# Osteobone Bone Defect Repair Material

# Summary Report of Clinical Trial

**Name of Applicant:** Jiangsu Yenssen Biotech Co., Ltd.

**Medical institutions responsible for Clincal Trial:**

1. Department of Oral and Maxillofacial Surgery, The Ninth People's Hospital, Shanghai JiaoTong University School of Medicine;
2. Department of Orthopaedics, The Ninth People's Hospital, Shanghai JiaoTong University School of Medicine;
3. Department of Orthopaedics, Ruijin Hospital, Shanghai JiaoTong University School of Medicine;
4. Department of Oral and Maxillofacial Surgery, Dental Hospital, The Fourth Military Medical University;
5. Department of Orthopaedics, The First Affiliated Hospital of Suzhou University;
6. Department of Orthopaedics, The First People's Hospital of Changzhou

**Host institution for Clinical Trial:** The Ninth People's Hospital, Shanghai JiaoTong University School of Medicine

**Head of Clinical Trial:** Zhang Zhiyuan

**Date:** Dec. 24, 2011

**Statistical Institution for Clinical Trial:** Department of Biostatistics, Shanghai JiaoTong University School of Basic Medicine

**Head of Statistics:** Wang Bingshun

**Date:** Dec. 24, 2011

## 1. Background

1.1 Products for the clinical trial

Osteobone bone defect repair material, hereinafter referred to as "Osteobone", is researched, developed and produced by Jiangsu Yenssen Biotech Co., Ltd.

Osteobone was used as study group material for this clinical trial. While Baiameng hydroxyapatite bioceramic material was used as control group for this clinical trial, which is developed by Academician Zhang Xindong of Biomaterial Engineering Research Center, Sichuan University and had been approved by SFDA.

1.2 Product features

Osteobone is a kind of porous bioceramic material with inorganic elements, being of better biocompatibility. Meanwhile, three-dimensional structure design of Osteobone is more suitable for the growth of bone tissue so as to accelerate the process of bone tissue repairing.

1.3 Data and conclusion from animal experiments

Osteobone had been used in animal experiments with success by Shanghai Orthopedics Research Center. The animal experiments had confirmed the safety and efficacy of this material.

1.4 Conclusion from toxicity test and immune reactions

The toxicity test was conducted according to GB/T1688.5-2003 and the results conformed to this Standard. The sensitization test was conducted according to GB/T1688.10-2000 and the results conformed to this Standard. All the tests were conducted and approved by Chinese National Inspection Center for Drugs and Medical Device.

1.5 Clinical trial results with small samples

Before this clinical trial, Osteobone had been used for repairing the defect of human maxilla and mandible in China and America with small samples according to Helsinki Declaration and IRB standards, which had gained the preliminary data of its safety and efficacy. There was no rejection and inflammation on these patients after surgery. The new bone obviously grew two months after the treatment. The new bone became compact bone being of better function three months after the treatment. One longest follow-up visit on patients was over nine years, whose repairing bone has better function without any adverse reaction It demonstrates the safety and efficacy of Osteobone. These successful clinical trials had been reported for many times at authoritative international academic conference. These clinical data of small samples provided scientific basis on numbers of patients for this clinical trial with large samples and multicenter.

## 2. Objectives of the clinical trial

This clinical trial was conducted to test the safety and efficacy of Osteobone in repairing human defected bone.

## 3. Institutions responsible for clinical trial

3.1 This clinical trial was conducted simultaneously in six study sites for medical device affiliated five general hospitals approved by SFDA. And the Ninth People’s Hospital, Shanghai JiaoTong University School of Medicine, was the host institution of this clinical trial.

**Study site one:** Department of Oral and Maxillofacial Surgery, The Ninth People's Hospital, Shanghai JiaoTong University School of Medicine

**Study site two:** Department of Orthopaedics, The Ninth People's Hospital, Shanghai JiaoTong University School of Medicine

**Study site three:** Department of Orthopaedics, Ruijin Hospital, Shanghai JiaoTong University School of Medicine

**Study site four:** Department of Oral and Maxillofacial Surgery, Dental Hospital, The Fourth Military Medical University

**Study site five:** Department of Orthopaedics, The First Affiliated Hospital of Suzhou University

**Study site six:** Department of Orthopaedics, The First People's Hospital of Changzhou

3.2 Institution for reading imaging of bone formation

To guarantee the double blind of data evaluation, the Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, arranged two doctors major in medical image diagnosis, who were not involved in patients selection, surgery, follow-up visit and so on, to read and grade X-ray pictures and CT imaging of all selected patients before and after surgery.

