrozole in ABCSG-12 was investigational.
The initial zoledronic acid dose in the pivotal study was 8 mg i.v. monthly for the entire 3 year treatment period. At the time this dose was selected from ongoing registration studies for the prevention of skeletal related events in patients with advanced malignant disease involving bone. However, the dose and schedule of zoledronic acid was gradually reduced during the first year of the trial because of the emergence of safety alerts regarding renal insufficiency in patients treated with the 8 mg dose. Therefore, the randomization to the zoledronic acid treatment arms was suspended from June 2000 till November 2000 when ABCSG decided to resume randomization to zoledronic acid at a dose of 4 mg i.v. q 6 months for the 3 years of study treatment. This new dosing was consistent with the dose used in other trials investigating the use of zoledronic acid in the adjuvant setting. At that time 268 patients had been randomized to the trial and potentially received a higher zoledronic acid

dose. However, a total of 1803 patients were enrolled in the pivotal study. To address the potential impact of the change in dosing regimen and the temporary randomization interruption on the DFS outcome, two subgroup analyses of DFS were performed: 1) Including only patients after resumption of randomization in the zoledronic acid arms at the 4 mg q 6 months dosing schedule, and 2) including only patients after resumption of randomization in the four study arms. The results of these analyses were consistent with the results of the primary ITT DFS analysis.
The MAH has subsequently provided a satisfactory response demonstrating that the small number of patients that received zoledronic acid 8 mg (10.6% of patients in the ITT population) did not have a significant impact on either the efficacy or safety evaluations.

The proposed dose reductions were introduced in order to avoid renal toxicity. The optimal dose-regimen for the claimed anti-tumor effect outside bone has not been defined.

Figure 1 Trial design schematic for ABCSG-12

Primary objectives:	To compare 1) tamoxifen vs. anastrozole and 2) zoledronic acid vs. no zoledronic acid
Primary endpoint:	Disease Free Survival
Secondary endpoints:	Recurrence Free Survival, Overall Survival, Change in Bone Mineral Density (BMD Substudy)
Zoledronic acid dosing:	4 mg i.v. every 6 months
Duration of study:	3 years of treatment + 5 years of follow-up



Note: Patients were assessed for disease recurrence and death during the entire study, i.e. during both the treatment phase (first 3 years), and during the additional 5 years of follow-up.
* Stratification factors at randomization: age, preoperative (neoadjuvant) chemotherapy, tumor stage, lymph node status, type of surgery, axillary node dissection, intraoperative radiation, and region of participating center.

Patients with primary, operated breast cancer can be stratified into 3 categories according to their risk of recurrence. The estimated risk of recurrence in 10 years is <10% for patients at low risk, 10%-50% in patients at intermediate risk and >50% in patients at high risk of recurrence. Currently, this risk stratification is based on a number of factors including age, tumor size, histopathological grade, vascular invasion, axillary lymph node involvement, ER/PgR status and HER2 status. In the future, the results of gene profile expressions are also likely to be included in the risk assessment.

The MAH advocates that many patients at low or intermediate risk of recurrence can be adequately treated with adjuvant hormonal therapy alone (Goldhirsch 2007; NCCN 2009).

Major determinants for the choice of adjuvant treatment are the hormone receptor and HER2 status. Patients with hormone receptor positive tumors may receive endocrine treatment alone or a combination of endocrine therapy and chemotherapy. Patients with HER2 overexpression or amplification should be considered eligible for adjuvant treatment with trastuzumab.

According to European standards, adjuvant chemotherapy is generally recommended for patients with intermediate and high risk for disease recurrence. In *premenopausal* patients the standard endocrine

adjuvant therapy is 20 mg tamoxifen daily for 5 years. An alternative would be ovarian function ablation (by bilateral oophorectomy or Gonadotropin-releasing hormone analogues) combined with tamoxifen. In *postmenopausal* patients there is best evidence for the initial use of an aromatase inhibitor (AI) for 5 years. Although these standards may change over time, a recent Cochrane review has examined the role of LHRH agonists in premenopausal EBC. It concluded that "data from currently published clinical trials of LHRH agonists in the adjuvant setting for premenopausal women with endocrine-sensitive EBC are supportive of clinical benefit. Nonetheless, definitive comparisons against current clinical standards of care that include third generation chemotherapy regimens and tamoxifen are required before their place in the adjuvant setting can be properly defined".
Based on these recommendations the endocrine therapies used in the pivotal trial are not considered representative of current European standards which is a major deficiency of this application.

References:

1. *Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology 2009; 20 (Supp 4): iv10-14*

2. *LHRH agonist for adjuvant therapy of early breast cancer in premenopausal women (Cochrane Review). The Cochrane Libery 2009; Issue 4*

In conclusion, anastrozole used as comparator drug does not represent the standard of care in this setting. Both the control arm (anastrozole) and the duration of tamoxifen treatment (3 years) are questionable. According to clinical practice, patients should receive at least 5 years of tamoxifen and node positive – about 30% of subjects in the main study- premenopausal women should receive a combined treatment of adjuvant chemotherapy and hormone therapy. The MAH maintains that the optimal "standard" treatment for specific subgroups of pre-menopausal women with ER+ EBC represents a dynamic and changing scenario with a number of remaining open questions and that the endocrine therapy used in study ABCSG-12 should not represent a major obstacle to conclude that adjuvant zoledronic acid provides additional and meaningful clinical benefit.

DFS is accepted as a primary end-point in the adjuvant treatment of premenopausal women, considering the unfeasibility of very long term studies that would be necessary to assess OS. According to CPMP/EWP/205/95/Rev.3/Corr.2 "Guideline on the evaluation of anticancer medicinal product in man" in the adjuvant setting, effects on DFS are considered relevant to the individual patient. As the use of adjuvant therapy may limit therapeutic options at time of recurrence OS data should be reported. For established areas of adjuvant therapy, e.g. breast and colorectal cancer, and if benefit-risk is considered favourable for the experimental regimen based on DFS and available safety and survival data, mature survival data may be reported post-licensing". Therefore, RFS, OS and safety are suitable secondary endpoints in the proposed indication. Bone health (BMD) was only investigated in a substudy including 415 patients.

Fixed and symmetrical assessments were used in the assessment of possible disease recurrence. The frequency of these assessments is considered acceptable in the adjuvant setting. Patients were evaluated for disease recurrence and death during the study treatment phase (3 years), but also during an additional 5 years of follow-up. Patients were studied for a maximum total duration of 8 years. The follow-up was too short in the ABCSG-12 study to detect long term events. Accordingly, a relative low number of events were observed.

The study was unblinded as placebo infusions were considered unethical. All DFS events were apparently validated by an objective method which constituted the basis to confirm recurrence. It is acknowledged that DFS is a more objective endpoint less prone to bias compared to PFS in the metastatic, even in an unblinded trial. Due to the investigator initiated aspect of this trial, Novartis has subsequently performed a systematic verification of the objective evidence of all 162 cancer relapse events. In addition, it has been stressed that the timing of assessments for disease recurrence was fixed and symmetrical between treatment arms and that a sensitivity analysis investigating the possible impact of missed assessments showed consistent results with the primary analysis.

Standard statistical analyses have been performed. An adequate number of supportive analyses have been planned in order to demonstrate the consistency and robustness of the results. The original sample size (N=1250) was based on a very optimistic expectation to detect a difference of 10% (70% and 80%) in the 5-year DFS between the treatment groups. Due to an unexpectedly low overall event rate, a new and more realistic sample size (N=1800) was calculated based on the assumption that the hazard was constant and the 5-year disease-free survival under standard therapy was 92.6% and improved to 95.9% with a hazard quotient of 1.8.

The reason for choosing the pre-menopausal population is not clear. The requested marketing authorization for adjuvant treatment of premenopausal women is perplexing. Notwithstanding the supportive safety data from Novartis-sponsored trials that dealt with postmenopausal women, all patients of the ABCSG-12 study were treated with goserelin for ovarian suppression. The obvious goal of goserelin treatment is to abolish (or minimize) the estrogen release from the ovaries, just a result that occurs in a natural way after menopause. Postmenopausal women with hormone receptor-positive breast cancer are admittedly a more homogeneous population than their premenopausal counterpart. Furthermore there are some major imbalance, missing information and confounding factors in the pivotal study to be considered:

- The age of patients enrolled in the ABCSG-12 study ranged from approx. 27 to 56 years. This is considered a too wide age range as it is held that the course of breast cancer disease (in the case of hormone-dependent disease, the previous bodily exposure to estrogen as well), may be very different along the above mentioned age range.
- Moreover, an imbalance with respect to age randomization is observed: patients ≤ 40 years were 22% more in the anastrozole arms than in the tamoxifen arms.
- No information is given about their ovarian function at study entry.
- About one third of the patients had positive nodal status: how were they distributed as a function of age and receptor status?
- Thus, the pivotal study suffers from many confounding factors, not to quote the absence of stratification for HER2 expression. An imbalance of HER2 expression among patient subgroups could significantly impact on DFS results. A multivariate analysis including HER2 status should have been conducted.

It seems as if the study was initially designed to evaluate the efficacy of zoledronic acid (the dosing schedule was repeatedly amended with the eventual atypical schedule of 4mg every 6 months) in preventing treatment-induced and/or cancer-induced bone disease (metastases) in patients given goserelin plus anastrozole versus those given goserelin plus tamoxifen. The two regimens, in fact, are expected to differentially affect bone. Ongoing data had conceivably prompted attention on progression of cancer disease independently on bone health. By achieving statistical significance, an important priority in the scientific community was gained. The above considerations likely explain why the design of the study seems to be not adequately tailored to support the claimed indications .

Apparently the investigation of whether zoledronic acid added to standard adjuvant treatment would have an effect on DFS and OS was originally a secondary objective of the trial. According to the Documentation of Statistical Methods, Appendix 16.1.9, a "precision" of the primary objective of the trial was introduced on 12 March, 2008. According to the MAH and Gnant et al. the efficacy analyses were conducted as of 31 March, 2008. As such, the apparent change/modification in the final statistical plan was incorporated *before* the final data analysis and does not *per se* constitute a problem as long as all changes have an appropriate trail. The trial was unblinded but the assessment of disease relapse is less prone to bias. Nevertheless, the MAH should elaborate on the precise timing of events and specifically clarify what exactly prompted the need for a change of the primary and secondary objectives of the trial .

