Department of Medicine, The University of Hong Kong, Queen Mary Hospital

SUBJECT INFORMATION SHEET

Study title:	**The Effect of Zoledronate on the Prevention of Pneumonia in Hip Fracture Patients (Zoo-P): An Open-label, Pragmatic, Randomised Controlled Trial**
Principal Investigators:	Professor Tan Choon Beng Kathryn
Name of Institution:	Department of Medicine, The University of Hong Kong
Address of Institution:	Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pok Fu Lam Road, Hong Kong

Name of Subject _____ _____

(Surname) (First Name)

Subject Screening / CRF Number: _____

You are being invited to take part in a clinical trial under the direction of Professor Tan Choon Beng Kathryn. This study has been approved by the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster, which is a committee charged to ensure that the rights of human subjects are protected during the study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your family doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

This document explains the purpose, procedures, risks, benefits and precautions of the clinical study. Your participation in this study is entirely voluntary. Your decision whether or not to participate will not prejudice you or your medical care. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time. You should sign the consent section of this form only once you have fully read and understood this Patient Information sheet and once your study doctor has answered all your questions to your satisfaction. You should also be clear about your rights and obligations as a participant in this clinical study before you give written consent. If you decide to participate, you will be given a copy of the signed consent form to keep.

WHAT IS THE PURPOSE OF THE STUDY?

Nitrogen-containing bisphosphonates (N-BPs; such as alendronate and zoledronate) are medications widely used for the treatment of osteoporosis and fracture prevention. Although alendronate is the first-line anti-osteoporosis medication in many countries, zoledronate infusion has also been used clinically for years, is more convenient (it is usually given once every 12 months), and also avoids the gastrointestinal irritation side effect of alendronate. Zoledronate also has a proven better efficacy than alendronate and can additionally reduce risk of mortality. Thus, zoledronate is considered the most efficacious N-BP in clinical use. In recent studies, zoledronate has also been shown to have potential to reduce risk of developing various cardiovascular diseases as well as preventing pneumonia, which is a leading cause of death in patients with hip fracture. The major aim of this study is to evaluate if zoledronate reduces risk of pneumonia in hip fracture patients using a randomized control trial. This study also examines other health benefits brought about by using zoledronate.

WHY HAVE I BEEN CHOSEN?

This study recruits a total of around 2700 participants. You have been chosen because you are aged 60 or above with recent X-ray confirmed fragility hip fracture at proximal femur at Caritas Medical Centre, Prince of Wales Hospital, Queen Mary Hospital, and United Christian Hospital in Hong Kong. You have also understood the requirements of this study and have provided written consent to participate and adhere to the data collection procedures.

You also do **not** have any of the following:

- Known to be hypersensitive to any N-BPs;
- Poor renal function;
- Regular user of anti-osteoporosis medications (including bisphosphonates, denosumab, teriparatides, and raloxifene) or oral or intravenous systemic glucocorticoids in the previous year; and
- Currently participating in another clinical trial.

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. Your decision of whether to take part or not will not affect your current and future medical care and legal rights. Updated Information will be provided to you during the research project. Information provided to you may affect your decision on continuing participation in this research. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you decide to take part in this open-label, multi-centre, pragmatic, randomized controlled trial, you will be randomly assigned to one of the two study groups, namely **Group 1** (receive zoledronate infusion with usual care) and **Group 2** (receive usual care). The chance you have of getting the study drug (i.e. zoledronate) is a one in four.

On the first day of the study, we will first record and measure your baseline characteristics, such as age, sex, body mass index, renal function, history of fracture, chronic respiratory diseases (such as obstructive pulmonary disease, bronchiectasis, and asthma), and other medical history. 12ml of non-fasting peripheral blood specimen will be collected by a registered nurse. The specimens may be subjected to laboratory analysis for bone-related biomarkers such as quantification of your baseline calcium and vitamin D levels, as well as your renal function. You will then receive the study treatment according to the following regimen:

- ***Group 1 (Experimental Group):*** **Zoledronate 5mg intravenous infusion** once on the same day, then receive usual care as in Group 2.
- ***Group 2 (Control Group):*** Receive **usual care** only. Usual care includes, but is not limited to, rehabilitation, routine outpatient follow-up, calcium and vitamin D supplementation, and anti-osteoporosis medication.

With your consent, your electronic medical records will be available for use in this study. You will be followed up for the next 12 months using electronic medical records, which we will record any incidence of pneumonia, development of other health conditions, and any adverse events that occurred. To ensure your recovery progress is recorded accurately, our research staff may call you or your family members during the period.

WHAT DO I HAVE TO DO?