3.3 Statistical institution for clinical trial

Department of Biostatistics, Shanghai JiaoTong University School of Basic Medicine

## 4. General design of clinical trial

4.1 Methods for clinical trial

The clinical trials were conducted in multi study sites by the methods of randomization, blind and positive parallel control.

4.1.1 Recruited patients were randomly assigned to either study or control groups. The grouping principle of study group and control group adopted the methods of randomization and blind. The patient signed consent form and would gain a bar code so as to record all the information and data of this patient. The curative effects would be evaluated by two doctors, who were not involved in patient selection, surgery and follow-up visit. The Department of Biostatistics, Shanghai JiaoTong University School of Basic Medicine, responsible for making up blind codes of materials, Jiangsu Yenssen Biotech Co., Ltd, and leading researchers would discover the blind after finishing the clinical trial.

4.1.2 Principles for the blind method

a) Blind codes

The codes were randomly born out through software SAS 9.13 by the biostatisticians, who were not involved in the data management statistics of this clinical trial. The ratio between study group material and control group material was 1:1. Each clinical study site applied the material on the patients according to serial number of the material and patient recruited sequence. The blind codes, in duplicate, were stored in Jiangsu Yenssen Biotech Co., Ltd and the Ninth People's Hospital affiliated Shanghai JiaoTong University School of Medicine during the period of this clinical trial.

b) Implementation of the blind

To ensure both patients and researchers randomly use material, different materials were packed with the same outer package.

b) Principle of breaking the blind code

The biostatisticians, who made the blind code, needed to prepare a emergency letter for each material. This letter contained the definite group of this material. The emergency letter, together with the material of corresponding material, would be distributed to each clinical study site. The

emergency letter was used for emergency events, such as serious adverse events.

It was required to record the date and reason for discovering the blind code once opening the emergency letter and informed Jiangsu Yenssen Biotech Co., Ltd. The signature of the person discovering the blind was also required. It was considered as shedding case once opening the letter.

All the emergency letters, including opened and unopened letters, must be taken back together with the reports of the finished cases.

4.2 Study subjects

4.2.1 Numbers of clinical trial cases

According to bone repairing efficiency of the similar material from its clinical trial, the efficiency of study group material was about 90%, while that of control group material was about 75%. Suppose the comparison between study group and control group using non-inferiority testing. Suppose $\alpha$ equals 0.025, the efficiency of test (1-β) equals 0.9, and cut-off level of non-inferiority equals 10%. Thus, more than 90% of 60 patients of each group could prove the above assumption. Suppose the shedding rate of follow-up visit is 20%. The planed recruited patients were 72 for each group.

4.2.2 Criteria of patient selection

a) Age between 18 and 65, male or female;

b) Patients needed bone graft because of bone defect caused by following reasons:

- Surgery after benign bone tumor
- Bone defect caused by bone trauma
- Bone defect in dental implant

c) The size of bone defect was from 1.2cm x 1.2cm x 1.2cm to 5cm x 5cm x 5cm;

d) Signed the consent form.

4.2.3 Criteria of patient exclusion

a) Had participated in any other clinical studies within 4 weeks prior to this clinical trial;

b) The bone defect was caused by aggressive or malignant bone tumor;

c) Had used drugs, which may affect or promote bone metabolism, within the last 3 months;

d) Bone defect caused by active or infectious lesions, or metabolic bone disease;

e) Had heart diseases;

f) Had dysfunction of the liver and kidney;

g) Metal disorder without behavior capacity;

h) Had hypersensitive condition;

i) Pregnant or lactating women.

4.2.4 Criteria of patient withdraw

a) Had any condition listed in criteria of exclusion is discover;

b) Patient decided to withdraw from the trial not because of adverse events;

c) Patient did not follow the instruction of clinical application.

All the shedding cases were required to record the reasons.