RESULTS

Patient flow

Table 2 Patient disposition by treatment arm – Study ABCSG-12 (ITT population)

	Zoledronic acid			Control		
	Anastrozole (N=450) n(%)	**Tamoxi-fen (N=450) n(%)**	**Total (N=900) n(%)**	**Anastrozole (N=453) n(%)**	**Tamoxi-fen (N=450) n(%)**	**Total (N=903) n(%)**
Patients with no treatment information in database	11 (2.4)	16 (3.6)	27 (3.0)	16 (3.5)	17 (3.8)	33 (3.7)
Treated patients	439 (97.6)	434 (96.4)	873 (97.0)	437 (96.5)	433 (96.2)	870 (96.3)
Completed 3-yr treatment	352 (78.2)	323 (71.8)	675 (75.0)	316 (69.8)	331 (73.6)	647 (71.7)
Treatment ongoing	38 (8.4)	29 (6.4)	67 (7.4)	27 (6.0)	22 (4.9)	49 (5.4)
Prematurely discontinued therapy(1)	49 (10.9)	82 (18.2)	131 (14.6)	94 (20.8)	80 (17.8)	174 (19.3)
-Recurrence under treatment	10 (2.2)	10 (2.2)	20 (2.2)	17 (3.8)	12 (2.7)	29 (3.2)
-Intolerance to study medication	12 (2.7)	22 (4.9)	34 (3.8)	32 (7.1)	19 (4.2)	51 (5.6)
-Patient refused to continue trt	14 (3.1)	24 (5.3)	38 (4.2)	23 (5.1)	20 (4.4)	43 (4.8)
-Additional malignant tumor	3 (0.7)	3 (0.7)	6 (0.7)	5 (1.1)	5 (1.1)	10 (1.1)
-Other (2)	10 (2.2)	23 (5.1)	33 (3.7)	17 (3.8)	24 (5.3)	41 (4.5)
Patients terminated from study	48 (10.7)	48 (10.7)	96 (10.7)	61 (13.5)	58 (12.9)	119 (13.2)
-Follow-up (5 years) completed	28 (6.2)	25 (5.6)	53 (5.9)	25 (5.5)	28 (6.2)	53 (5.9)
-Desire of patient	8 (1.8)	9 (2.0)	17 (1.9)	11 (2.4)	15 (3.3)	26 (2.9)
-Patient did not appear for two consecutive visits (during therapy)	0 (0.0)	5 (1.1)	5 (0.6)	1 (0.2)	5 (1.1)	6 (0.7)
-Patient died	12 (2.7)	9 (2.0)	21 (2.3)	24 (5.3)	10 (2.2)	34 (3.8)
-Cause of death: carcinoma	10 (2.2)	8 (1.8)	18 (2.0)	22 (4.9)	9 (2.0)	31 (3.4)
-Did not die from carcinoma	2 (0.4)	0 (0.0)	2 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
-Cause of death unknown	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.1)

(1) Premature discontinued treatment considered both start of follow-up (FU01) and study termination (ES01) during 3 years of treatment

(2) 'other' contains patients with reason of therapy discontinuation 6='other' in Follow-up page (CRF FU01) and terminated study within first 3 years due to 2='Desire of patients', 3= 'Patients did not appear for two consecutive visits (during therapy)' and 4='Pregnancy' in study termination CRF (CRF CE01) if the reason of therapy discontinuation is missing.

All patients enrolled in the trial have been accounted for. The overall rates of premature discontinuation from study drug were 15% for patients in the zoledronic acid arm compared to 19% for patients in the control arm. As explained by the MAH, the small discrepancy between the two treatment groups (+/- zoledronic acid) was due to a relatively lower number of discontinuations in the anastrozole+zoledronic acid arm (11%). A relatively low number of patients discontinued treatment due to AEs across all treatment groups (3-7%).

An imbalance was noted in the premature discontinuation of treatment that was higher in the control arm than that reported for the zoledronic arm (19.3% vs. 14.6%). In particular, the difference was mainly related to the premature discontinuation rates in the anastrozole control subgroup (20.8%) and in the anastrozole/zoledronic subgroup (10.8%). The reasons for the imbalance in premature discontinuation of study drug remain unclear.

The MAH has demonstrated that the main causes of censorings were administrative reasons (data cut-off reached or 8 years of study completed without a DFS event) and that other reasons of censoring were reasonably well balanced between treatment arms. Importantly, the number of patients with a follow-up gap > 18 months was very limited end equally distributed across treatment arms. In summary, no systematic bias has been identified that could have a major impact on study results.

Table 3: Baseline demographics

Table 1. Demographic and Baseline Disease Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Tamoxifen (N=451)	Tamoxifen plus Zoledronic Acid (N=449)	Anastrozole (N=453)	Anastrozole plus Zoledronic Acid (N=450)
Age at study entry				
Median — yr	45.5	45.3	45.0	44.5
Range — yr	27.6–56.5	27.5–56.3	25.9–56.3	28.8–56.4
≤40 yr — no. (%)	80 (17.7)	67 (14.9)	88 (19.4)	91 (20.2)
>40 yr — no. (%)	370 (82.0)	382 (85.1)	364 (80.4)	358 (79.6)
Cancer stage — no. (%)				
T1	338 (74.9)	335 (74.6)	348 (76.8)	339 (75.3)
≥T2	99 (22.0)	98 (21.8)	93 (20.5)	97 (21.6)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	13 (2.9)
Nodal status — no. (%)				
Negative	301 (66.7)	295 (65.7)	303 (66.9)	302 (67.1)
Positive	136 (30.2)	138 (30.7)	139 (30.7)	135 (30.0)
Unknown	13 (2.9)	16 (3.6)	10 (2.2)	12 (2.7)
Histologic grade — no. (%)				
1 or 2	344 (76.3)	344 (76.6)	344 (75.9)	339 (75.3)
3	93 (20.6)	89 (19.8)	97 (21.4)	98 (21.8)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	12 (2.7)
Estrogen-receptor status — no. (%)†				
Negative	16 (3.5)	19 (4.2)	15 (3.3)	17 (3.8)
Low expression	51 (11.3)	61 (13.6)	54 (11.9)	58 (12.9)
Medium expression	166 (36.8)	149 (33.2)	167 (36.9)	153 (34.0)
High expression	204 (45.2)	204 (45.4)	206 (45.5)	210 (46.7)
Unknown‡	14 (3.1)	16 (3.6)	11 (2.4)	12 (2.7)
Progesterone-receptor status — no. (%)†				
Negative	40 (8.9)	32 (7.1)	34 (7.5)	36 (8.0)
Low expression	52 (11.5)	64 (14.3)	58 (12.8)	59 (13.1)
Medium expression	160 (35.5)	142 (31.6)	149 (32.9)	131 (29.1)
High expression	185 (41.0)	195 (43.4)	200 (44.2)	212 (47.1)
Unknown‡	14 (3.1)	16 (3.6)	12 (2.6)	12 (2.7)
Preoperative chemotherapy — no. (%)				
No	406 (90.0)	404 (90.0)	408 (90.1)	405 (90.0)
Yes	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)
Unknown	21 (4.7)	22 (4.9)	21 (4.6)	19 (4.2)

* All patients received goserelin. Percentages may not total 100 because of rounding.
† Hormone-receptor status was defined by the Reiner score for staining,[23] which is based on a scale of 10 to 100%, with 10 to 50% indicating low expression of the estrogen and progesterone receptors, 51 to 80% indicating medium expression, and 81 to 100% indicating high expression.
‡ Patients in this category were identified as having protocol violations; they were included in the intention-to-treat analysis but excluded from the Cox regression analyses.

Baseline patient demographics appear to be well balanced in all groups, with respect to age at study entry, cancer stage, nodal status, histologic grade and hormonal receptor status. The median age of these pre-menopausal patients with EBC was 44 years. However, an imbalance in the number of patients aged <40 yrs between anastrozole and tamoxifen both in association with zoledronic acid is noticed.

Baseline disease characteristics

Table 4 Baseline disease characteristics by treatment arm – Study ABCSG-12 (ITT population)

	Zoledronic acid			Control (no zoledronic acid)		
	Anastrozole (N=450) n(%)	**Tamoxi-fen (N=450) n(%)**	**Total (N=900) n(%)**	**Anastrozole (N=453) n(%)**	**Tamoxi-fen (N=450) n(%)**	**Total (N=903) n(%)**
Cancer T-stage (pT)						
pT1a or yT0 or yT1a (<= 0.5 cm)	6 (1.3)	3 (0.7)	9 (1.0)	6 (1.3)	7 (1.6)	13 (1.4)
pT1b (0.5 cm <= 1 cm)	96 (21.3)	82 (18.2)	178 (19.8)	93 (20.5)	82 (18.2)	175 (9.4)
pT1c (>1 cm <= 2 cm)	241 (53.6)	254 (56.4)	495 (55.0)	253 (55.8)	252 (56.0)	505 (55.9)
pT2 (>2 cm <= 5 cm)	93 (20.7)	93 (20.7)	186 (20.7)	88 (19.4)	94 (20.9)	182 (20.2)
pT3 (>5 cm <= 10 cm)	5 (1.1)	4 (0.9)	9 (1.0)	5 (1.1)	4 (0.9)	9 (1.0)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
Cancer T-stage (pT) category						
=T1	343 (76.2)	339 (75.3)	682 (75.8)	352 (77.7)	341 (75.8)	693 (76.7)
>=T2	98 (21.8)	97 (21.6)	195 (21.7)	93 (20.5)	98 (1.8)	191 (21.2)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
Preoperative chemotherapy						
No preoperative	386 (85.8)	382 (84.9)	768 (85.3)	389 (85.9)	379 (84.2)	768 (85.0)
Preoperative w/o CR	23 (5.1)	21 (4.7)	44 (4.9)	20 (4.4)	23 (5.1)	43 (4.8)
Preoperative with CR	3 (0.7)	2 (0.4)	5 (0.6)	3 (0.7)	2 (0.4)	5 (0.6)
Missing	38 (8.4)	45 (10.0)	83 (9.2)	41 (9.1)	46 (0.2)	87 (9.6)
Number of affected lymph nodes metastatically involved						
No lymph nodes	304 (67.6)	298 (66.2)	602 (66.9)	304 (67.1)	305 (67.8)	609 (67.4)
1-3 lymph nodes	118 (6.2)	124 (27.6)	242 (26.9)	123 (27.2)	118 (26.2)	241 (26.7)
4-9 lymph nodes	19 (4.2)	14 (3.1)	33 (3.7)	18 (4.0)	16 (3.6)	34 (3.8)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
Number of affected lymph nodes category						
Negative	304 (67.6)	298 (66.2)	602 (66.9)	304 (67.1)	305 (67.8)	609 (67.4)
Positive (1-9)	137 (30.4)	138 (30.7)	275 (30.6)	141 (31.1)	134 (29.8)	275 (30.5)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
Tumor grading						
G1	65 (14.4)	74 (16.4)	139 (15.4)	54 (11.9)	66 (14.7)	120 (13.3)
G2	276 (61.3)	273 (60.7)	549 (61.0)	293 (64.7)	280 (62.2)	573 (63.5)

	Zoledronic acid			Control (no zoledronic acid)		
	Anastrozole (N=450) n(%)	**Tamoxi-fen (N=450) n(%)**	**Total (N=900) n(%)**	**Anastrozole (N=453) n(%)**	**Tamoxi-fen (N=450) n(%)**	**Total (N=903) n(%)**
G3	93 (20.7)	85 (18.9)	178 (19.8)	89 (19.6)	85 (18.9)	174 (19.3)
Gx, Iobular	7 (1.6)	4 (0.9)	11 (1.2)	9 (2.0)	8 (1.8)	17 (1.9)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
Tumor grading category						
G1/2	341 (75.8)	347 (77.1)	688 (76.4)	347 (76.6)	346 (76.9)	693 (76.7)
G3	93 (20.7)	85 (18.9)	178 (19.8)	89 (19.6)	85 (18.9)	174 (19.3)
Gx, lobular	7 (1.6)	4 (0.9)	11 (1.2)	9 (2.0)	8 (1.8)	17 (1.9)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
ER-ICA						
Negative	17 (3.8)	20 (4.4)	37 (4.1)	14 (3.1)	16 (3.6)	30 (3.3)
+	57 (12.7)	62 (13.8)	119 (13.2)	54 (11.9)	50 (11.1)	104 (11.5)
++	155 (34.4)	151 (33.6)	306 (34.0)	170 (37.5)	169 (37.6)	339 (37.5)
+++	212 (47.1)	203 (45.1)	415 (46.1)	207 (45.7)	204 (45.3)	411 (45.5)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
ER-ICA category						
Negative, +, ++	229 (50.9)	233 (51.8)	462 (51.3)	238 (52.5)	235 (52.2)	473 (52.4)
+++	212 (47.1)	203 (45.1)	415 (46.1)	207 (45.7)	204 (45.3)	411 (45.5)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
PgR-ICA						
Negative	36 (8.0)	32 (7.1)	68 (7.6)	35 (7.7)	40 (8.9)	75 (8.3)
+	59 (13.1)	66 (14.7)	125 (13.9)	59 (3.0)	54 (12.0)	113 (12.5)
++	131 (29.1)	142 (31.6)	273 (30.3)	149 (32.9)	160 (35.6)	309 (34.2)
+++	215 (47.8)	196 (43.6)	411 (45.7)	201 (44.4)	185 (41.1)	386 (42.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
PgR-ICA category						
Negative, +, ++	226 (50.2)	240 (53.3)	466 (51.8)	243 (53.6)	254 (56.4)	497 (55.0)
+++	215 (47.8)	196 (43.6)	411 (45.7)	201 (44.4)	185 (41.1)	386 (42.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)
Type of surgery						
Breast-conserving	361 (80.2)	359 (79.8)	720 (80.0)	366 (80.8)	361 (80.2)	727 (80.5)
Modified radical	80 (17.8)	77 (17.1)	157 (17.4)	79 (17.4)	78 (17.3)	157 (17.4)

