Study Consent

Official Title: Zoledronic Acid for Osteoporotic Fracture Prevention (ZEST II)

ClinicalTrials.gov ID (NCT number): NCT02589600

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University of Pittsburgh Physicians
Department of Medicine

Part of
University of Pittsburgh
Medical Center

Division of Geriatric Medicine

**Osteoporosis Prevention
and Treatment Center**

1110 Kaufmann Medical Building
3471 Fifth Avenue
Pittsburgh, PA 15213
412-692-2220

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY
Title: ZEST II for Osteoporotic Fracture Prevention

Principal Investigator:
Susan Greenspan, MD
Professor of Medicine
Director of Osteoporosis Prevention and Treatment Center
University of Pittsburgh
3471 Fifth Avenue, Suite 1110
Pittsburgh, PA 15213
(412) 692-2477

Co-Investigator:
David Nace, MD
Director of Long Term
University of Pittsburgh Institute on Aging, Medical Director
3471 Fifth Avenue, Suite 500
Pittsburgh, PA 15213
412-692-2360

Study Coordinator:
Julie Wagner, PA-C, MPA
412-692-2478
E-mail: wagnerjm@pitt.edu

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Why is this research study being done?

The purpose of this research study is to find if a yearly intravenous (IV)

drug called Zoledronic acid (Reclast®) works to reduce fractures in female long-term care (LTC) residents with osteoporosis. Osteoporosis is a thinning and weakening of the bones that can cause fractures (broken bones). An IV drug is one that is given through a vein in your arm. Zoledronic acid (Reclast®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment and prevention of osteoporosis in postmenopausal women and to reduce the incidence of fracture in postmenopausal women with osteoporosis.

This 3-year research study is being done at your facility by the Osteoporosis Prevention and Treatment Center at the University of Pittsburgh and will involve 5 study visits over the next 3 years.

Who is being asked to take part in this research study?
You are being asked to participate because you are a female LTC resident, age 65 or older, with osteoporosis or at risk for fracture. Approximately 514 female LTC residents will be eligible to take part in the research study. **Participants will be randomly assigned (by chance, a 50-50 chance such as with flipping a coin) to either Zoledronic Acid 5mg IV (Reclast®) or placebo (an intravenous solution containing no study drug).** Of the 514 participants, 257 will receive the study drug and 257 will receive the placebo. All participants will receive calcium and vitamin D supplements.

What procedures will be done for research purposes?
If you decide to take part in this research study, the study visits will be done at your facility where you will go through some procedures that are not part of your standard medical care. The screening visit that you already had done determined that you are eligible to take part in this research study which **will involve 5 study visits over the next 3 years, plus up to 6 safety checks before and after your yearly dose of zoledronic acid 5mg IV (Reclast®) or placebo.** We will **obtain your written informed consent** before any research study procedures are done. If you would like to take part but are not able to make decisions alone, we will obtain written informed consent from your legal guardian (the person legally responsible for your care) with your agreement.

Baseline / Randomization Visit
This visit will take a total of approximately 1 ½ hours of your time and will

involve the following procedures which may occur over several days:

1. **Brief physical exam** (blood pressure, pulse, temperature).
2. You will be asked about changes in your health since the screening visit and if you have had any broken bones or falls since then.
3. Approximately 4 teaspoons of **blood will be drawn** from your arm for tests that measure your bone health. A sample of your blood will be frozen and saved for later testing and for possible future tests which may include research on aging, function, bone and muscle health, and overall health.
4. If you are able to take acetaminophen (Tylenol®) (i.e. if you have no liver abnormalities), **you will be given acetaminophen** (two 500 mg tablets, to be taken by mouth) 1 hour before the IV infusion and then every 6 hours for the next 72 hours to manage possible flu-like symptoms such as fever.
5. Individual single packets of Biofreeze® may also be made available to you (at no cost to you) if needed to manage possible muscle aches and pains following the infusion. The ointment may be rubbed onto the skin up to 2 times per day for 2-3 days.
6. **You will receive IV study drug [zoledronic acid 5 mg IV (Reclast®) or placebo].** The study drug infusion will be given by a nurse or physician's assistant who is a member of the research team. This requires a small catheter (a thin tube) be placed in a vein in your arm using a needle. The study drug IV solution will be given through the IV catheter. There is approximately ½ cup of solution which will be given over approximately 60 minutes. After the infusion is complete, the IV catheter will be removed. This IV study drug is given yearly including at baseline, Month 12, and Month 24.
7. You will receive calcium and vitamin D supplements as needed based on your dietary calcium questionnaire to achieve the Institute of Medicine and National Osteoporosis Foundation recommended calcium of approximately 1200 mg/daily (divided dose from diet or supplement) taken at meals and vitamin D (at least 800 IU/daily).