**5. Ethical principles and patient consent**

a) The design of this clinical trial conformed to Helsinki Declaration and GCP standards;

b) The design of this clinical trial and the content of the consent form were approved by IRB committee of six clinical study sites;

c) The clinical investigators needed to explain the content of consent form to the patients in detail before clinical trial.

d) Consent form should contain the content as follows:

- Objectives, methods and duration of this clinical trial;
- Expected and potential effect and risks;
- Are there any other treatment;
- The testing subjects participating the clinical trials are voluntary and may withdraw from the clinical trials at any stage;
- The data of testing subjects should be confidential. IRB committee, SFDA and the applicant, Jiangsu Yenssen Biotech Co., Ltd have right to refer back to the information of the testing subjects if necessary;
- Clinical study site should provide related clinical files to the testing subject if he asks for it;
- The testing subject will be compensated once he is damaged by clinical trail;
- Other necessary items relate concerning protecting testing subjects.

**6. Material and methods for clinical trial**

6.1 Study group: Osteobone bone defect repairing material provided by Jiangsu Yenssen Biotech Co., Ltd. Specifications: 6 $cm^3$ / bottle / patient in department of oral and maxillofacial surgery; 9 $cm^3$ / bottle / patient in department of orthopedics. Batch number: 080322.

6.2 Control group: Baiameng hydroxyapatite bioceramic material produced by Biomaterial Engineering Research Center, Sichuan University, and purchased by Jiangsu Yenssen Biotech Co., Ltd.

6.3 Selection reason of control group material

Baiameng hydroxyapatite bioceramic material had been approved by approved. Its safety and effectiveness had been confirmed.

6.4 Packaging of the material

Study group material and control study group were packed with the same boxes. Each box contained corresponding bar code. All the materials were

randomly assigned with serial number. The content of outer packing contained serial number, usage and dosage, specifications, storage, batch number, shelf-life, applicant and so on.

6.5 Issue the materials

The recruited patients were randomly assigned to study group and control group at the ratio of 1:1.

6.6 Store the materials

The materials are stored, managed and issued by designated personnel. The materials for this clinical trial were stored in shade and dry area.

6.7 Record the material

The clinical institution recorded the storage of the material so as to be checked supervisor in each interview. The unused material was required to be returned to Yenssen Biotech. The researcher should record the dosage of material for each patient so as to judge the compliance of the recruited patients, which was good for judging the effectiveness and safety of the material.

6.8 Usage and dosage

Usage: Guarantee the implant bed is clean and there's exudation from bone cavity before implanting material. The material is infiltrated by the blood exuding from bone defected area. Fill the material into the bone defected area of the recruited patients, directly covered by soft tissue. Then suture it.

Dosage: Fill the same volume as defected area of material into the defected area.

## 7. Reasons for the deadline of the clinical trial

According to the theory of repairing mechanism of normal bone tissue, new bone will start to grow in the eighth week after treatment and basically end up in the twelfth week. Thus, the best effect of bone repair is that the implanted material will be absorbed in three months and the new bone is formed. The

material, ‘Baiameng’ in control group is a kind of absorbable and degradable material approved by China FDA. While the material, ‘Osteobone’ in study group is also a kind of degradable inorganic material. According to previous animal experiments and pre-clinical trials, it has demonstrated that this material can be basically absorbed and degrade, and the new bone will replace the defected area within three months after treatment. According to these data, the follow-up period of this clinical trial was designed to be 24 weeks. It was expected that the implanted material will be absorbed and degrade in the twelfth week after treatment. Thus, 24 weeks follow-up period is enough to observe the effectiveness and safety of the implanted material.

**8. Case report form (CRF)**

This CRF was designed by multi clinical institutions after discussion so as to guarantee its scientific rationality. This form contains key points of the clinical trial. See attachment.

**9. Assessment sheet for image of clinical efficacy**

The clinical efficacy of bone repair was judged by radiological image. This clinical trial adopted the highest standard and way for identifying radiological image so as to guarantee the science and feasibility of this clinical trial. The host institution for this clinical trial appointed two physicians with professional qualification in radiological imaging to evaluate the images. These two physicians did not contact any clinical information of the patients so as to ensure the blind of the clinical trial. To avoid mutual interference of the physicians, there were two assessment sheets for image of clinical efficacy for each patient, sheet A and sheet B, see attachments. Two physicians separately recorded assessment results. They could not know each other’s assessment data. If there was differences of data between two sheets submitted for statistical analysis, it was required to be re-assessed by

radiography director and the above mentioned two physicians and get agreed data.