	Zoledronic acid			Control (no zoledronic acid)		
	Anastrozole (N=450) n(%)	Tamoxi-fen (N=450) n(%)	Total (N=900) n(%)	Anastrozole (N=453) n(%)	Tamoxi-fen (N=450) n(%)	Total (N=903) n(%)
Missing	9 (2.0)	14 (3.1)	23 (2.6)	8 (1.8)	11 (2.4)	19 (2.1)

Source: [Study ABCSG-12-Table 11-2]

Baseline disease characteristics were also well balanced between patients receiving +/- zoledronic acid. The majority of patients had previously received breast-conserving surgery (approximately 80%). Only about 5% of patients had received neoadjuvant chemotherapy. About 20% had pT > 2 cm and approximately 1/3 of patients had involvement of axillary lymph nodes. It is questionable whether these patients were adequately treated according to European standards.

It is acknowledged that the current recommendations regarding the need for adjuvant chemotherapy are likely to change over time with the appearance of new tools (e.g. genetic profiling) that will enable us to select the optimal treatment for patients on an individual basis. However, it is considered premature to deviate from current standard recommendations from a regulatory point of view. The MAH recognizes that based on the 2009 St. Gallen Recommendations, 28% of patients in study ABCSG-12 were candidates for adjuvant chemotherapy in addition to hormonal therapy. A sensitivity analysis has therefore been performed in patients who were optimally treated with hormonal therapy alone according to the 2009 St. Gallen recommendations.

Furthermore, the MAH has been asked to clarify why no HER2 status is available for these patients as knowledge of the HER2 status is also essential in the risk stratification of patients with EBC. The HER2 status of patients in study ABCSG-12 is not available because routine HER2 testing was not included as a recommended prognostic factor for risk stratification in EBC until 2005. The pivotal trial was initiated in 1999 and recruitment ended in 2006. About 20% of patients with EBC have HER2+ positive tumors. The MAH has emphasized that HER2 is often associated with other prognostic factors of poor outcome that were infrequent in the ABCSG-12 study population why the percentage of patients with HER2+ tumors included in the study is expected to have been low. However, it should be stressed in section 4.1 of the SmPC that the adjuvant effect of zoledronic acid has not been investigated in relation to HER2 status.

The proposed indication should adequately describe the baseline disease characteristics of the patient population studied in ABCSG-12 as well as the adjuvant endocrine regimens studied. The current proposal is considered too broad.

Populations analyzed

Table 5 Efficacy analysis populations by treatment group – Study ABCSG-12

	Zoledronic acid			Control		
Population	Anastrozole N=450 n(%)	Tamoxifen N=450 n(%)	Total N=900 n(%)	Anastrozole N=453 n(%)	Tamoxifen N=450 n(%)	Total N=903 n(%)
ITT	450 (100.0)	450 (100.0)	900 (100.0)	453 (100.0)	450 (100.0)	903 (100.0)
BMD sub-population	105 (23.3)	103 (22.9)	208 (23.1)	102 (22.5)	105 (23.3)	207 (22.9)

Source: [Study ABCSG-12-Table 11-1]

No per protocol analyses of efficacy endpoints were planned in the protocol or SAP.

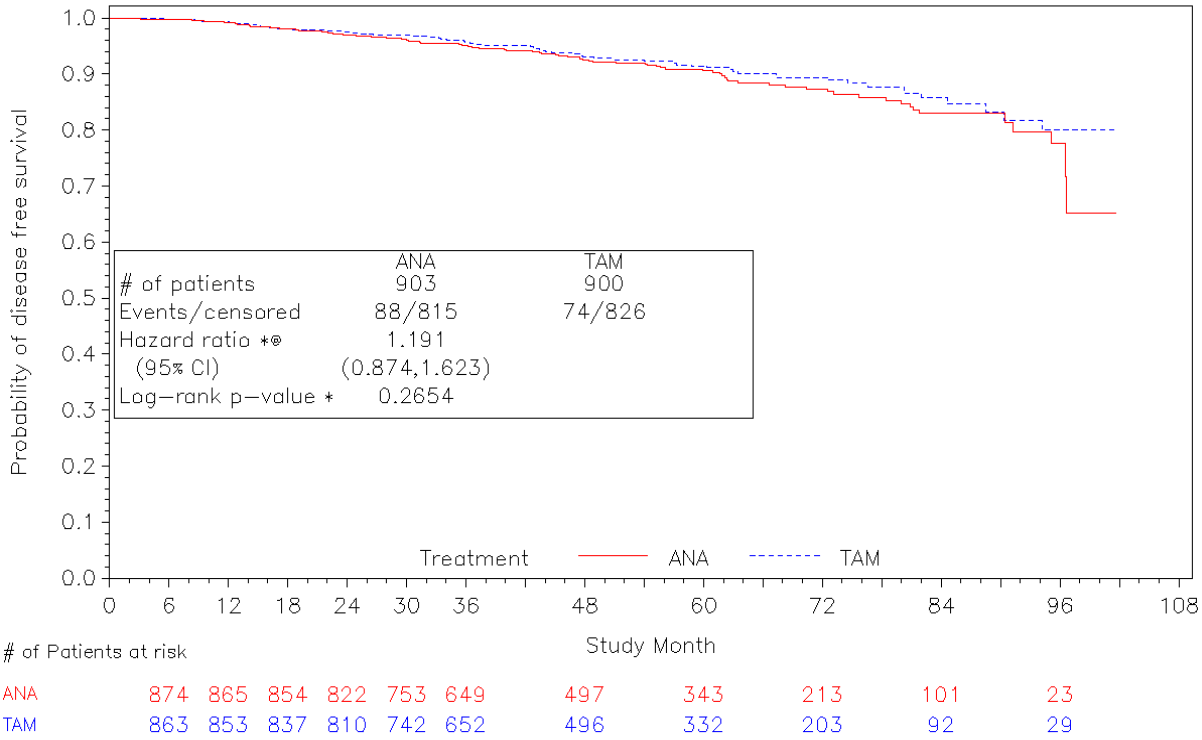
Primary endpoint (DFS)

The median duration of follow-up for DFS was 53 months. 162 patients developed DFS events that were all validated by an objective method (most frequently histology followed by CT and bone scan). Numerically, there were fewer patients with distant and locoregional recurrences, particularly in the

breast, axilla, bone and lung, in patients treated with zoledronic acid. These data are in support of an anti-tumor activity of zoledronic acid outside bone, but they should be interpreted with caution because all sites of recurrence were not systematically recorded by investigators in patients with simultaneous multiple sites of recurrence.

The results of the univariate Cox regression model and log-rank test stratified by zoledronic acid therapy show that there was no significant difference in DFS between patients treated with anastrozole and patients treated with tamoxifen (HR=1.19; 95% CI: (0.87, 1.62), log-rank p=0.265).

Figure 2: Kaplan-Meier plot of DFS by treatment arm: Comparison of anastrozole with tamoxifen – Study ABCSG-12 (ITT population)



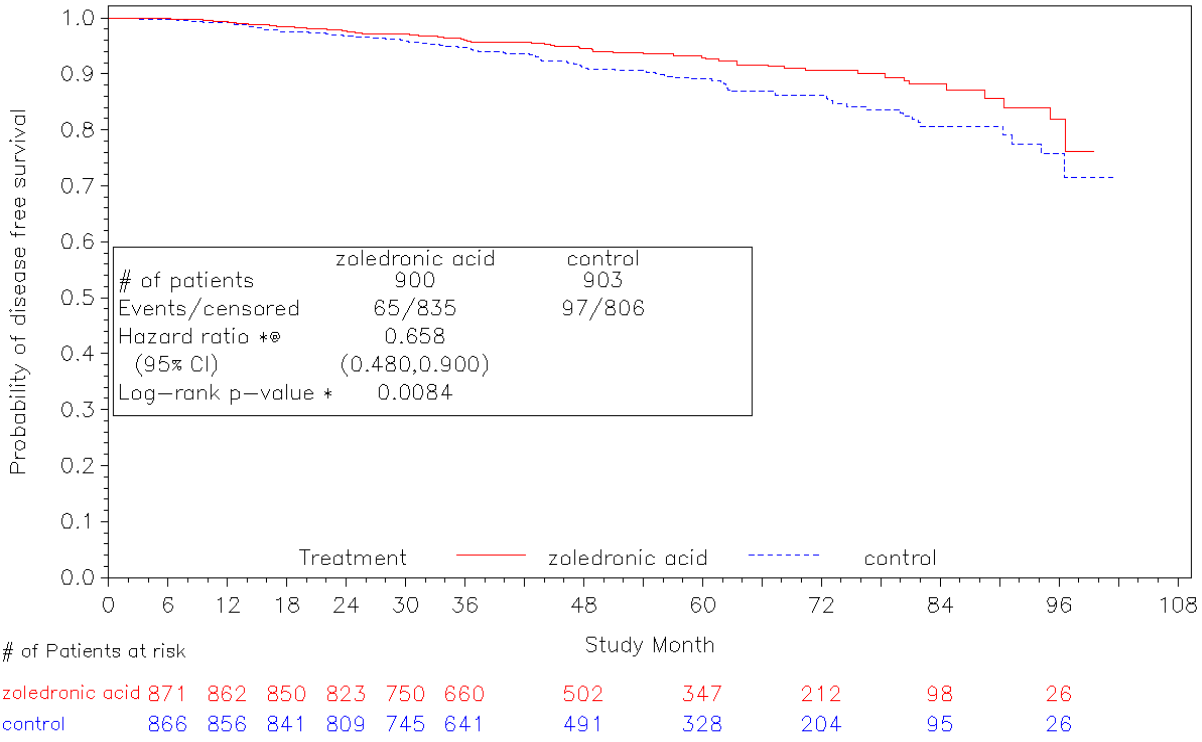
@ Hazard ratio of ANA over TAM

* Hazard ratio and log−rank test were stratified by zoledronic acid therapy

In contrast, zoledronic acid in combination with endocrine therapy significantly reduced the risk for DFS events by 34% compared to endocrine therapy alone (control) in a univariate Cox regression model and log-rank test stratified by endocrine therapy: HR=0.66; 95% CI: (0.48, 0.90); log-rank p-value=0.008. The 5-year estimated Kaplan-Meier rates for DFS were 92.9% in the zoledronic acid arm and 89.1% in the control arm, resulting in an absolute improvement of 3.8% for DFS which corresponds to a NNT of 26.

