The Cleveland Clinic Foundation
Consent to Participate in a Research Study

Study title: A Prospective Pilot Study to Evaluate Efficacy and Safety of Euflexxa for the Treatment of Osteoarthritis
Sponsor: Ferring Pharmaceuticals, Parsippany, NJ
PI: Carlos Higuera, MD Phone: 216-636-1136
Study Coordinator: Alison Klika
After hours phone contact #: page Jaiben George as at 83116

You are being invited to participate in a research study. A research study is designed to answer specific questions about new ways to prevent, detect, and treat disease. Being in a research study is different from being a patient. The purpose of this document is to provide a written summary of the discussion and exchange of research information you had with the research team. It is also for use as a reference during the study.

Please note:

- **You are being asked to participate in a research study**
- **Ask as many questions as needed so you can make an informed decision.**
- **Carefully consider the risks, benefits, and alternatives of the research**
- **Your decision to participate is completely voluntary and will have no effect on the quality of your medical care if you choose not to participate. You can also withdraw from the study at anytime.**

1. INFORMATION ON THE RESEARCH

Why is the research study being done?

- The purpose of this research study is to evaluate whether Euflexxa® injections effect the inflammatory molecules inside your joint. In addition, this study will examine the effect of Euflexxa® injections on your perceived activity level, overall health-related quality of life, and satisfaction, as well as time to total knee replacement.
- The drug being used is Euflexxa®.
    - Euflexxa® is FDA approved for treatment of pain in knee osteoarthritis.
    - It has been used in humans and it is not considered an experimental drug
    - Generic name: Intraarticular Hyaluronic Acid (1% Sodium Hyaluronate). Brand name: Euflexxa®
    - This drug does not require surgical procedure or anesthesia
- We are asking you to participate in this study so we can learn more about osteoarthritis and its treatment.

What is involved if you decide to take part in this research study?

- If you are eligible to be in the study, and you choose to participate, you will receive Euflexxa injections at the initial visit, week 1, week3, 6-month, 6-months and 1 week, 6-months and 2 weeks. Your in-office visit will take place at the initial visit, 1 week, 2 week, 6 week, 3 month, 6 month, 1-year, and 2-year. Knee joint aspiration will be performed prior to initial injection, at week 6, and 6-month visit. Visual analogue scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Knee Society Score (KSS), Short Form-12 (SF-12), UCLA activity score (UCLA), and questions regarding whether or not the patient received a total knee arthroplasty will be asked at each visit **(Table 1).**

Table 1.

	Index visit /Visit 1	Visit 2 (Week 1 ± 3 days)	Visit 3 (Week 2 ± 3 days)	Visit 4 (Week-6±2 weeks) (visit 4)	Visit 5 (3-month±2 weeks)	Visit 6 (6-month±4 weeks)	Visit 7 (One week from visit 6 ± 3 days)	Visit 8 (Two weeks from visit 6 ± 3 days)	Visit 9 (1-year±2 months)	Visit 10 (2-year±2 months)
Aspiration	X			X		X				
Injection	X	X	X			X	X	X		
VAS	X	X	X	X	X	X			X	X
WOMAC	X	X	X	X	X	X			X	X
KSS	X	X	X	X	X	X			X	X
SF-12	X	X	X	X	X	X			X	X
UCLA	X	X	X	X	X	X			X	X
Knee Surgery?	X	X	X	X	X	X			X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

- The following are aspects of this study that comprise the **standard of care**: disease assessment, vital sign measurements, and monitoring for adverse events at each visit.
- The following are aspects of this study that are **in addition to the standard of care**: Euflexxa injections, knee aspiration.
- You do not have to be accompanied home from visits.
- Results will not be shared outside of research team.
- The study duration is 2 years.
- Sample/specimen collection:
  - Synovial fluid sample (fluid inside the joint) will be collected by aspiration with a syringe.
  - The sample will be centrifuged (spun down) in a laboratory and the pellet (bottom solid part) will be sent out to Rush University Medical Center for future RNA sequencing analyses. The samples will be labeled with a unique identification codes linking them to their respective site and patient information. The sample

identification codes will be the only link between the received samples and the collection site, and thereby, the patient. This will be used if Rush University Medical Center needs to request additional information, or if patient requests a sample to be returned or destroyed. Cleveland Clinic will keep the identification sheet locked and secured. The results of these tests will not be shared with the patients and will not be documented in the medical record.

- The top layer (fluid) will be used for biomarker measurements. Some tests will be performed in Cleveland Clinic, while some will be performed by outside laboratory. Some samples may have extra remaining volume after all tests are completed. This remaining sample fluid will be frozen and stored securely for future research. The samples will be labeled with unique identifiers and stored separately from the identifying sheet. Investigators may contact the patients in the future or review their medical records to obtain updated clinical information. Patients may request the samples to be returned or destroyed by contacting the principal investigator in writing: Carlos Higuera, MD, 9500 Euclid Ave/ Desk A41, Cleveland, Ohio 44195. This request will eliminate future release of samples and information to new investigators. However, if samples and information have already been released to an investigator, it cannot be returned. Any previous use of the sample cannot be retracted.

