

**Title:**

**An open, prospective, non-randomized, controlled, multicenter study to evaluate clinical outcome of Astra Tech OsseoSpeed™ Implant in women over 60 years of age with osteoporosis/osteopenia**

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**An open, prospective, non-randomized, controlled, multicenter study to evaluate clinical outcome of Astra Tech OsseoSpeed™ Implant in women over 60 years of age with osteoporosis/osteopenia**

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**Background and overall aim**

Osteoporosis is a systemic skeletal disease affecting more than 75 million people in Europe, Japan and USA [1]. It is defined as a condition of decreased bone mineral density (BMD) and changes in the microarchitecture of the bone tissue. This leads to decreased bone strength and an increased risk of fractures, primarily in the hip, spine and wrist.

The most common form of osteoporosis is called primary osteoporosis and affects mainly elderly patients. It is three times more common in women than in men and this can be explained by the lower peak bone mass in women as well as by the hormonal changes that occur at the menopause. Furthermore, women live longer than men and thus have larger reductions in bone mass. It has been estimated that 30% of all postmenopausal women have osteoporosis [2].

It is still not clear whether systemic osteoporosis also results in osteoporosis of the jaws and systemic osteoporosis was for a long time considered a contraindication for treatment with dental implants. This view has changed over the years but there are still many dentists who consider not to treat osteoporotic patients with dental implants due to fear of unsuccessful outcomes.

The overall aim of the study is to compare treatment with dental implants (the Astra Tech OsseoSpeed™ implant) in the maxilla of postmenopausal women with and without systemic osteoporosis/osteopenia.

**Study objectives**

*Primary objective*

The primary objective is to compare marginal bone level (MBL) alterations following treatment with the OsseoSpeed™ implant in the maxilla of post-menopausal women with and without systemic osteoporosis/osteopenia. Marginal bone level alterations will be evaluated by radiological assessments and MBL values at prosthetic insertion will be used as baseline.

*Secondary objectives*

The secondary objectives of the study are to evaluate (i.e. compare between the groups):

- Implant survival
- Implant stability, by using resonance frequency analysis (RFA)
- Condition of periimplant mucosa by assessment of Bleeding on Probing (BoP), Probing Pocket Depth (PPD) and Attachment Level (AL)
- Safety by recording of adverse events (AEs) and adverse device effects (ADEs)
- Patient reported outcomes by the Oral Health Impact Profile (OHIP)

*Additional objective*

The additional objective of the study is to evaluate the correlation between BMD in the skeleton (hip/spine) with BMD in the maxilla.

## Study design

This will be an open, prospective, non-randomized, controlled parallel-group multicenter study to document the outcome of treatment with the OsseoSpeed™ implant in the maxilla of postmenopausal women with systemic osteoporosis/osteopenia. Two groups will be included in the study: *Group A (osteoporosis/osteopenia)* consisting of postmenopausal women with low BMD values (T-score  $\leq -2$ ) and *Group B (control)* consisting of postmenopausal women with normal BMD values (T-score  $\geq -1$ ). Each subject will receive 2-8 splinted implants in the maxilla and two-stage surgery will be used.

A total of 104 subjects fulfilling all of the inclusion criteria and none of the exclusion criteria will be included. Fifty-two subjects will be included in group A (osteoporosis/osteopenia group) and fifty-two in group B (control). Four centers will be involved in the study, each center treating 13 osteoporotic/osteopenic subjects and 13 control subjects.

The study will be a five-year follow-up study comprising of 13 visits:

### *Visit 1 – Screening*

The screening visit will include collection of demographic data as well as clinical and radiographic assessments. Subjects fulfilling all inclusion criteria and none of the exclusion criteria after the screening visit will be scheduled for BMD measurements in the hip and the spine, using dual energy X-ray absorptiometry (DXA). Subjects fulfilling all inclusion criteria for either Group A or Group B and none of the exclusion criteria will be scheduled for Visit 2.

### *Visit 2 - Pre-surgical planning*

Subjects will undergo a dental quantitative computed tomography (CT) examination in order to determine the BMD at the planned implant sites. The treatment plan will be discussed with the subject.