The updated data presented at ASCO 2010 are reassuring and showed that at a median follow up of 62 months the difference in DFS between the group treated with zoledronate and the control group is consistent.

Figure 3: Kaplan-Meier plot of DFS by treatment arm: Comparison of zoledronic acid with control – Study ABCSG-12 (ITT population)



# of Patients at risk

zoledronic acid	871	862	850	823	750	660	502	347	212	98	26
control	866	856	841	809	745	641	491	328	204	95	26

@ Hazard ratio of zoledronic acid over control
* Hazard ratio and log−rank test were stratified by endocrine therapy

Similar results were obtained in supportive Kaplan-Meier estimates of DFS rates and unstratified log-rank tests.

No significant interaction has been demonstrated between zoledronic acid and endocrine therapy which was a prerequisite for the use of the 2x2 factorial design.

The following four factors were identified as significant risk factors: Cancer T-stage (pT), number of affected lymph nodes, tumor grading, and PgR. When adjusting for these factors in a multivariate analysis, treatment with zoledronic acid also turned out as a significant predictor of improved DFS.

Various sensitivity analyses have been performed in order to investigate the robustness of the data: Even when censoring DFS at the start of non-study medications or at the time of missed visits, consistent results (HRs) can be demonstrated. No systematic biases have been identified.

Table 6 Cox regression model and log-rank test for sensitivity analyses of disease free survival (ITT population)

			Cox model			
Arms	**N**	**Events/censored**	**Hazard ratio**	**95%CI**	**p-value***	**Log-rank test p-value****
Backdating DFS events with ≥ 1 missed assessment visit						
Zoledronic acid	900	65 / 835	0.66	(0.48,0.90)	0.009	0.008
No zoledronic acid	903	97 / 806				
Backdating DFS events with 1 missed assessment visit and censoring DFS events with ≥ 2 missed visits**						
Zoledronic acid	900	64 / 836	0.65	(0.48,0.90)	0.009	0.008
No zoledronic acid	903	96 / 807				
Censoring DFS after new anticancer, bisphosphonate (zoledronic acid or pamidronate), or endocrine therapy in the absence of recurrence						
Zoledronic acid	900	63 / 837	0.69	(0.50, 0.95)	0.021	0.021
No zoledronic acid	903	90 / 813				
Censoring DFS at the start of endocrine therapy after 3 years of study treatment in the absence of recurrence						
Zoledronic acid	900	63 / 837	0.68	(0.49, 0.94)	0.019	0.018
No zoledronic acid	903	91 / 812				
Censoring DFS after the start of new anticancer therapy, any form of bisphosphonate, or endocrine therapy in the absence of recurrence						
Zoledronic acid	900	62 / 838	0.66	(0.48, 0.92)	0.013	0.013
No zoledronic acid	903	90 / 813				

Cox model is stratified by endocrine therapy and includes zoledronic acid [0: control vs. 1: zoledronic acid]. Hazard ratio of zoledronic acid over control
* Based on a Wald test from Cox model
**Based on stratified log rank test

In an exploratory subgroup analysis of DFS by risk factors, consistent HRs were also obtained across all subgroups analyzed. As expected, broad confidence intervals were observed in subgroups with a low patient number.

Figure 4.1: Forest plot of DFS by 6 risk factors: Comparison of zoledronic acid with control stratified by endocrine therapy– Study ABCSG-12 (ITT population)

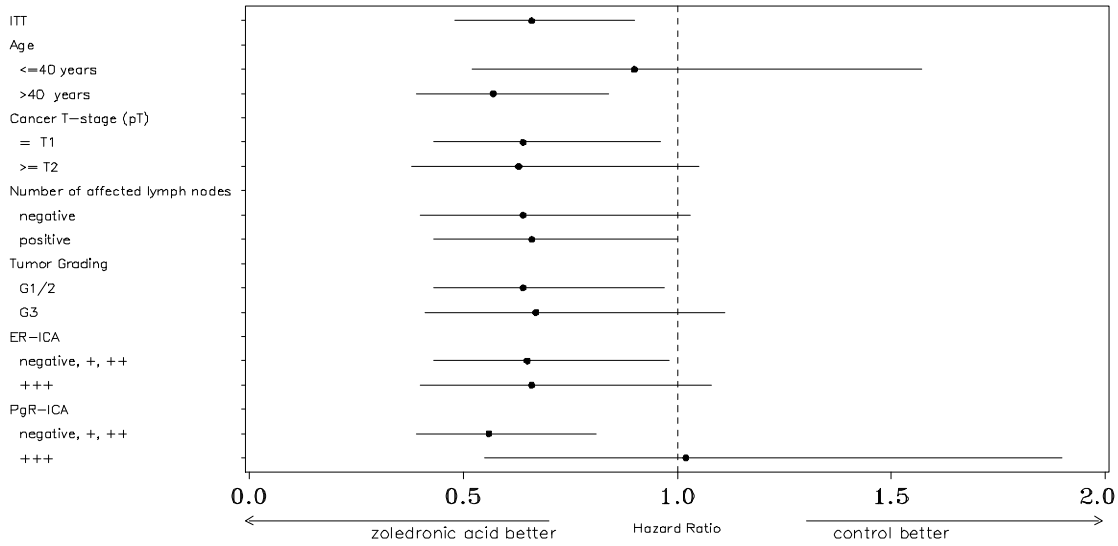
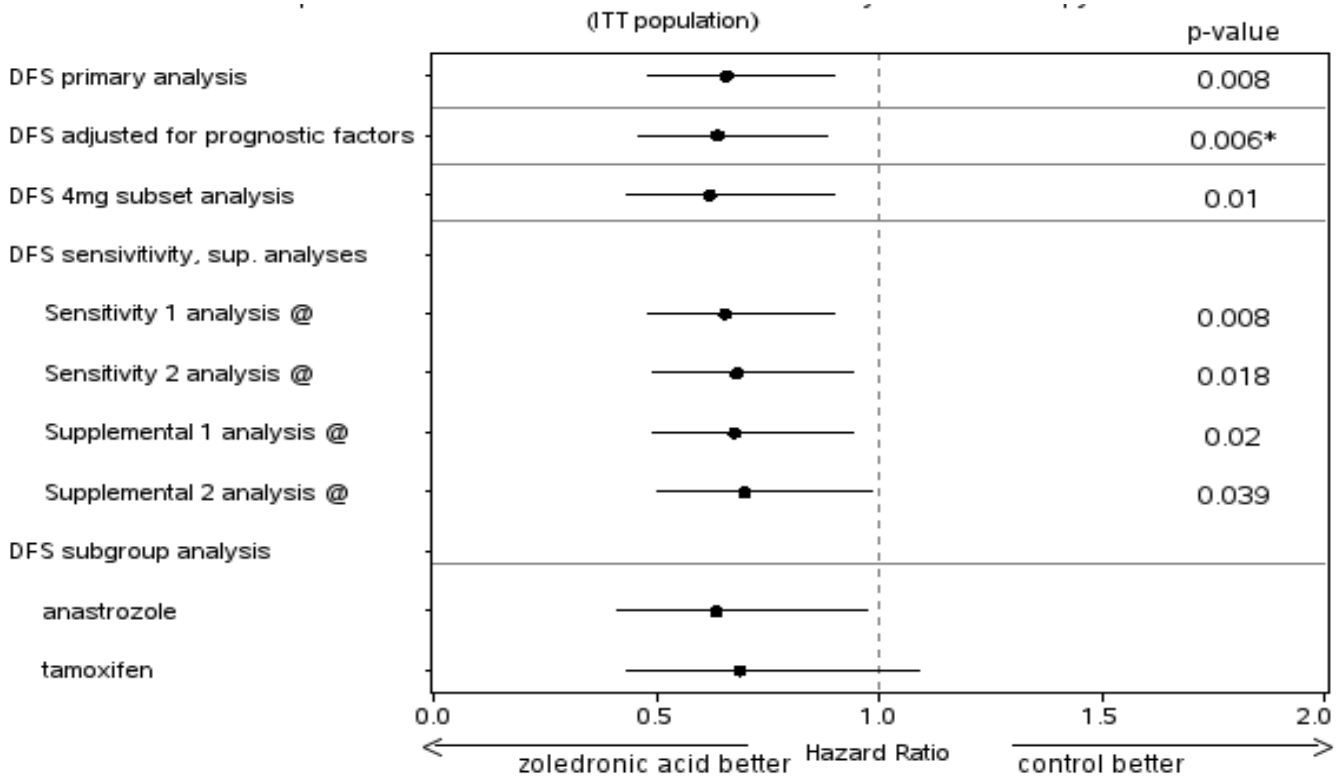


Figure 4.2 summarizes the results of the primary DFS analysis and supplemental subgroup and sensitivity analyses.

Figure 4.2: Summary of primary DFS analysis and supplementary, sensitivity and subgroup supportive analyses of DFS stratified by endocrine therapy – Study ABCSG-12 (ITT population)



Source: Post-text Tables 14.2-1.2a, 14.2-1.36, 14.2-1.2b, 14.2-1.13, 14.2-1.16, 14.2-1.8, 14.2-1.9, 14.2-1.22
* p-value based on Wald test from Cox model stratified by endocrine therapy. All other p-values based on log rank test stratified by endocrine therapy
@ Sensitivity 1- Censoring DFS events with >= 2 missed assessment visits and backdating events with 1 missed assesment visit
Sensitivity 2- Censoring DFS at the start of hormonal therapy after 3 years of study treatment in the absence of disease recurrence
Supplemental 1- Excluding second non-breast primary cancers
Supplemental 2- Excluding all second primary cancers

Source: [ABCSG-12–Figure 11-3]

Overall, consistent results have been demonstrated, also in the subset of patients treated only with zoledronic acid 4 mg i.v. q 6 months. The results of subgroup analyses should be interpreted with caution. Although not powered to primarily address this question, it is noteworthy that the DFS subgroup analysis shows that Zoledronic acid has a significant effect on DFS in the anastrozole subgroup, but not in the tamoxifen subgroup. As anastrozole is not considered the standard therapy in premenopausal early BC and furthermore is characterized by a more detrimental effect on the bone compared to tamoxifen, one may argue that the significant effect of zoledronic acid on DFS is observed in a subset treated suboptimally (anastrozole). Would zoledronic acid be beneficial in patients treated exclusively with the confirmed standard tamoxifen?

To add further support, an additional sensitivity analysis for efficacy was performed in patients who according to the 2009 St. Gallen recommendations were candidates for treatment with hormonal therapy without chemotherapy. In this sensitivity analysis, the following patients were excluded:

- Patient with **any** of these criteria: 4 or more axillary lymph nodes involved and/or tumor size > 5 cm and/or lower expression of steroid hormone receptors and/or grade 3 tumors.
- Patients with **all** of these criteria: low numbers of involved lymph nodes (one to three) and histological grade 2 and tumor size between 2 and 5 cm.

The MAH has indicated that 1303 patients of the 1803 (72%) in study ABCSG-12 could be optimally treated with endocrine therapy as per the 2009 St. Gallen consensus panel recommendations. In fact, this is expected as the St. Gallen consensus panel specifically recognized the ABCSG-12 trial as an example of a patient population that could be optimally treated with hormonal therapy alone (Goldhirsch, et al 2009).

