Clinical Research Protocol

Utilization of a cutaneous therapy in situ microdevice

Protocol Number:	
Version Date:	11/11/25
Investigational Product:	Utilization of a cutaneous therapy in situ microdevice
IND Number:	
Development Phase:	
Sponsor:	Raymond Cho Department of Dermatology 1701 Divisadero St. 4th Floor San Francisco, CA 94143
Funding Organization:	
Principal Investigator:	Raymond Cho Telephone: (650)520-0208 E-mail: Raymond.cho@ucsf.edu

Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Raymond Cho with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number:

Protocol Title: MICRODEVICE-BASED CUTANEOUS THERAPY OPTIMIZATION

Protocol Date: 11/11/25

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Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Address _____

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Phone Number _____

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LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IF	Immunofluorescence
IHC	Immunohistochemistry
IRB	Institutional Review Board
PI	Principal Investigator
PK	Pharmacokinetic
SAE	Serious Adverse Experience

PROTOCOL SYNOPSIS

TITLE	**MICRODEVICE-BASED CUTANEOUS THERAPY OPTIMIZATION**
SPONSOR	Raymond Cho
FUNDING ORGANIZATION	None
NUMBER OF SITES	1
RATIONALE	This study will aim to establish the feasibility of clinical application of an *in situ* candidate drug screening microdevice in atopic dermatitis and psoriasis, and the ability of the device to predict response to FDA-approved standard of care skin disease treatments. We will also investigate preliminary correlations between drug response as assessed by the microdevice and molecular features of the treated rashes.
STUDY DESIGN	This is a pilot study aimed at determining the feasibility of using an in situ microdevice to measure local improvement in cutaneous inflammation to different FDA approved skin therapies.
PRIMARY OBJECTIVE	The primary objectives are to evaluate the safety of microdevice placement and removal based on assessment of adverse events, and to determine the feasibility of microdevice analysis based on the ability to place and retrieve the device with sufficient tissue, of sufficient quality, for downstream histopathology/molecular analysis and interpretation of at least 80% of the device reservoirs.
SECONDARY OBJECTIVES	The secondary objectives are to test feasibility of utilizing quantitative histopathologic assessment and/or transcriptional profiling to determine whether there is local improvement in lesional rash-affected skin with clinically relevant skin inflammation treating agents.
NUMBER OF SUBJECTS	20 patients
SUBJECT SELECTION CRITERIA	Inclusion Criteria: > 18 years of age, patients with atopic dermatitis or psoriasis; if female patient with child bearing potential (on oral contraceptive pills or intrauterine device for at least 30 days) Exclusion Criteria: None
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	After placement, the microdevice will dwell in lesional inflamed skin for approximately 72 +/- 24 hours, enabling micro-doses of drugs to be released from the reservoirs and elicit local responses.

CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	The in situ microdevice will contain a subset of the following FDA approved medications: Triamcinolone, 5-fluorouracil, Calcipotriene, Tapinarof, Crisaborole, Tacrolimus, Adalimumab, Etanercept, Certolizumab, Infliximab, Secukinumab, Ixekizumab, Apremilast, Risankizumab, Ustekinumab, Hydroxychloroquine, Methotrexate, Mycophenolate, Azathioprine, Chloroquine, Cyclosporine, Tofacitinib, Deucravacitinib, Dupilumab, Tralokinumab, Guselkumab, Tildrakizumab, Baractinib, Abrocitinib, Upadacitinib, Lebrikizumab, Nemolizumab, Ruxolitinib, Bimekizumab, Roflumilast.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The study will last ~3 days. The device is placed on day 0 and left in place for ~ 72 hours. If logistical issues arise, it is acceptable (i.e. not a deviation) for the device to be removed up to 104 hours after placement and still be evaluated for the research protocol. Please note that the biomaterials of the microdevice are acceptable from a safety standpoint for long-term dwelling in tissue.
CONCOMMITANT MEDICATIONS	Allowed: all Prohibited: none
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	The primary endpoint is the evaluation of the safety and feasibility of the microdevice, specifically assessing adverse events associated with device placement and removal. This endpoint is appropriate as it directly addresses the study's primary objective of evaluating the safety of microdevice placement and removal based on assessment of adverse events, and to determine the feasibility of microdevice analysis based on the ability to place and retrieve the device with sufficient tissue, of sufficient quality, for downstream histopathology analysis and interpretation of at least 80% of the device reservoirs.
SECONDARY ENDPOINTS	The secondary endpoint is feasibility testing for evaluation of local improvement in lesional rash-affected skin with clinically relevant skin inflammation treating agents using quantitative histopathologic assessment, immunofluorescence, and/or transcriptional profiling of skin tissue. This endpoint is appropriate as it directly addresses the study's eventual goal of measuring local improvement in lesional rash-affected skin.
OTHER EVALUATIONS	
SAFETY EVALUATIONS	Safety and feasibility of device placement and harvesting will be assessed per the criteria for the primary objectives. Additional safety