### *Visit 3 – Surgery I (Implant placement)*

The surgical procedure will be performed under local anesthesia. After a crestal incision, 2-8 implants will be placed in the maxilla. Cover screws will then be inserted into the implants and the mucoperiosteal flaps sutured back for a tight seal.

### *Visit 4 - Post-operative check-up*

One week after implant placement the subjects will return for control of the implants and the healing process.

### *Visit 5 – Surgery II (Abutment placement)*

At 12 weeks after implant placement, a second surgical procedure will be performed. A small mucosal incision will be made under local anesthesia, the cover screws will be removed and healing abutments will be connected to the implants.

### *Visit 6 – Impression*

After 1 week of soft tissue healing, impressions will be taken for fabrication of the screw-retained permanent restoration(s).

### *Visit 7 – Permanent restoration (PR)*

The screw-retained permanent restoration will be delivered between 4 and 8 weeks after the impression visit.

### *Visits 8-13 – Follow-up (PR+6 to 60 months)*

The subject will return for follow-up visits at 6, 12, 24, 36, 48 and 60 months after permanent restoration.

## Rationale for study design

An open study design has been chosen primarily for ethical reasons since the subjects with osteoporosis and osteopenia will be followed-up and treated by their GP:s and therefore will be informed about their diagnosis. Furthermore, the treating dentists (the Investigators) need to be informed about the subjects' medication etc. to be able to offer proper therapy. However, the primary variable of the study, i.e. marginal bone alterations, will be assessed by blinded independent radiologists.

The reason for including both osteoporotic and osteopenic subjects in Group A is the fact that it would be difficult to find a sufficient number of subjects with osteoporosis (T-score  $\leq -2.5$ ) in need of 2-8 implants in the maxilla. By choosing a T-score  $\leq -2$  as an inclusion criterion the subjects will still have a reduced, and for the study relevant, BMD and the possibilities of recruiting the required number of subjects will be markedly increased.

A control group (Group B) was included to assure a relevant comparison of the results from Group A (osteoporosis/osteopenia) with non-osteoporotic women treated in the same way.

In order not to jeopardize the treatment results for the subjects, in case the systemic osteoporosis/osteopenia actually has an effect on the implant treatment success, a two-stage surgery protocol was chosen.

The subjects will be followed-up for 5 years after prosthetic restoration. The largest marginal bone alterations are normally seen within the first year after implant placement. By studying the subjects for more than 5 years after implant placement, long-term alterations will be revealed and the possibility to detect a difference between the groups will increase.

## Risk/benefit assessment

In this study subjects with osteoporosis will be treated with dental implants. This patient group has previously often been excluded from implant therapy but since previous studies have shown successful results in osteoporotic subjects after implant treatment [3-6] we expect good results in both study groups.

The osteoporotic/osteopenic group will presumably consist both of women with known osteoporosis and women with previously unknown osteoporosis. The osteoporotic subjects will be treated according to routine health care. This means that some of the patients may have been treated with bisphosphonates prior to implant treatment. There is recent data available, describing cases of osteonecrosis of the jaws after dental surgery in patients concomitantly treated with bisphosphonates [7]. This complication seems to be rare and there is not enough data existing to prove a causal link between the use of oral bisphosphonates and osteonecrosis of the jaws. However, we can not ignore a small but possible risk for subjects on bisphosphonates to develop osteonecrosis of the jaws. In order to minimize this risk, we have chosen not to include patients who have been taking oral bisphosphonates for 3 years or more. The subjects will also be carefully informed about the risks of osteonecrosis of the jaws before entering the study. This is in accordance with a position paper published by the American Association of Oral and Maxillofacial Surgeons [8]. In summary, we assess the risk of entering the study as low. The benefit of entering, on the other hand, would be for a patient to have an unknown osteoporosis diagnosed and treated. The risk benefit analysis therefore must be considered as favorable for entering the study.

N.B. Oral bisphosphonates is not considered a contraindication for implant treatment.