Univariate Cox regression model and log-rank test both stratified by hormonal therapy demonstrated that in this group of patients optimally treated with hormonal therapy alone, the addition of zoledronic acid to hormonal therapy resulted in a DFS benefit, with a 38% reduction in the risk of DFS event (HR=0.623; 95% CI [0.38-1.01], log rank p-value=0.052). The results in this subgroup of patients are fully consistent with the clinical benefit observed with zoledronic acid in the ITT population (HR=0.66; 95%CI [0.48-0.90]), thus further reinforcing the overall consistency and robustness of the DFS data in study ABCSG-12. The broader 95% CI is expected considering the smaller number of patients.

Table 2-2: DFS in all patients vs. patients treated as per St. Gallen 2009 in study ABCSG-12 (ITT population)

			Cox model[1]			
		Number of events/ censored times	**Hazard ratio[2]**	**95%CI**	**p-value[3]**	**Log-rank test p-value[4]**
All patients (ITT)						
Zoledronic acid	N= 900	65/ 835	0.658	(0.48,0.90)	0.009	0.008
Control	N= 903	97/ 806				
Patients optimally treated with endocrine therapy alone as per St. Gallen 2009						
Zoledronic acid	N= 645	27/618	0.623	(0.38,1.01)	0.054	0.052
Control (No zol)	N= 658	43/ 615				

[1] Cox model is stratified by endocrine therapy and includes zoledronic acid therapy [0:control vs. 1:zoledronic acid]
[2] Hazard ratio of zoledronic acid over control
[3] based on Wald test from Cox model
[4] p-value based on stratified log rank test
Source: ABCSG-12 CSR–Table 11-8, [Table 14.2-X.6-EU]

To prove the adequacy of the 3-year combined adjuvant endocrine therapy, the Applicant highlighted the "excellent" outcomes of the control arm (no zoledronic) and, to further support this claim, made a comparison with a subsets of patients from the Oxford meta-analysis (EBCTCG 2005) who had key baseline characteristics similar to the ABCSG-12 study population, but were treated with 5 years tamoxifen. The DFS rates at 5 years were similar, between the two reports, even better in the ABCSG-12 control arm than in the EBCTCG subpopulation (89.1% vs. 84.3%). This was interpreted by the MAH as a proof of adequacy of the control arm. However, this interpretation has been rejected. The following baseline patients' characteristics were reported for both populations: menopausal status, node status and ER status. Other relevant prognostic factors like T size, grading, perivascular tumor invasion, and HER2 status were not studied. Thus, the two populations could differ on terms of several prognostic factors and consequently are not comparable.

On the basis on the aforementioned considerations, in study ABCSG-12 control treatments are not considered representative of current European standards. This represents a major deficiency of this application.

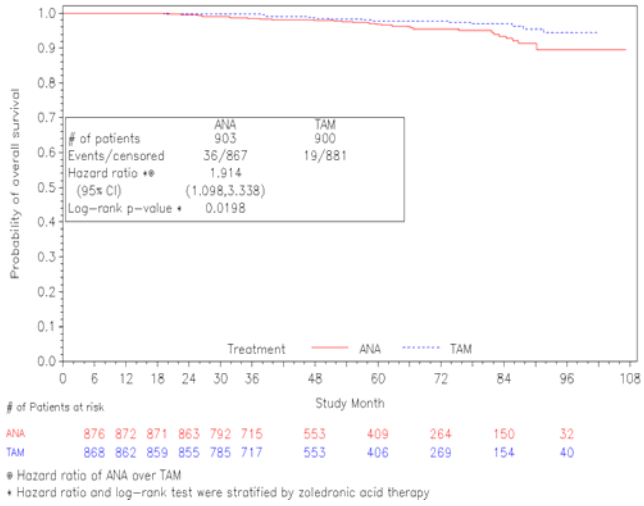
Secondary endpoints

In line with the results of the primary endpoint, DFS, no significant difference was found in the risk of RFS events between patients treated with tamoxifen and anastrozole, whereas there was a significant reduction in the risk of RFS events in the zoledronic acid arm compared with the control arm, (HR-0.66, 95% CI: (0.48, 0.91), log-rank p-value =0.010).

In general a low number of patients died during the study which is also expected in the adjuvant setting. However, OS was improved in the tamoxifen group over the anastrozole group. The total number of deaths was 55 (36 in anastrozole group and 19 in tamoxifen group).
In the adjuvant setting, it is generally difficult to demonstrate an OS benefit because most events will appear in a distant future. Although the number of deaths in this trial was numerically lower in patients treated with zoledronic acid compared to controls, the improvement was not statistically significant.

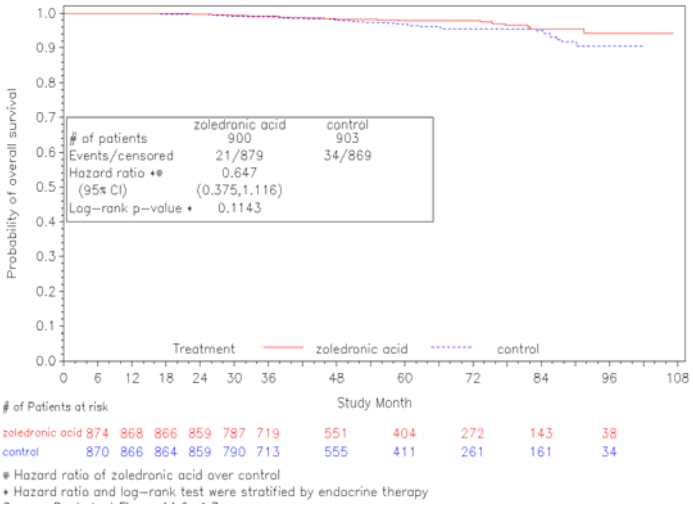
Figure 5: Kaplan-Meier plots of overall survival (OS) by treatment arm – Study ABCSG-12 (ITT population)

1. Anastrozole vs. Tamoxifen



Source: [Study ABCGS-12-Figure 11-8]

2. Zoledronic acid vs. Control (no zoledronic acid)



Source: [Study ABCSG-12 Figure 11-9]

The MAH has been asked to present possible explanations for the relatively higher number of deaths (5.3%) in the anastrozole-control arm and to provide updated OS data.

In an update with study cut-off of 1 December 2009 (+18 months of follow-up), the total number of deaths had only increased to 65 (+10 deaths). The median follow-up for OS was approximately 69 months in the zoledronic acid arm vs. 66 months in the control arm.

Table 13-1: OS analysis results reported for Core and Updated databases of study ABCSG-12

	Core DB (for submission)		Updated DB (for EMA questions)	
Data cut-off date	1-Jun-2008		1-Dec-2009	
Median follow-up time	57 months		67 months	
Zoledronic acid vs. Control	**zoledronic acid**	**control**	**zoledronic acid**	**control**
Total N (ITT)	900	903	900	903
Deaths (n)	21	34	26	39
OS analysis*	HR=0.65 (95%CI: 0.37–1.12) p=0.114		HR=0.65 (95%CI: 0.40–1.07) p=0.091	
Anastrozole vs. Tamoxifen	**Anastrozole**	**tamoxifen**	**Anastrozole**	**tamoxifen**
Total N (ITT)	903	900	903	900
Deaths (n)	36	19	41	24
OS analysis*	HR=1.91 (95%CI: 1.10–3.34) p=0.020		HR=1.69 (95%CI: 1.02–2.80) p=0.039	

* Novartis analysis results from the Core and updated DBs were based on a stratified log-rank test and a stratified Cox model including only treatment arm as covariate, both stratified by therapy. All p-values were from the log-rank test on the ITT population.

Source: ABCSG-12 CSR–Table 14.2-1.22, ABCSG-12 CSR–Table 14.2-1.23, [Table14.2-1.22-EU], [Table 14.2-1.24-EU]

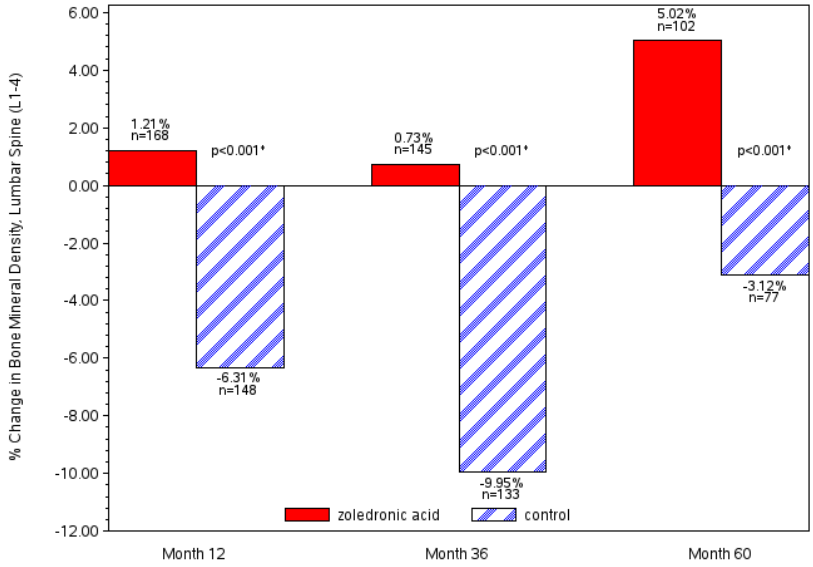
Comparing zoledronic acid with no zoledronic acid:
26 deaths were reported in the zoledronic acid arm vs. 39 in the control arm. HR=0.65 (95% CI 0.40-1.07), p=0.091

Comparing anastrozole with tamoxifen:
41 deaths were reported in the anastrozole arm vs. 24 in the tamoxifen arm. HR=1.69 (95% CI 1.02-2.80, p=0.020).

No obvious imbalances have been identified between the anastrozole group and the tamoxifen group in terms of sites of first recurrence or therapies received after disease recurrence. However, the submitted OS data are still very immature why it's premature to draw conclusions on this basis, although interesting trends are noted, particularly in the +/- zoledronic acid comparison.
The Applicant should commit to submit updated survival analyses when available.

BMD substudy
In the pivotal trial a substudy including 415 patients evaluated the change in BMD at the lumbar spine and hip trochanter over time. Patients not treated with zoledronic acid had a substantial bone loss from baseline to 36 months with a mean change in lumbar spine (L1-4) BMD of -9.95%. As expected, the BMD loss was larger in control patients treated with anastrozole compared to control patients treated with tamoxifen. In contrast, patients in the zoledronic acid arm maintained their BMD with a mean change at the lumbar spine (L1-L4) of 0.73% at 36 months. Between the end of study medication at 36 months and follow-up at 60 months there was a partial recovery in the control arm (mean change from baseline -3.12%) whereas there was a mean increase in BMD of 5.02% in patients formerly treated with zoledronic acid. In conclusion, zoledronic acid also prevents bone loss in premenopausal patients treated with adjuvant endocrine therapy.

Figure 6: Percentage change from baseline in BMD at lumbar spine (L1 to L4) over 60 months – Study ABCSG-12 (BMD substudy population)



Source: [ABCSG-12–Figure 11-10]

Zoledronic acid was shown to be effective in preventing bone loss in estrogen-deprived premenopausal patients and the results have confirmed those previously obtained in postmenopausal patients.