- The results will not be shared with anyone outside of research team.

2. ALTERNATIVES

What are the alternatives to participation in the research study?

- If you decide not to participate in this study, your care at Cleveland Clinic will not be affected. You will still receive standard of care (NSAIDs, steroid injections, total knee replacement).

3. RISKS

What are the risks of participating in the research study?

	Mild	Moderate	Severe
Likely **9%**	• Transient pain the injected joint		
Less Likely **1-4%**	• Back pain • Upper respiratory tract infection • Injury • Musculoskeletal pain • Joint swelling		

Rare **0-1%**	• Persistent pain in extremity • Osteoarthritis	• Infection	.

- However, because this is a small study, it is difficult for us to adequately quantify ALL of the risks that this procedure could entail.
- All data collected will be stored on password protected computers. No data will be transferred to portable devices or personal computers.

4. BENEFITS

What are possible benefits of participating in the research?

The potential benefit of this study includes the possibility of having less knee pain and possibly delaying knee replacement. Additionally, if you take part in this study; you may help others in the future as this technology may be used more frequently.

5. COSTS

Are there any costs to you if you participate in this study?

You and/or your insurance company will be responsible for:

- Usual and customary treatment and care involved prior to and following study period
- Transportation

The sponsor is responsible for (or, will pay the costs of):

- Study related visits, tests, and follow-up care

Note: Prior to starting the study your insurance company will be queried to see what you will be responsible for.

6. COMPENSATION

Are there any payments to you if you participate in this study?

You will be paid a stipend of $40 dollars for your initial visit, 1 week, 2 week, 6 week, 3 month, 6 month, 6 month+1 week, 6 month+2 weeks, 1-year, and 2-year visits. Additionally, you will be provided free parking for your initial visit, 1 week, 2 week, 6 week, 3 month, 6 month, 6 month+1 week, 6 month+2 weeks, 1-year, and 2-year visits.

The IRS requires CCF to report payments to an individual of $600 or greater (in a calendar year) on a Form 1099-MISC. Your name, address and social security number will be collected to track the payments made to you and, if you receive $600 or greater, will be used to process a Form 1099-MISC.

7. RESEARCH RELATED INJURY

What will happen if you are injured as a result of taking part in the research?

In the event you are injured as a result of participation in this research, medical care is available to you. The costs of such medical care will be billed to you or your insurance company. There are no plans to provide compensation for lost wages, direct or indirect losses. The Cleveland Clinic will not voluntarily provide compensation for research related injury. You are not waiving any legal rights by signing this form. Further information about research related injury is available by contacting the Institutional Review Board at (216) 444-2924.

8. PRIVACY AND CONFIDENTIALITY

What will happen to your information that is collected for this research?

Cleveland Clinic has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. Anyone who sees information about you must keep it confidential. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The only people who will know that you are in the research study and will see the information about you are members of the research team. There are a few limited exceptions that are discussed later in this section of the consent form. Otherwise, no one else will be able to see or use the information about you, or provided by you during the research, unless you give your written permission. When the study is over and the results are public, no information linked to you will be included unless you give your written permission.

9. CONFLICT OF INTEREST

Do the researchers or institution have any conflicts of interest relating to this study?

Dr. Carlos Higuera has no conflict of interest with Ferring pharmaceuticals – the sponsor of this study.

10. QUESTIONS

Who do you call if you have any questions or problems?

If you have any questions about the research or develop a research-related problem, you should contact Dr. Carlos Higuera at 216-636-1136. After non-business hours you should contact the Cleveland Clinic page operator at (216) 444-2200 and ask for the Orthopaedic resident on call if you develop medical problems after surgery. If you have questions about your rights as a research subject, you should contact the Institutional Review Board at (216) 444-2924.

11. VOLUNTARY PARTICIPATION

What are your rights as a research participant?

You do not have to join this study. You do not need to participate in this study to get treatment. If you do not join, your care at Cleveland Clinic will not be affected. You will still receive a total knee replacement as you would have previously.

Your participation in this study is voluntary. You may choose whether you wish to be in this study and whether to remain in the study at all times after enrollment. If you withdraw from the study, you will not lose any benefits to which you are entitled

1. If you want to stop being in the research study please notify Dr. Carlos Higuera at 216-636-1136.
2. If you leave the research study early you will still receive your regular medical care.
3. You will be informed of any new information that may affect your decision to continue in the study.

You may be taken out of the research study if:

- A bad effect develops and staying in the study would not be in your best interest.
- You fail to follow the instructions you are given.
- The study is cancelled.
- There may be other reasons that we do not know at this time.

12. SIGNATURES

Statement of Participant

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

_____
Printed name of Participant

_____ _____
Participant Signature Date

Statement of Person Conducting Informed Consent Discussion

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____
Printed name of person obtaining consent

_____ _____
Signature of person obtaining consent Date