## Study population

### *Inclusion criteria*

For inclusion in the study subjects must fulfill all of the following criteria:

1. Provision of informed consent
2. Postmenopausal women aged 60 years and over
3. In need of 2-8 implants in maxilla
4. A history of edentulism in the area of implant treatment of at least 6 months.
5. A BMD value suitable either for group A **or** group B:

**Group A (Osteoporosis/osteopenia):** BMD at least 2 standard deviations below mean peak bone density of young adults for the spine and total hip (T-score $\leq$ -2SD). Absolute values (g/cm<sup>2</sup>) will be used.

**Group B (Control):** BMD not more than 1 standard deviation below mean peak bone density of young adults for the spine and total hip (T-score $\geq$ -1SD). Absolute values (g/cm<sup>2</sup>) will be used.

### *Exclusion criteria*

Any of the following is regarded as a criterion for exclusion from the study:

1. Unlikely to be able to comply with study procedures, as judged by the investigator.
2. Untreated, uncontrolled caries and/or periodontal disease
3. Known or suspected current malignancy
4. History of chemotherapy within 5 years prior to surgery
5. History of radiation in the head and neck region
6. History of other metabolic bone diseases, e.g. Paget's disease, hyperparathyroidism, fibrous dysplasia or osteomalacia
7. A medical history that makes implant insertion unfavorable
8. Need for systemic corticosteroids
9. Previous or current use of intravenous bisphosphonates (esp. zoledronic acid)
10. Use of oral bisphosphonates for  $\geq$  3 years
11. History of bone grafting and/or sinus lift in the planned implant area
12. Current need for bone grafting and/or sinus lift in the planned implant area
13. Present alcohol and/or drug abuse
14. Involvement in the planning and conduct of the study (applies to both Astra Tech AB staff or staff at the study site)
15. Previous enrolment in the present study.
16. Participation in a clinical study during the last 6 months.

## Study products

The OsseoSpeed™ implant is a screw-shaped and self-tapping implant with diameters of 3.5S, 4.0S, 4.5, 5.0 and 5.0S mm. Implants are available in lengths of 8, 9, 11, 13, 15, 17 and 19 mm. MicroThreads™ characterize the coronal aspect of the OsseoSpeed™ implant.

The OsseoSpeed™ surface is developed by a TiO<sub>2</sub>-blasting procedure creating a rough surface, which is then modified through a cleaning process in diluted hydrofluoric acid.

## Statistical methods

The primary objective is to test the hypothesis that the alteration in MBL from prosthetic restoration to the 5-year follow-up visit is equal (i.e. a two-sided hypothesis) in patients in group A and in group B. The hypothesis will be tested by means of the Wilcoxon rank sum test. A p-value less than 5% at the 5-year follow-up visit will be considered statistically significant. In addition, the time to certain degrees of alterations will be estimated by means of Kaplan-Meier plots and the hypothesis that the time is equal in group A and B will be tested by means of the log-rank test.

The secondary objectives are to test:

- The hypothesis that the survival rate is equal among implants on patients in group A and B by means of the Fisher's exact test (i.e. implant level). Furthermore, the time to implant loss will be estimated by means of Kaplan-Meier plots and the hypothesis that the time is equal in group A and B will be tested by means of the log-rank test.
- The hypothesis that the proportion of survived implants is equal in patients in group A and B by means of the Wilcoxon rank sum test (i.e. patient level).
- The hypothesis that the condition of peri-implant mucosa is equal in patients in group A and B by means of the Wilcoxon rank sum test.

The evaluation of the correlation between skeletal and maxillary BMD will be estimated by means of the Spearman's rank correlation coefficient on patient level.

All safety variables will be summarized by means of descriptive statistics. No hypotheses will be tested.

The hypothesis that the OHIP is equal in patients in group A and B will be tested by means of the Wilcoxon rank sum test

All hypotheses will be tested at all visits. P-values will be calculated but not called statistically significant except for the primary objective at the final visit.

## Study timetable

Estimated date of first subject enrolled: November 2007  
 Estimated date of last subject completed: October 2016

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