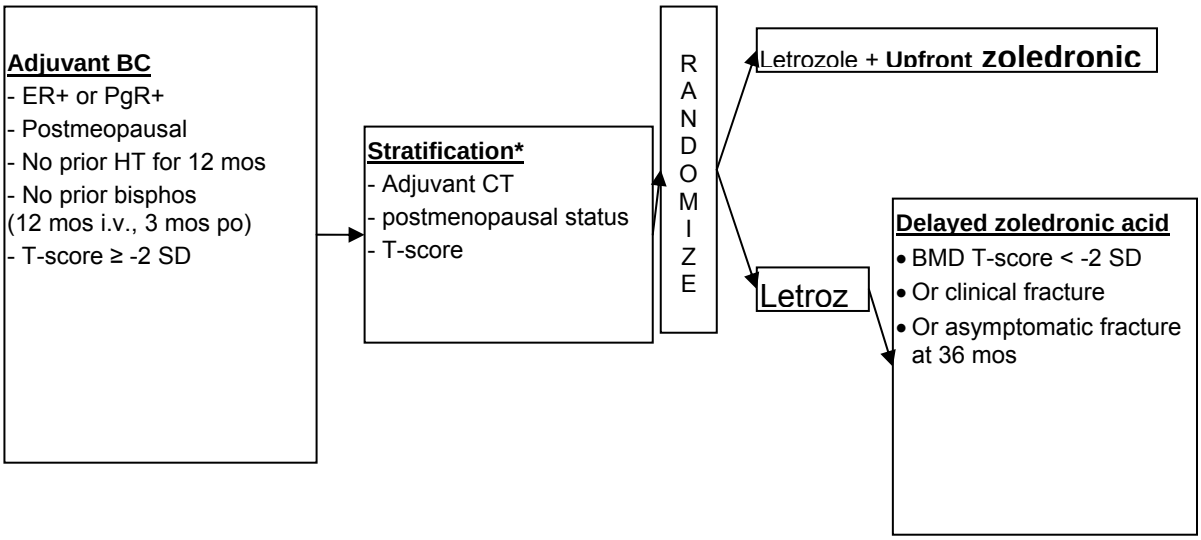
Clinical studies in special populations
N/A

Analysis performed across trials (pooled analyses AND meta-analysis)

Efficacy data from the 4 controlled trials [ABCSG-12], [FEM345D2405], [FEM345D2406], and [ZOL446EUS32] were not combined for analysis because of the difference in study populations, control groups, efficacy assessments, primary endpoints, and study conduct between ABCSG-12 and the 3 Novartis-sponsored trials.

Supportive studies
For the purpose of this application, the MAH has submitted the results of 3 Novartis sponsored supportive studies (**FEM345D2405** (N=1065), **FEM345D2406** (N= 527) and **ZOL446EUS32**) (N=602) that mainly lend support to the safety evaluation since 1) their main objective was different (to evaluate the use of zoledronic acid in the prevention of cancer treatment-related bone loss), and 2) they were performed in a different target population (*postmenopausal* women with primary HR+ BC, but possibly at a more advanced stage (stage IIIa was also included) who 3) received a different adjuvant therapy (letrozole 2.5 mg p.o. daily). The Zoledronic acid dose regimen was identical to the one used in the pivotal study (4 mg q 6 months). Patients were randomized to upfront or delayed zoledronic acid treatment until occurrence of one of the following post-baseline events: T-score < -2.0 SD at either the lumbar spine or total hip, any clinical fracture unrelated to trauma, or an asymptomatic fracture discovered at the Month 36 scheduled visit. Osteopenic patients were excluded from the study. The primary endpoint in all 3 studies was the percent change in lumbar spine bone mineral density (BMD). The secondary endpoints were DFS and OS in Study FEM345D2405 and Study FEM345D2406, whereas only DFS was defined as secondary endpoint in Study ZOL446EUS32.

Figure 7 Schematic of study design of AIBL trials



AIBL trials include protocol ZOL446EUS32, FEM345D2405 and FEM345D2406.

Abbreviations: BC, breast cancer; HT, hormonal therapy; bisphos, bisphosphonates; CT, chemotherapy; induced postmenopause, recently post-menopausal vs. postmenopausal.

Study Treatment: Letrozole 2.5 mg p.o. daily; zoledronic acid 4 mg i.v. q 6 months (upfront or delayed start).

Primary Endpoint: Percent change from baseline in lumbar spine BMD, as measured by dual energy x-ray absorptiometry (DEXA), at 12 months.

*** Stratification:** In Study ZOL446EUS32, recently postmenopausal vs. postmenopausal was not a stratification factor.

Results: Primary endpoint (BMD): Upfront treatment with zoledronic acid 4 mg i.v. q 6 months significantly increased BMD in lumbar spine from baseline to month 36 after which it overall remained stable. In contrast, patients receiving delayed zoledronic acid experienced a progressive decrease in BMD in lumbar spine which only partially returned towards baseline in the last part of the study, presumably in relation to the delayed initiation of zoledronic acid. Secondary endpoint (DFS): The results regarding DFS are not consistent but they suggest that patients treated upfront with zoledronic acid had a lower risk of DFS events than patients in the delayed arm. In the largest of the trials (FEM345D2405) the HR for DFS was 0.591 (95% CI: 0.381, 0.917). In the other studies a numerical trend favored the upfront treatment with zoledronic acid, but the results did not reach statistical significance. In two studies the numbers of local and distant metastases were numerically lower in the upfront arm compared to the delayed arm, whereas the last study showed the opposite trend. Unfortunately, the interpretation of the DFS results is hampered by several methodological differences: Both the study populations as well as the adjuvant treatments were different but these are minor concerns. Most importantly, the AIBL studies were neither designed, nor powered to show a difference in terms of DFS between patients receiving early versus delayed zoledronic acid. Therefore, stratification factors related to risk for recurrence were not balanced between treatment arms at the time of randomization and patients were not systematically screened for disease recurrence. In conclusion, these studies mainly support the relatively safe use of zoledronic acid in this adjuvant setting.

Discussion on clinical efficacy

In the pivotal study **ABCSG-12** 900 patients were enrolled in the + zoledronic acid treatment arms and 903 patients in the control arms. The median duration of follow-up for DFS was 53 months. 162 patients developed DFS events that were all validated by an objective method (most frequently histology followed by CT and bone scan). Numerically, there were fewer patients with distant and locoregional recurrences, particularly in the breast, axilla, bone and lung, in patients treated with zoledronic acid. These data are in support of an anti-tumor activity of zoledronic acid outside bone, but they should be interpreted with caution because all sites of recurrence were not systematically recorded by investigators in patients with simultaneous multiple sites of recurrence.

No difference in DFS was observed between patients treated with anastrozole and tamoxifen (by Cox regression analysis and log rank test). In contrast, endocrine therapy + zoledronic acid significantly reduced the risk for DFS events by 34% compared to endocrine therapy alone both in a univariate Cox regression model and a log-rank test stratified by endocrine therapy: HR=0.66; 95% CI: (0.48, 0.90); log-rank p-value=0.008. The 5-year estimated Kaplan-Meier rates for DFS were 92.9% in the zoledronic acid arm and 89.1% in the control arm, resulting in an absolute improvement of 3.8% for DFS which corresponds to a NNT of 26. Similar results were obtained in supportive Kaplan-Meier estimates of DFS rates and unstratified log-rank tests. No significant interaction has been demonstrated between zoledronic acid and endocrine therapy which was a prerequisite for the use of the 2x2 factorial design. Various sensitivity analyses have been performed in order to investigate the robustness of the data: Even when censoring DFS at the start of non-study medications or at the time of missed visits, consistent results (HRs) can be demonstrated. No systematic biases have been identified. In an exploratory subgroup analysis of DFS by risk factors, consistent HRs were also obtained across all subgroups analyzed. Finally, to add further support, an additional sensitivity analysis for efficacy was performed in patients who according to the 2009 St. Gallen recommendations were candidates for treatment with hormonal therapy without chemotherapy. The MAH has indicated that 1303 patients of the 1803 (72%) in study ABCSG-12 could be optimally treated with endocrine therapy as per the 2009 St. Gallen consensus panel recommendations. In fact, this is expected as the St. Gallen consensus panel specifically recognized the ABCSG-12 trial as an example of a patient population that could be optimally treated with hormonal therapy alone (Goldhirsch, et al 2009). Univariate Cox regression model and log-rank test both stratified by hormonal therapy demonstrated that in this group of patients optimally treated with hormonal therapy alone, the addition of zoledronic acid to hormonal therapy resulted in a DFS benefit, with a 38% reduction in the risk of DFS event (HR=0.623; 95% CI [0.38-1.01], log rank p-value=0.052). The results in this subgroup of patients are fully consistent with the clinical benefit observed with zoledronic acid in the ITT population (HR=0.66; 95%CI [0.48-0.90]), thus further reinforcing the overall consistency and robustness of the DFS data in study ABCSG-12.

In line with the results of the primary endpoint, DFS, no significant difference was found in the risk of RFS events between patients treated with tamoxifen and anastrozole, whereas there was a significant reduction in the risk of RFS events in the zoledronic acid arm compared with the control arm, (HR-0.66, 95% CI: (0.48, 0.91), log-rank p-value =0.010).

In general a low number of patients died during the study which is also expected in the adjuvant setting. However, OS tended to improve in the tamoxifen group over the anastrozole group at the time of the primary analysis. The total number of deaths was 55 (36 in anastrozole group and 19 in tamoxifen group). Although the number of deaths in this trial was numerically lower in patients treated with zoledronic acid compared to controls, the improvement was not statistically significant.
In an update with study cut-off of 1 December 2009 (+18 months of follow-up), the total number of deaths had only increased to 65 (+10 deaths). The median follow-up for OS was approximately 69 months in the zoledronic acid arm vs. 66 months in the control arm. No obvious imbalances have been identified between the anastrozole group and the tamoxifen group in terms of sites of first recurrence or therapies received after disease recurrence. However, the submitted OS data are still very immature why it's premature to draw conclusions on this basis, although interesting trends are noted, particularly in the +/- zoledronic acid comparison. The Applicant should commit to submit updated survival analyses when available.

A substudy including 415 patients evaluated the change in BMD at the lumbar spine and hip trochanter over time. Patients not treated with zoledronic acid had a substantial bone loss from baseline to 36 months with a mean change in lumbar spine (L1-4) BMD of -9.95%. In contrast, patients in the zoledronic acid arm maintained their BMD with a mean change at the lumbar spine (L1-L4) of 0.73% at 36 months.

The MAH has submitted the results of 3 Novartis sponsored supportive studies (**FEM345D2405** (N=1065), **FEM345D2406** (N= 527) and **ZOL446EUS32**) (N=602) that mainly lend support to the safety evaluation since 1) their main objective was different (to evaluate the use of zoledronic acid in the prevention of cancer treatment-related bone loss), and 2) they were performed in a different target population (*postmenopausal* women with primary HR+ BC, but possibly at a more advanced stage (stage IIIa was also included) who 3) received a different adjuvant therapy (letrozole 2.5 mg p.o.daily). The Zoledronic acid dose regimen was identical to the one used in the pivotal study. Upfront treatment with zoledronic acid 4 mg i.v. q 6 months significantly increased BMD in lumbar spine from baseline to month 36 after which it overall remained stable. In contrast, patients receiving delayed zoledronic acid experienced a progressive decrease in BMD in lumbar spine which only partially

returned towards baseline in the last part of the study, presumably in relation to the delayed initiation of zoledronic acid. The results regarding DFS are not consistent but they suggest that patients treated upfront with zoledronic acid had a lower risk of DFS events than patients in the delayed arm. In the largest of the trials (FEM345D2405) the HR for DFS was 0.591 (95% CI: 0.381, 0.917). In the other studies a numerical trend favoured the upfront treatment with zoledronic acid, but the results did not reach statistical significance. In two studies the numbers of local and distant metastases were numerically lower in the upfront arm compared to the delayed arm, whereas the last study showed the opposite trend. Unfortunately, the interpretation of the DFS results is hampered by several methodological differences.