Monitoring/Follow-up Procedures

Procedures done for your safety and to check how well the study drug works and whether or not you have any side effects are called "monitoring" or "follow-up" procedures. You will have **brief safety checks done up to 2 days prior to receiving the annual IV study drug and 1-3 days after.** A member of the research team will visit you to do a safety check up to 2 days prior to the infusion when **samples of blood** (approximately 4 tsp.)

will be drawn from your arm for safety measures. Another safety check will be done 1-3 days after the study drug infusion, when a member of the research team will make a telephone call to check on how you are feeling.

Months 12, 24, and 36

Visits at Months 12, 24, and 36 will each take a total of approximately 3-4 hours of your time and will involve the following procedures which may occur over several days:

1. At months 12, 24, and 36: **Brief physical exam** (blood pressure, pulse, temperature).
2. At months 12, 24, and 36: You will be asked about changes in your health since your previous visit and if you have had any broken bones or falls since then.
3. At months 12, 24, and 36: You will have **blood tests** for safety checks. Blood will also be saved and frozen for tests of bone health and for possible future testing which may include research on aging, function, bone health, and overall health. No more than approximately 4 teaspoons of blood will be drawn at each of these study visits**.**
4. At Months 12, 24 and 36: Bone density test of your spine (front and side, and trabecular bone score [TBS] which is an indicator of bone strength), hip (total hip) forearm, and total body. This bone density test, known as a **DXA scan**, uses a special low-radiation x-ray machine. This will inform us about your bone health and the amount of muscle and fat in your body, and it will also include vertebral fracture assessment (VFA) to show if any of the small bones in your spine are broken. For the DXA procedure, you will be asked to lie on a padded table for a total of approximately 50 minutes. You will need to lie still for several minutes at a time while the arm of the machine passes over these body regions to measure the thickness of your bones. For the DXA scan of your wrist, you will sit in a chair with your arm on the table for approximately 10 minutes.
5. At Months 12, 24 and 36: You will be asked some questions about your **daily activities**, **energy level**, your **ability to do physical tasks**, and about your **thinking ability** (remembering words, identifying objects, following instructions), **mood, outlook** and **recent falls**. This information will be gathered using questionnaires.
6. At months 12, 24 and 36: We will **test your grip strength, balance and physical ability and your ability to do routine daily tasks such putting on a sweater.** You may be asked to do things like get up from a chair or walk down a hallway.

7. At months 12 and 24: If you are able to take acetaminophen (Tylenol®) (i.e. if you have no liver abnormalities), **you will be given acetaminophen** (two 500 mg tablets, to be taken by mouth) 1 hour before the IV infusion and then every 6 hours for the next 72 hours to manage possible flu-like symptoms such as fever. Biofreeze® single packets may also be made available to you (at no cost to you) if needed to manage possible muscle aches and pains following the infusion. The ointment may be rubbed onto the skin up to 2 times per day for 2-3 days.
8. At months 12 and 24**: You will receive IV study drug [zoledronic acid 5 mg IV (Reclast®) or placebo].** This requires a small catheter (a thin tube) be placed in a vein in your arm using a needle. The study drug IV solution will be given through the IV catheter. There is approximately ½ cup of solution which will be given over approximately 45 minutes. After the infusion is complete, the IV catheter will be removed.