If your study doctor decides you are eligible to take part in the study and you agree to do so by signing the consent section of this form, you will have to follow the instructions listed below:

- Take the study product accordance to the instruction.
- If you experience any adverse events, consult other doctors or are admitted into the hospital, please contact the research staff (Tel: 2831 5083).
- You cannot participate in other clinical research project(s) during participation of this clinical research project.
- Ask questions if you have any enquiries.

WHAT IS THE PRODUCT THAT IS BEING TESTED?

The product being tested in this study is an N-BP, zoledronate, which is widely used in osteoporosis treatment and fracture prevention. It provides some extra benefits compared with the current first-line N-BP, alendronate. N-BPs are also found to be anti-inflammatory and immune-modulatory, and previous studies have proven it may provide other health benefits in hip fracture patients, such as reducing risk of cardiovascular events, as well as preventing pneumonia occurrence through modulating macrophages in response to pneumonia.

WHAT ARE THE SIDE EFFECTS OF TAKING PART?

Zoledronate has been recorded to have the following side effects:

Fever is the most common side effects. Other rare adverse effects include fatigue, chest pain, lower limb edema, conjunctivitis, nausea, vomiting, constipation, diarrhea, dysphagia, appetite loss, hypotension, hypocalcemia, granulocytopenia, pancytopenia, bone, joint and muscle pain, administration time-associated increase in serum creatinine kinase, headache, difficulty breathing, and cough. These adverse effects have a very low incidence and the study product is generally considered as safe. We have also ensured the participants do not have previous record of zoledronate allergy.

Infusion-related side effects:

Some people may experience infusion-related reactions during zoledronate infusion. This often presents as fever and muscle / joint pain. You do not have to worry as you will be under medical care during zoledronate infusion.

If you suffer these or any other adverse effects, you should seek medical attention immediately. For any concerns related to the side effects of zoledronate, we encourage you to contact the research staff by 2255 5859.

WHAT ARE THE DISADVANTAGES AND RISKS OF TAKING PART?

- Although a pharmaceutical product is used in this study, adverse effect associated with the drug is uncommon. If you are in the control group, you will not be receiving the drug. The (additional) medical care you will receive no matter which group you are assigned to will not differ from your usual medical care. Therefore, additional risk associated with participating in this study will be minimal.
- If you are in the treatment group, the study drug that you receive will be administered via intravenous infusion, which may cause infusion-related reactions such as fever and muscle / joint pain. You will be under close medical care throughout the process, and infection associated with

intravenous drug administration is minimal.

- Blood samples will be taken at the first of the study. There may be pain or bruises with venipuncture. Some people may experience dizziness when observing blood. The chance of infection resulting from venipuncture is very low.
- If you have private medical insurance, your insurance status usually would not be affected by taking part in the study. Please contact insurance company before agreeing to take part in the study to ensure that your participation will not affect your medical insurance.

WHAT ARE THE BENEFITS OF TAKING PART?

Zoledronate has been demonstrated by previous studies to be able to reduce inflammation and mediate the immune system, hence reducing cardiovascular risks in hip fracture patients. It may also mediate macrophage response to pneumonia, hence reducing the chance of developing pneumonia in hip fracture patients. It is also possible, however, that by participating in this clinical study you may not obtain any direct benefit for your health. The information we obtain from this study may help us to examine the effect of zoledronate in reducing risk of pneumonia, which may promote the optimal use of the drug to achieve long-term bone health and prevent pneumonia in patients with hip fracture.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, on receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He / She will explain the reasons.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

The study product only needs to be administered once a year, after which all participants will receive usual care. In case of early termination of the study and after completion of the study, the effect on the care that participants receive will be minimal.

WHAT IF SOMETHING GOES WRONG?

There has been substantial clinical experience of using zoledronate, and that you have been told about the side effects and adverse reactions of using it. Therefore, if you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain about any

aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

You have a right to privacy, and all information that is collected because of this study is confidential to the limit that is possible by law. Except as required by law, you will not be identified by name, address, telephone number, or any other direct personal identifier such as your Identity Card number. The information obtained from this study, including the results of any tests carried out during the study, how you respond to the product, any adverse event you may have experienced and information regarding your general health, will be held in both computerized and manual filing system, although these will not identify you by name. You will be identified by a unique code number and information about the code will be kept in a secure location and access limited to research study personnel. These records will only be kept for as long as necessary and during that time will be kept confidential and, to the extent permitted by applicable laws and regulations will not be made publicly available.