Conclusions on clinical efficacy

A reduction by 34% in the risk of DFS events was observed when zoledronic acid was added to endocrine therapy compared to endocrine therapy alone (HR=0.66; 95% CI: (0.48, 0.90); log-rank p-value=0.008) in premenopausal women with hormone-receptor positive EBC. The 5-year estimated Kaplan-Meier rates for DFS were 92.9% in the zoledronic acid arm and 89.1% in the control arm, resulting in an absolute improvement of 3.8% for DFS which corresponds to a NNT of 26. This result is considered of clinical relevance and in line with the results obtained with other adjuvant therapies in EBC. In addition, a prophylactic effect of zoledronic acid against treatment-related bone loss has also been demonstrated in this adjuvant setting. However, uncertainties remain regarding the demonstrated anti-tumor activity of zoledronic acid. Confirmation of the results is needed in a well-defined EBC population that has been treated with standard adjuvant regimens.

Clinical safety

Safety data are from: 1) the pivotal study ABCSG-12, 2) three supportive studies with data cut-off 30-june-2008 (the AIBL-studies), 3) the PSUR 11 (data cut-off 31-aug-2009). Finally, there was a blinded review of only the SAEs and deaths from 4 ongoing clinical trials (AZURE, SWOG307, NATAN, SUCCESS with data cut-off 02-oct-2009)

The data submitted by the MAH is sufficient to make judgements on safety. Although there are some problems such as missing information on concomitant medication, reporting of prematurely discontinuation, the ad-hoc conversion of toxicity grading from the ABCSG-12 study to the CTCAE reporting system, the overall impression is that the data from these studies do not signal any significantly increased frequency or severity of adverse effects from zoledronic acid compared to what is already known.

The suggested use of zoledronic acid as part of adjuvant therapy in premenopausal women with early breast cancer is evaluated separately as clinical efficacy. However, the use of any drug for any indication is a balance between efficacy (in this case DFS and OS) on one hand and the adverse effects from the drug on the other hand. In the case of this application, the assessment of the adverse effects from zoledronic acid is complicated by the fact that it has been given in combination with various other drugs, such as goserelin, tamoxifen, anastrozole, letrozole. In the AIBL studies the patients were also allowed to receive adjuvant chemotherapy. This makes good sense in terms of the proposed use of the drug, but it makes the assessment of which side-effects to blame on zoledronic acid and which side-effects to blame on the other drugs difficult.

The safety data from the **ABCSG-12** study **(n=1741)**, and the 3 AIBL-studies **[ZOL446EUS32] (n=600)**, **[FEM345D2406] (n=523)**, and **[FEM345D2405] (n=1060)** were pooled for safety analysis: Collectively, these 4 trials provide safety data from a **total of 3925 safety patients** of whom **2213 were treated with zoledronic acid**.

The numbers of patients in the safety analysis is sufficient to provide estimates of frequencies of most expected side-effects, and to provide signals of unexpected toxicities from its proposed new indication. In addition, deaths data from 4 large ongoing clinical trials have been provided to further clarify the risk-benefit of zoledronic acid.

In the ABCSG-12 study the initial dose of zoledronic acid was 8 mg per month and this was later changed to 4 mg q 6 months. However, the durations of exposure to both doses/schedules were similar and most patients received treatment for 30 months or more.

Table 7: (MAH Table 1.7):

Table 1-7 Duration of exposure to zoledronic acid - Study ABCSG-12 (Safety population)

	Zoledronic acid		
	4 mg patients [1] N=780	8 mg patients [2] N=95	Total N=875
Duration of exposure to zoledronic acid therapy (months) [3]			
N	778	94	872
Mean (SD)	31.34 (7.976)	32.24 (8.120)	31.44 (7.991)
Median	35.52	35.37	35.52
Range	1.4 – 39.2	3.2 – 37.7	1.4 – 39.2
Categorical duration of exposure- n (%)			
0 - < 6 months	14 (1.8)	2 (2.1)	16 (1.8)
≥ 6 - 12 months	30 (3.9)	5 (5.3)	35 (4.0)
≥ 12 - 18 months	20 (2.6)	3 (3.2)	23 (2.6)
≥ 18 - 24 months	50 (6.4)	1 (1.1)	51 (5.8)
≥ 24 - 30 months	95 (12.2)	3 (3.2)	98 (11.2)
≥ 30 - 36 months	288 (37.0)	44 (46.8)	332 (38.1)
≥ 36 - 39 months	280 (36.0)	36 (38.3)	316 (36.2)
≥ 39 months	1 (0.1)	0	1 (0.1)
Total patient years [4]	2032	253	2284
Number of infusions [5]			
Mean (SD)	5.16 (1.323)	4.24 (1.614)	5.07 (1.383)
Median	6.00	5.00	6.00
Range	1.0 – 7.0	1.0 – 8.0	1.0 – 8.0

Concomitant medications were not recorded in the phase III pivotal controlled trial ABCSG-12 which was unfortunate since the evaluation of possible interactions may have been relevant in terms of toxicity.

In the ABCSG-12 study as well as the 3 AIBL-studies a significant fraction of patients discontinued therapy prematurely, for a variety of reasons; thus, in the ABCSG-12 study, a higher fraction of premature discontinuation was observed in the anastrozole arm (22%) compared to the anastrozole plus zoledronic acid arm of the study (11%). The large fraction of patients that discontinued prematurely is somewhat surprising, considering that the patients received standard adjuvant therapy according to the MAH and investigators. Furthermore, in the ABCSG-12 study, the prematurely discontinuation due to AE was not registered systematically in the CRF which was unfortunate.

In the ABCSG-12 study, the CTCAE criteria were not used which is unfortunate. Instead, an ad-hoc algorithm was used to convert data to the CTCAE grading system. The conversion of grading of adverse effects from mild, moderate and severe into the CTCAE grading system I-IV (-V) seems convenient; however, it is impossible to determine how many of the grade III/IV CTCAE side-effects were in fact grade III and how many were grade IV. This could potentially have important clinical implications.

The AE incidence rates in both the ABCSG-12 study and in the AIBL-studies were calculated by dividing the number of patients with an event by the sum of patient-year exposure of all patients in each treatment arm. For any particular AE, the patient-year for patients who had such AE was censored at the AE onset date of the first occurrence of such event. This makes it difficult to estimate the "total-burden" of a particular side-effect, because it makes a difference clinically whether an AE is observed only once or for example after each single administration of zoledronic acid. This may be important considering the various concomitant medications that were used in these studies.

Overall, the types and frequencies of AEs are clearly described, and besides AEs known prior to this study to be related to zoledronic acid, no new safety signals were identified: Thus, previously known AEs from zoledronic acid were evidently reported from both the pivotal study ABCSG-12 and the AIBL-studies: **In the ABCSG-12 study**, the most frequently reported AEs in patients treated with zoledronic acid were:

1) Bone pain from 33.6% to 46.1% (in SPC only common), 2) Fatigue from 20.5 to 23.4% (in SPC only common), 3) Headache from 13.6% to 20.2% (in SPC only common), 4) Arthralgia from 9.7% to 23.9% (in SPC only common), 5) Sleep disorder from 11.3 to 12.5% (in SPC only common), 6) Pyrexia from 8.7% to 11.6% (only slightly more common than in SPC), 7) Nausea from 6% to 12% (only slightly more common than in SPC).

It should be noted that in the ABCSG-12 study, the supposed hormone-related side effects were not recorded. These side-effects may or may not have been exacerbated by the use of zoledronic acid. The MAH rightly states that this might have resulted in a risk of under- and over-reporting of some side-effects.

In the AIBL-studies, the frequencies of adverse effects were higher, because all types of adverse events were registered, including those thought to be due to the antihormonal therapy. This contrasts with the ABCSG-12 study where these side effects were not registered. The frequencies of side effects (shown in percent for the most frequent) are shown for patients treated with zoledronic acid upfront first followed by the frequency in the group of patients in the delayed group that never received zoledronic acid:
1) Arthralgia 45.2% vs. 45.6%, 2) Hot flush 29.3% vs. 33.0%, 3) Bone pain 14.6 vs. 8.0%, 4) Myalgia 14.1% vs. 12.1%, 5) Back pain 12.1% vs. 13.8%, 6) Pyrexia 11.9% vs. 1.8%, 7) Headache 11.6% vs. 10.4% 8) Pain in extremity 11.2% vs. 13.7%, 9) Nausea 10.2% vs. 9.1%, 10) Musculoskeletal pain 10.0% vs. 8.4%.
The frequency of any particular side effect is clearly dependent on any co-administered medication; in this case it depends on the side effects from the anti-hormonal therapy.

Severe AEs in the ABCSG-12 study:
The frequencies of severe AEs were low in general; the most frequently reported severe AEs in both groups were 1) bone pain (5.4% in the zoledronic acid group and 3.7% in the control group), 2) endometrial hyperplasia (4.1% in the zoledronic acid group and 3.8% in the control group) and 3) uterine polyp (4.1% in the zoledronic acid group and 3.2% in the control group). The majority of SAEs were reported with a relatively similar frequency in both groups.
SAEs that occurred with a **higher frequency in the zoledronic acid group** than in the control group were 1) **back pain** (0.7% vs. 0.2%), 2) **musculoskeletal pain** (0.6% vs. 0.1%), 3) **pain in extremity** (0.5% vs. 0.1%), 4) **arthropathy** (0.3% vs. 0.1%), and 5) **breast pain** (0.3% vs. 0.1%).

Severe adverse events in the AIBL-studies:
Grade 3/4 AEs occurred in comparable rates between the ZOL 4 mg upfront (n=312, 28.9%) and ZOL 4 mg delayed groups (n=313, 28.4%).

Grade 3/4 AEs with an incidence ≥ 1.0% in either treatment group are arthralgia (3.6% upfront vs. 3.2% delayed), osteoarthritis (1.4% upfront vs. 1.2% delayed), bone pain (1.1% upfront vs. 0.6% delayed), myalgia (1.1% upfront vs. 0.8% delayed), hypertension (1.0% upfront vs. 0.5% delayed start), and depression (0.5% upfront vs. 1.0% delayed).
CTC grade 3/4 arthralgia, myalgia, and depression were frequently reported prior to the initiation of zoledronic acid treatment in the ZOL 4 mg delayed group. In contrast, the CTC grade 3/4 AEs occurred more frequently after the initiation of zoledronic acid treatment in the ZOL 4 mg delayed group in the following AEs: osteoarthritis, bone pain, and urinary tract infection.

Adverse effects of special interest:
ONJ:
There are no cases of confirmed ONJ in the ABCSG-12 population over the 3-year treatment period.
In the AIBL-studies, the ZOL 4 mg upfront group incidence rates of confirmed ONJ and confirmed plus possible ONJ in the 3 AIBL studies were 0.3% and 0.5%, respectively. The ONJ incidence rate in the ZOL 4 mg delayed group was zero.