Possible Repeat Tests

It is possible that the blood tests performed as part of the research study procedures may need to be repeated. Due to the fragile nature of the samples, which must be transported back to the UPMC Clinical Laboratory for processing, the specimens may deteriorate or become damaged despite the best precautions. These repeat blood tests would be done at your LTC facility by the research staff as soon as possible after the need for retesting became known. The risks remain the same as outlined in the risks section of this consent form; however, repeat testing would increase the total amount of blood drawn for that study visit's tests to approximately 8 teaspoons.

What will happen to your blood samples?

Your blood samples and any components of your cells not used for the tests listed above may be frozen and stored indefinitely for possible future research, which may include research on aging, function, bone health, and overall health. These samples will be labeled with a unique code to de-identify them, and the de-identified samples may be available to secondary investigators not listed on the consent form.

Participants in this research study may experience the following risks:

- Risks of the Study Drug. As with any drug, there may be adverse

events or side effects that are currently unknown, and it possible that certain of these unknown risks could be permanent, serious, or life-threatening.

Zoledronic Acid (Reclast®):

The most common side effects are fever; pain in your bones, joints or muscles; pain in your arms and legs, and headache.

Other side effects include flu-like symptoms (fever, chills, bone, joint, or muscle pain, fatigue); nausea, vomiting, and diarrhea. The majority of flu-like symptoms occurs within 3 days following the dose of Reclast® and usually lasts about 3 days but can last up to 7-14 days. These temporary fever and flu-like symptoms can be treated with acetaminophen (Tylenol) to be taken every 6 hours, as needed, for 72 hours following the IV study drug, for participants who are able to take acetaminophen.

Allergic reactions, such as hives, swelling of your face, lips, tongue, or throat may occur. A rare side effect is eye inflammation. Serious and rare side effects can include:

- Low calcium levels in your blood (hypocalcemia). The study doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Reclast®. Take the calcium and vitamin D as your study doctor tells you to do.
- Severe kidney problems. You should drink at least 2 glasses of fluid within a few hours before receiving Reclast® to reduce the risk of kidney problems.
- Severe jaw bone problems (osteonecrosis). You should let your study doctor know if you are scheduled for a tooth extraction before receiving the study drug. It is important for you to practice good mouth care during treatment with Reclast®.
- Unusual thigh bone fractures. Tell your study doctor if you have new or unusual pain in your hip, groin, or thigh.

You should not receive Reclast® if you are already receiving Zometa® because both Reclast® and Zometa® contain zoledronic acid. Do not take Reclast® if you have low levels of calcium in your blood, have kidney problems, or have a history of allergic reaction to bisphosphonates (such as Fosamax® and Actonel®).

Placebo: Subjects in the placebo group will have the same risks as described in this risks section except for those associated with zoledronic acid (Reclast®) as described above. There is a potential risk for bone loss in not receiving the study drug, however you will receive calcium and vitamin D supplements which have been shown to reduce bone loss. If we find that you have significant bone loss during the study, you will be informed and appropriate treatment options will be discussed with you. You will be allowed to continue in the study for follow-up visits on a therapy chosen by your physician.

Intravenous (IV) line placement: The risks of IV insertion may include pain, infection, inflammation of the vein (phlebitis), and IV fluid accidentally entering the surrounding tissue (infiltration).

Acetaminophen: Common side effects include itchiness or rash, constipation, nausea, and vomiting. Serious side effects include liver failure.

Biofreeze® : The main ingredients of this mild topical ointment are camphor and menthol. Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat. Stop using and call us at once if you have severe burning, stinging, or irritation.

Calcium and vitamin D supplements: Mild constipation from the calcium supplement occurs commonly. This may be eliminated by adding fiber to your diet. There are no known side effects for vitamin D when taken within the recommended daily allowance of up to 800 IU, or up to 4000 IU daily.