	and feasibility parameters will be documented for the retrieval process, including: 1. Any adverse events associated with the percutaneous retrieval procedure. 2. Any technical challenges or complications with the process of device retrieval. 3. Any logistical or workflow challenges with the device retrieval procedure. 4. Re-evaluation of biopsy site at follow-up visit in 14 days for wound infection.
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through Visit 2, an interim analysis for safety will be conducted by the investigator. Serious adverse events will be monitored by on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	The small region of tissue removed from the rash will be analyzed by multi-parameter immunohistochemistry (IHC), immunofluorescence (IF) and/or spatial transcriptomics to determine the anti-inflammatory effects of each drug being evaluated on the device at the end of the device implantation period. The transcriptomic analysis will be normalized and compared in microdose treated wells vs mock treated wells and differential expression discerned at a significance level of 5% in a single test, in a two-group comparison, using a Negative Binomial mode. Although the main goal here is qualitative analysis to assess whether IHC, IF, or transcriptomic approaches can be utilized on the acquired tissue samples.
Rationale for Number of Subjects	An initial cohort of at least 20 patients will have all their devices removed to initially establish the safety and feasibility of device placement and surgical retrieval, as well as post-retrieval processing and analysis. Safety and feasibility of device placement and harvesting will be assessed per the criteria for the primary objectives. Based on the results of these first 20 patients, subsequent enrolled patients in expansion cohort 2 will be selected based on having adequate thickness of skin lesions.

1. BACKGROUND

The product to be studied is an investigational microdevice designed for in situ drug testing atopic dermatitis and psoriasis. The device, measuring 750μm in diameter and 5mm in length, contains up to 20 drug-loaded reservoirs for percutaneous delivery. Its feasibility and safety will be assessed for predicting local cutaneous responses to standard-of-care therapies and exploring correlations with transcriptomic features and clinical outcomes in a pilot study.

Several IND protocols utilize this in situ therapy testing microdevice for cancers, the most relevant being IND #141449 (Principal Investigator: Dr. Oliver Jonas) for its utilization in cutaneous T-cell lymphoma, a type of skin cancer. We are adapting use of this in situ therapy testing microdevice to test therapies in atopic dermatitis and psoriasis (see letter of authorization to refer to IND #141449 from Oliver Jonas, PI). The differences in this study and the reference study IND 141449 do not pose new risks or potential adverse events. In addition, this same in situ therapy testing microdevice is used in UCSF IRB #23-38782.

A microdevice capable of testing the local in-vivo response to many distinct drug compounds or combinations by releasing microdoses of each into distinct regions of tissue is currently being utilized in cancer clinical trials. We aim to adapt this device for utilization in atopic dermatitis and psoriasis. Analyzing the tissue near the device enables assessment of local drug efficacy for each reservoir. The doses of the drugs and biologic products will not be increased under this protocol.

The microdevice is a small construct of cylindrical shape measuring 750μm in diameter and 5mm in length which houses up to 20 reservoirs (Notes Section 1, Figure 1). It is made of PEEK (poly-ether-ether-ketone), a biocompatible material used in other implantable constructs including joint replacements. PEEK has been shown to be safe for long-term residence in the body, and implantable medical devices made of the same materials have been FDA-approved for long-term use in patients. The microdevice is radio-opaque and can be visualized by x-ray, CT, ultrasound, and MRI. The device is nonferromagnetic and MRI-compatible.