Renal toxicity:
ABCSG-12 study:
The incidence of **renal function deterioration was 1.1% (10/870) and 0.8% (7/858) for the zoledronic acid and control (no zoledronic acid) groups, respectively**

AIBL-studies:
Renal function deterioration was reported for 25 patients (2.5%) in the ZOL 4 mg upfront group and 16 patients (1.6%) in the ZOL 4 mg delayed group. Among the 16 patients in the ZOL 4 mg delayed group whose renal function deteriorated only one patient received zoledronic acid infusion: Thus, 15 of these 16 patients may be thought of essentially as untreated controls.

Atrial fibrillation,
In ABCSG-12, there was one reported SAE of atrial fibrillation in the anastrozole (control) Arm.
In the AIBL studies, the incidence of AEs related to atrial fibrillation was 0.9% in the ZOL 4 mg upfront group and 1.0% in the ZOL 4 mg delayed group.

Hypocalcaemia events were infrequent and mostly mild.

The frequency and severity of **APR and ocular adverse effects** do not signal any new risks compared to the SPC.

In general, the laboratory findings (**haematological and biochemistry adverse effects**) were mild, with no important increased risk of laboratory abnormalities in patients treated with zoledronic acid compared to controls.

Pharmacovigilance system

As agreed with the EMA no detailed description of the pharmacovigilance system has been provided with this application, as this is out of the scope of the current variation.

Risk Management plan

An updated RMP (v.3) has been submitted. No new safety concerns have been found so no major changes in the RMP have been proposed.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects
In the pivotal study **ABCSG-12** 900 patients were enrolled in the + zoledronic acid treatment arms and 903 patients in the control arms. The median duration of follow-up for DFS was 53 months. 162 patients developed DFS events that were all validated by an objective method (most frequently histology followed by CT and bone scan). Numerically, there were fewer patients with distant and locoregional recurrences, particularly in the breast, axilla, bone and lung, in patients treated with zoledronic acid. These data are in support of an anti-tumor activity of zoledronic acid outside bone, but they should be interpreted with caution because all sites of recurrence were not systematically recorded by investigators in patients with simultaneous multiple sites of recurrence.

Specifically, no difference in DFS was observed between patients treated with anastrozole and tamoxifen (by Cox regression analysis and log rank test. In contrast, endocrine therapy + zoledronic acid significantly reduced the risk for DFS events by 34% compared to endocrine therapy alone both in a univariate Cox regression model and a log-rank test stratified by endocrine therapy: HR=0.66; 95% CI: (0.48, 0.90); log-rank p-value=0.008. The 5-year estimated Kaplan-Meier rates for DFS were 92.9% in the zoledronic acid arm and 89.1% in the control arm, resulting in an absolute improvement of 3.8% for DFS which corresponds to a NNT of 26. Similar results were obtained in supportive Kaplan-Meier estimates of DFS rates and unstratified log-rank tests. No significant interaction has been demonstrated between zoledronic acid and endocrine therapy which was a prerequisite for the use of the 2x2 factorial design. Various sensitivity analyses have been performed in order to investigate the robustness of the data: Even when censoring DFS at the start of non-study medications or at the time of missed visits, consistent results (HRs) can be demonstrated. No systematic biases have been identified. In an exploratory subgroup analysis of DFS by risk factors, consistent HRs were also obtained across all subgroups analyzed.

To add further support, an additional sensitivity analysis for efficacy was performed in the 1303 patients (72%) who according to the 2009 St. Gallen recommendations were candidates for treatment with hormonal therapy without chemotherapy. Univariate Cox regression model and log-rank test both stratified by hormonal therapy demonstrated that in this group of patients optimally treated with hormonal therapy alone, the addition of zoledronic acid to hormonal therapy resulted in a DFS benefit, with a 38% reduction in the risk of DFS event (HR=0.623; 95% CI [0.38-1.01], log rank p-value=0.052). The results in this subgroup of patients are fully consistent with the clinical benefit observed with zoledronic acid in the ITT population (HR=0.66; 95%CI [0.48-0.90]), thus further reinforcing the overall consistency and robustness of the DFS data in study ABCSG-12.

In line with the results of the primary endpoint, DFS, no significant difference was found in the risk of RFS events between patients treated with tamoxifen and anastrozole, whereas there was a significant reduction in the risk of RFS events in the zoledronic acid arm compared with the control arm, (HR-0.66, 95% CI: (0.48, 0.91), log-rank p-value =0.010).

In general, a low number of patients died during the study which is also expected in the adjuvant setting. However, OS tended to improve in the tamoxifen group over the anastrozole group. The total number of deaths was 55 (36 in anastrozole group and 19 in tamoxifen group) at the time of the primary analysis. Although the number of deaths in this trial was numerically lower in patients treated with zoledronic acid compared to controls, the improvement was not statistically significant.

In an update with study cut-off of 1 December 2009 (+18 months of follow-up), the total number of deaths had only increased to 65 (+10 deaths). The median follow-up for OS was approximately 69 months in the zoledronic acid arm vs. 66 months in the control arm. No obvious imbalances have been identified between the anastrozole group and the tamoxifen group in terms of sites of first recurrence or therapies received after disease recurrence. However, the submitted OS data are still very immature why it's premature to draw conclusions on this basis, although interesting trends are noted, particularly in the +/- zoledronic acid comparison.

A substudy including 415 patients evaluated the change in BMD at the lumbar spine and hip trochanter over time. Patients not treated with zoledronic acid had a substantial bone loss from baseline to 36 months with a mean change in lumbar spine (L1-4) BMD of -9.95%. In contrast, patients in the zoledronic acid arm maintained their BMD with a mean change at the lumbar spine (L1-L4) of 0.73% at 36 months.

Uncertainty in the knowledge about the beneficial effects
Adjuvant endocrine therapy is recommended for the majority of pre-menopausal patients with early stage HR+ BC. The CHMP acknowledges that a lively debate is ongoing within oncology societies as to whether subgroups of pre-menopausal women with HR+ EBC should be offered adjuvant endocrine therapy only as their tumors are less responsive to chemotherapy and their risk of recurrence modest. This subset of patients clearly needs to be further characterized. Currently, it is difficult to draw the line.
Meanwhile, the optimal endocrine regimen also needs to be defined. The purpose of the endocrine therapy is to prevent BC cells from receiving growth stimulation from endogenous estrogen. In pre-menopausal women, this is at present achieved via 5 years treatment with tamoxifen, with ovarian suppression with a LHHRH agonist (or ovarian ablation) or alternatively with a combination of tamoxifen and ovarian suppression. Currently, the optimal duration of ovarian suppression is unknown. It is also unclear which patients will benefit from the combination of ovarian suppression and tamoxifen. Finally, the role for aromatase inhibitors (AIs) in pre-menopausal women has not been determined. Therefore, at lot of unknown variables remain and the results of ongoing trials are awaited before the present "standards" may be changed. The challenge will be to integrate clinical, pathological as well as molecular prognostic and predictive factors.

The CHMP agrees that the current recommendations regarding the need for adjuvant chemotherapy are likely to change over time with the appearance of new tools (e.g. genetic profiling) that will enable us to select the optimal treatment for patients on an individual basis. However, it is considered premature to deviate from current standard recommendations from a regulatory point of view. So far the magnitude of the adjuvant benefit of zoledronic acid has not been determined as add-on to regimens of current standards which is a clear disadvantage. Zoledronic acid may very well possess an inherent anti-tumor effect that should be added to the adjuvant effect provided by the endocrine therapy, but how large is this added benefit actually in a standard setting? This important information is missing.

The 3 supportive studies were mainly submitted in support of the safety analysis. They were performed in *post-menopausal* patients who received letrozole as adjuvant endocrine therapy and zoledronic acid as initial or delayed add-on therapy. Their major objective was to investigate the effect of zoledronic acid on BMD and the interpretability of the effects on DFS was hampered by important methodological differences.

The direct anti-tumor activity of zoledronic acid appears very promising, but it also represents, at least conceptually, a new property of this potent bisphophonate. Although a single pivotal trial would in principle be considered acceptable, it is in this situation considered essential to get supportive confirmation of the observed anti-tumor activity of zoledronic acid outside bone in a well-defined pre-menopausal EBC patient population that has been adequately treated with adjuvant regimens in compliance with modern European recommendations.

The Applicant should commit to submit updated survival analyses when available.

Risks

Unfavourable effects and uncertainty in the knowledge about the unfavourable effects
Although there are some problems such as missing information on concomitant medication, reporting of premature discontinuation, the ad-hoc conversion of toxicity grading from the ABCSG-12 study to the CTCAE reporting system, the overall impression is that the data from these studies do not signal any significantly increased frequency or severity of adverse effects from zoledronic acid compared to what is already known.

Benefit-risk balance
In premenopausal women with hormone-receptor positive EBC, a reduction by 34% in the risk DFS events was observed when zoledronic acid was added to endocrine therapy compared to endocrine therapy alone (HR=0.66; 95% CI: (0.48, 0.90); log-rank p-value=0.008. The 5-year estimated

Kaplan-Meier rates for DFS were 92.9% in the zoledronic acid arm and 89.1% in the control arm, resulting in an absolute improvement of 3.8% for DFS which corresponds to a NNT of 26. This result is considered of clinical relevance and in line with the results obtained with other adjuvant therapies in EBC. In addition, a prophylactic effect of zoledronic acid against treatment-related bone loss has also been demonstrated. Furthermore, the safety profile of zoledronic acid is well-known and acceptable in this adjuvant setting. However, uncertainties remain about the reproducibility of the results when zoledronic acid is used as add-on to standard adjuvant regimens.

Conclusions
The CHMP is of the opinion that the presented results of zoledronic acid as adjuvant therapy in EBC in premenopausal women do deserve attention as the result could be of clinical relevance. In addition, there are preclinical data offering a mechanistic explanation for the observed anti-tumor activity. However, as it has been stated previously the single pivotal ABCSG-12 study does not support convincingly and adequately the new indication for Zometa. 3 important questions remain to be answered before the R/B assessment can be completed:

1) The Applicant advocates for an extrapolation of the results to regimens of European standard, but this approach seems premature as long as these different adjuvant regimens have not proven to be equivalent. Therefore, the proposed broad indication of zoledronic acid as *adjuvant treatment of HR+ EBC in pre-menopausal women for whom hormonal therapy is recommended"* is presently not acceptable. Further data from properly designed clinical trials including as control arm the standard European treatment for the sought indication are needed in order to determine the potential benefit of zoledronic acid as add-on to standard endocrine therapy and to clearly identify the target population.

2) Are the results reproducible? So far, the adjuvant benefit of zoledronic acid has only been demonstrated in one, single trial which remains one of the major concerns. The CHMP considers it essential to obtain pre-licensing confirmation of the observed adjuvant anti-tumor activity outside bone in a different EBC trial, preferentially with DFS as primary endpoint.

3) Are the quality of the source data and the overall integrity of the results of the single pivotal trial ABCSG-12 reliable? This study was investigator initiated. The primary objective of the trial seems to have been modified by the investigators in collaboration with the MAH in close connection to the efficacy analyses conducted as of March 31, 2008. Despite the open-label aspect of the trial, this does not necessarily invalidate the results of the study as long as the final changes of the SAP were introduced before the data analysis. However, further clarifications are needed by the MAH. In addition, a CHMP-requested GCP inspection will most probably be needed should this application be considered approvable also be recommended in order to elucidate this issue further.

In conclusion, the overall assessment of the B/R of Zometa in the indication:

Zometa is indicated as adjuvant treatment of hormone receptor positive early breast cancer in premenopausal women for whom hormonal therapy is recommended.

is still considered negative due to the lack of confirmatory evidence of an anti-tumor activity of Zometa when used as add-on to an adjuvant regimen representative of European standards.