Participation in this research study will involve radiation exposure from the dual-energy x-ray absorptiometry (DXA) scans. You will have DXA scans of your spine (front and back, and TBS which is a measure of bone strength), vertebral fracture assessment (VFA), hip (total hip), forearm, and total body. If you complete all the DXA scans for the study as outlined above, the total radiation dose to your spine will be about 240 mrems (an mrem is a unit of radiation). The radiation dose to your hip will be about 30 mrems. The radiation dose to your wrist will be about 15 mrems, and the radiation dose to your total body would be about 3 mrem. For comparison, these radiation doses are a very small fraction of the maximum annual whole body radiation dose (5000

mrems) permitted by federal regulation to adult radiation workers. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. However, the risk associated with the amount of radiation exposure from participation in this study is considered to be low and comparable to everyday risks.

Blood draws: The risks and discomforts of having blood drawn may commonly include pain, feeling lightheaded or fainting, and the possibility of bruising or soreness at the site of the blood draw. In rare instances, infection at the site of the blood draw may occur.

Walking and Balance tests: There is a risk of falling or of discomfort (pain) while doing the walking and balance tests. The study coordinator is trained to intervene to prevent a fall from happening. You can decline to do any of the balance or walking tests that you do not want to do or that you feel is too painful. To protect your privacy, these tests will be done in a private room except for the walking test, which will be done in a cleared hallway.

There are possible benefits from taking part in this research study:
Some direct benefits from taking part in this research study are that you will also be given calcium and vitamin D supplements, therapies that have been shown to help prevent bone loss and broken bones. However, there is no guarantee that you will receive such a benefit. This study involves a placebo group and participants assigned to the placebo group are expected to receive no direct benefit from the intravenous placebo infusion. You will also know the mineral content of your bones from your DXA results and the composition of your body in terms of percentage of muscle and fat. The knowledge gained from your part in this study may help people who have osteoporosis in the future, particularly LTC residents.

What treatments or procedures are available if you decided not to take part in this study?
You may choose not to participate in this research study and either continue your current health treatment plan or discuss other therapies with your physician. Evaluations and treatments for osteoporosis are available outside of this study.

None of the tests or procedures done for research study purposes

will be billed to you or your health insurance (blood tests, DXA scans, calcium and vitamin D supplements, physical assessments and questionnaires, study drug). If you receive a bill or believe your health insurance has been billed for something that is part of the research study, notify the study coordinator as soon as possible.

Other tests and procedures that would normally be done as part of your conventional care will be your responsibility and charged to you or your health insurance, in the standard manner, for services and procedures that are done as part of your routine care. Any deductible or copayments that are part of your insurance coverage will apply.

Are participants paid for taking part in this study?

You will not be paid for participating in this research study. You will receive a study lap blanket as a thank you gift after your randomization visit has been completed.

If you believe that the research study procedures have resulted in an injury to you, immediately contact the Principal Investigator or Study Coordinator (see first page for contact info). Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of follow-up care. At this time, there is no plan for any additional financial compensation.

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will result in identifiable information that will be placed into your medical records held at UPMC and at the Osteoporosis Prevention and Treatment Center. The nature of the identifiable information resulting from your participation that may be recorded in your medical record includes DXA scan reports, past medical history, medications, lab values, physical exam, X-rays, dental exam reports, demographic information, questionnaires, physician order sheets, and progress notes

performed for research purposes and information related to any adverse events you may experience related to the study procedures.

This research study will also involve the recording of past, current and/or future identifiable medical information from your hospital and/or other health care provider (e.g. physician office) records. Information that may be recorded from your medical records for research purposes includes medical history, medications, lab values, X-rays, dental exam reports, hospitalizations, physical exam reports, physician order sheets, progress notes, and information related to any adverse events experienced.

To protect your privacy and maintain the confidentiality of information we obtain from you and from your medical records, we will keep all information about you in a secure location. All paper records that could identify you will be stored in a locked file cabinet, and all electronic records will be stored in password-protected files. Your identity on these records will be indicated by a case number rather than your name, and the code linking your name to this number will be maintained separately with very limited access by research team members.

Although we will do everything in our power to protect your privacy and the confidentiality of your records, just as with the use of your medical information for health care purposes, we cannot guarantee the confidentiality of your research records, including information that we obtained from you medical records.