## 10. The process of clinical trial

| Item | | Pre-operation | Operation | 1 week after operation (±3 days) | 12 weeks after operation (±1 week) | 24 weeks after operation (±2 weeks) |
|---|---|---|---|---|---|---|
| Basic medical record | Sign consent form | √ | | | | |
| | Confirm the criteria of patient selection and exclusion | √ | | | | |
| | Randomly enrolled in this trial | √ | | | | |
| | Fill in the basic information | √ | | | | |
| | Physical examination | √ | | √ | √ | √ |
| Safety | Routine blood and urine tests | √ | | | √ | |
| | Hepatorenal function | √ | | | √ | |
| | Blood phosphorus and calcium | √ | | | √ | |
| | Records of adverse events | | √ | √ | √ | √ |
| | Records of surgical incision healing condition | | | √ | | |
| Effectiveness | X-ray inspection | √ | | √ | √ | √ |
| | CT scanning | | | √ | | √ |
| | Bone formation scoring | | | √ | √ | √ |

| Item | | Pre-operation | Operation | 1 week after operation (±3 days) | 12 weeks after operation (±1 week) | 24 weeks after operation (±2 weeks) |
|---|---|---|---|---|---|---|
| Others | Follow-up visit | | | √ | √ | √ |
| | Summary of clinical trial | | | | | √ |
| | CRF review | | | | √ | √ |

10.1 Safety evaluation in clinical trial and lab test

10.1.1 Clinical evaluation

a) General physical condition: observe T, P, R and blood before and after operation, and at every follow-up visit.

Healing condition of surgical incision: Surgical incision can be divided into class I cleaning incision and class II non-cleaning incision according to incision location. The incision from skin is classified as class I cleaning incision. While the incision from mouth is classified as class II non-cleaning incision.

b) observe the healing condition of surgical incision

**Score the healing time:**

1 point = ≤ 14 days

0 point = > 14 days

**Healing grade and scoring standard of surgical incision:**

| Incision Type | | Standard | Healing Grade | Score |
|---|---|---|---|---|
| Class I cleaning incision | ☐ | 2 points | A healing | ☐ |
| | | 1 point | B healing | ☐ |
| | | 0 point | C healing | ☐ |
| Class II non-leaning incision | ☐ | 2 points | A healing | ☐ |
| | | 1 point | B healing | ☐ |
| | | 0 point | C healing | ☐ |

| | |
|---|---|
| **A Healing** | Class I incision: Complete healing within 14 days without infection<br>Class II incision: Better healing within 14 days without swelling |
| **B Healing** | Class I incision: There's suture reaction and mild infection. The healing time of the wound excesses 14 days<br>Class II incision: The wound heals not good and the healing time excesses 14 days. |
| **C Healing** | Class I incision: infected wound caused by foreign body reaction or the wound does not heal forming fistula.<br>Class II incision: Obviously infected wound or the wound does not heal forming fistula. |

**Evaluation on the healing of surgical incision**

Evaluate the healing rate of surgical incision based on both healing time and healing grade.

| Assessment | Scoring |
|---|---|
| Great | 3 points |
| Good | 2 points |
| Basic | 1 point |
| Bad | 0 point |

Totally good healing rate of surgical incision = Total cases with ‘great’ and ‘good’ x 100%

10.1.2 Assessment on laboratory safety index

a) Laboratory examination: Examine routine blood and urine, hepatorenal function, blood phosphorus and calcium before surgery and 12 weeks after the surgery.

b) Abnormal changes in laboratory safety index: Decided it according to abnormal changes in examination items.

10.2 Assessment on efficacy in clinical and image area

10.2.1 X-ray and CT image: Examine the implanting area by X-ray before surgery, 1 week, 12 weeks and 24 weeks after the surgery respectively. And examine the implanting area by CT 1 week, 12 weeks and 24 weeks after the surgery respectively. Grade bone formation according to examination results through X-ray and CT. X-ray image is mainly used for assessment on the properties of new bone and implanted material. While CT image is mainly used for supporting assessment on bone defect area and repairing volume.

10.2.2 Scoring observation of bone defect repairing