Your medical records will not be voluntarily disclosed by the study investigators. However, at any time during or after the study, direct access to your medical records will be given to regulatory authority, such as the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster so that they can verify that the information collected for the study is accurate. This will be done without violating your confidentiality to the extent permitted by the applicable laws and regulations.

Under the laws of Hong Kong (in particular the Personal Data (Privacy) Ordinance, Cap 486), you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. For any query, you should consult the Privacy Commissioner for Privacy Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

By consenting to participate in this study, you expressly authorize:

- the principal investigator and his research team and the ethics committee (Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster) responsible for overseeing this study to get access to, to use, and to retain your personal data for the purposes and in the manner described in this informed consent process; and

- the relevant government agencies (e.g. the Hong Kong Department of Health) to get access to your personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

WHAT WILL HAPPEN TO THE RESULT OF THE RESEARCH STUDY?

Your past and future medical records will be collected and analyzed by study investigators. The analyses involve comparing the chance of developing pneumonia, other cardiovascular events, refracture, and other health conditions. Such analyses will be able to inform us the efficacy of administering zoledronate as an anti-osteoporotic and immune-modulating drug in preventing pneumonia and other health issues among hip fracture population in Hong Kong. Certain statistical tests will be carried out on your data, along with that collected from others patients who entered the study. The results of this study may be published on journals or be presented at conferences. If the results are published, your identity will remain confidential. Any identifying information (name, address, etc.) will be removed from all records. You will not be identified personally in any presentation or report dealing with this study.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

This study is directed by Prof. Tan Choon Beng Kathryn, Department of Medicine, HKU, and is assisted by Associate Prof. Fang Xinshuo Christian, Department of Orthopedics and Traumatology, HKU. The obtained data will be managed by Assistant Prof. Cheung Ching Lung, Department of Pharmacology and Pharmacy, HKU. The study is funded by the aforementioned professors.

WHO HAS REVIEWED THE STUDY?

The Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster has reviewed and approved this study, which is a committee aims to ensure that the rights of human subjects are protected during the study.

WITHDRAWAL FROM STUDY

If you agree to participate in the study and change your decision later, you can withdraw from the study at any time. Your decision will not affect your ability to receive normal medical care and you will not lose any benefits to which you would otherwise be entitled.

You may also be withdrawn from the study due to following reasons even you wish to continue.

- If the study doctor thinks withdrawal from this study is the most beneficial decision to you.
- If you do not follow instructions from doctors.

- If research doctors or ethic committee(s) stop this research project due to any reasons.

If you want to leave the study at any time, please notify the study doctor or a member of the study staff as soon as possible. All information collected on you up until your withdrawal may still be used for the study.

FEES AND PAYMENTS

You will not have to pay for study product and other study-related procedures. You will not receive any payment for participation.

CONTACT FOR FURTHER INFORMATION

You are encouraged to ask questions at any time during the study. In case you would experience adverse events or have further questions about the study, please contact the research staff (Tel: 2255 5859). If you have any questions about your rights as a study subject, you can contact a third party without conflict of interest:

Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster
Tel: 2255 4086 / 2255 3923

CONTACT INFORMATION

Please contact the research staff by phone (Tel: 2255 5859) if:

- You think you get harm or injury related to this study
- You have any question regarding this clinical trial
- You want to ask for latest information, update or amend information

- End of Subject Information Sheet -

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SUBJECT CONSENT FORM

Protocol title:	**The Effect of Zoledronate on the Prevention of Pneumonia in Hip Fracture Patients (Zoo-P): An Open-label, Pragmatic, Randomised Controlled Trial**
Principle Investigators:	Professor Tan Choon Beng Kathryn
Name of Institution and Department:	Department of Medicine, The University of Hong Kong
Address of Institution:	Department of Medicine, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong

		Please ☑ box	
		Yes	**No**
1.	I confirm that I have read and understood the information sheet (1st edition on 7th Jan 2021) for the above study and have had the opportunity to ask questions.	☐	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐	☐
3.	I understand that sections of any of my medical notes may be looked at by responsible individuals from The University of Hong Kong, Queen Mary Hospital, or from regulatory authorities including the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐	☐
4.	I agree to take part in the above study.	☐	☐
5.	I agree to allow access to my electronic medical records for the above study.	☐	☐

Subject's Signature	Printed Name of Subject	Date dd/mm/yyyy
Witness's Signature (if applicable)	Printed Name of Witness	Date dd/mm/yyyy

I, the undersigned, have fully explained the relevant details of this study to the subject named. I am of the opinion that I have informed the subject named above about the nature of this study and its possible advantages and risks.

Investigator's Signature	Printed Name of Investigator	Date dd/mm/yyyy

* Copies of this consent form will be given to subject and researcher.