In addition to the investigators listed on the first page of this consent document and their research team, the following individuals may have access to your identifiable medical information related to this research study:

- UPMC hospitals may have access to identifiable information only for the purposes of (1) filling orders made by the researchers for hospital and health care services (e.g. laboratory tests) associated with the study, (2) addressing correct payment for tests and procedures ordered by the researchers, and/or (3) for internal hospital operations (e.g. quality assurance).
- Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information for the purpose of monitoring the appropriate

conduct of this research study.

- Authorized representatives of the sponsor(s) of this research study (see page 2), such as outside laboratories assaying blood samples, may review and/or obtain identifiable information related to your participation in this study for the purposes of monitoring the accuracy and completeness of the research data and for performing requires scientific analyses of the research data.
- In unusual cases, the investigators may be required to release identifiable information related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform the appropriate agencies as required by law.
- Authorized representatives of the U.S. Food and Drug Administration (FDA) may review and/or obtain identifiable information related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the FDA understands the importance of maintaining the confidentiality of your identifiable research and medical information, the University of Pittsburgh and UPMC cannot guarantee the confidentiality of this information after it has been obtained by the FDA.

According to University of Pittsburgh policy, **all research records must be maintained for at least 7 years following the final reporting or publication of a project.**

Your doctor may be involved as an investigator in this research study, but you are not under any obligation to participate in any research study offered by your doctor. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of the research study. Before agreeing to participate in this research study, or at any time thereafter, you may wish to discuss participation with another health professional that is not associated with the research.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your participation in this research study is completely voluntary. You

may want to discuss this research study with your family and friends and your personal physician before agreeing to participate. If there are any words you do not understand, feel free to ask us. The investigators will be available to answer your current or future questions. Whether or not you participate will have no effect on your current or future relationship with the University of Pittsburgh, UPMC, or its affiliated health care providers or health insurance providers.

If you decide you no longer wish to participate after you have signed the consent form, you should contact the principal investigator or the research coordinator (contact info on page 1). **To formally withdraw your consent for participation, you should provide a written and dated notice of this decision to the principal investigator** listed on the first page of this form. You may also withdraw, at any time, your authorization to allow the research team to review your medical records, but if you do so, you will no longer be able to participate in this research study. Any information obtained from you up to that point will, however, continue to be used by the research team. Your decision to withdraw from this research study will have no effect on your current or future relationship with the University of Pittsburgh or with UPMC or its affiliated health care and insurance operations.

The investigators may withdraw you from the research study if they feel that you cannot complete the study requirements safely (for example, if you need other treatment, cannot undergo the study procedures, do not follow the investigators' instructions, experience adverse events). **You might also be removed from the research study for other medical or administrative reasons** (for example, the research resources are no longer available or no longer funded by the research sponsor). We will notify you should this arise and advise you if there are available alternatives that may be of benefit at the time.

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to

ask questions about any aspect of this research study during the course of this study, and that any future questions, concerns, or complaints will be answered by a qualified member of the research team listed on the first page of this consent document at the telephone numbers given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. At any time I may also contact the Human Subjects Protection Advocate at the IRB Office, University of Pittsburgh (toll-free at 1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. **By signing this form I agree to participate in this research study and allow the use and disclosure of my medical record information for the purposes described above.** A copy of this consent form will be given to me.

_____ _____
Participant's Signature Date

_____
Participant's Name (Print)

The above-named individual is unable to provide direct consent for study participation because

_____
_____

Therefore, by signing this form, I give my consent for participation in this research study.

_____ _____
Representative's Name (Print) Representative's Relationship to Participant

_____ _____
Representative's Signature Date

_____ _____
Witness Signature Date

VERIFICATION OF EXPLANATION:

I certify that I have carefully explained the purpose and nature of this research study to the above-named participant in appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

Investigator's Signature	Date (Time if placed in medical record)

CERTIFICATION OF INFORMED CONSENT:

I certify that I have explained the nature and purpose of this research to the above individual and/or their proxy representative, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

Printed Name of Person Obtaining Consent	Role in Research Study
Signature of Person Obtaining Consent	Date