Each of the reservoirs is loaded with a unique drug or combination of drugs, which are released into a small (non-overlapping) region of rash-affected skin. After the incubation period (typically 72 +/- 24 hours), the device is retrieved with surrounding tissue and this specimen is processed and analyzed (Notes Section 2, Figure 3). Crosstalk between drugs from different reservoirs is eliminated by appropriate spatial separation of reservoirs and by drug and matrix formulation to limit local drug diffusion. In this manner, the anti-inflammatory effect from each reservoir can be analyzed independently and by pathway-specific markers. Importantly, drug amounts per reservoir are typically less than 1/100,000 of the systemic dose given for each drug and therefore the risk of systemic toxicity is negligible (Notes Section 3).

In this study, the microdevice will have a guidewire attached to one end that will extend outside the participant's body. (Notes Section 2, Figure 2 and Figure 3). This guidewire will aid in device localization and minimally invasive and surgical retrieval procedures. The guidewire is a 0.004" NiTi ("nitinol") semi-flexible wire of up to 15cm in length. This particular wire is super-elastic and robust and is resistant to kinking. Nitinol is a nickel-titanium alloy, which is considered safe for long-term implantation and is currently used in many interventional devices, including implantable venous filters, vascular stents, and vascular guidewires. As nickel is a common contact allergen, to minimize any risk of a local cutaneous allergic contact dermatitis, the wire will be secured to the skin with underlying gauze in participants with a known nickel allergy.

1.1 Overview of Non-Clinical Studies

This microdevice was used in a murine model of human melanoma, breast, and prostate cancer and was shown to predict systemic efficacy across multiple tumor models. It also demonstrated the ability to assay drug effect locally and show excellent predictive value for systemic efficacy for a range of anti- cancer drugs and tumor models. (Jonas, O., Landry, H. M., Fuller, J. E., Santini, J. T., Jr, Baselga, J., Tepper, R. I., Cima, M. J., & Langer, R. (2015). An implantable microdevice to perform high-throughput in vivo drug sensitivity testing in tumors. Science translational medicine, 7(284), 284ra57. https://doi.org/10.1126/scitranslmed.3010564.)

Furthermore, this microdevice technology utilized paclitaxel and doxorubicin in a patient-derived murine model of breast cancer and showed that the microdevice response correlated directly with the systemic drug response in this model for each of the drugs tested. (Tatarova, Z., et al (2022). A multiplex implantable microdevice assay identifies synergistic combinations of cancer immunotherapies and conventional drugs. *Nature Biotechnology*, *40*(12), 1823–1833.)

1.2 Overview of Clinical Studies

This in situ microdevice was utilized in six patients with high grade gliomas, who received drug releasing intratumoral microdevices containing temozolomide, lomustine, irinotecan, carboplatin, lapatinib, osimertinib, abemaciclib, everolimus, and doxorubicin. This study demonstrated the safety of usage of intratumoral microdevices and their efficacy in obtaining patient specific drug response profiling. None of the enrolled patients experienced either immediate (within 48 hours after surgery) or delayed (within 30 days) adverse events related to the microdevice. All twelve out of the twelve microdevices were successfully retrieved from the patient, and bloodwork remained stable before and after the operation. (Peruzzi P et al. Intratumoral drug-releasing microdevices allow in situ high-throughput pharmaco phenotyping in patients with gliomas. *Sci Transl Med* 2023;15(712):eadi0069.)

An additional study further demonstrated the safety and feasibility of this implantable microdevices in patients with non-small cell lung cancer undergoing resection. In this study, the microdevice contained 12 chemotherapeutic drugs, and was inserted into tumors

and successfully retrieved 13 out of the 14 times. The last microdevice remaining did not cause any adverse effects. There were no severe adverse reactions observed in the patients, and bloodwork revealed no detection of chemotherapeutic agents, allowing for high-throughput localized drug delivery. (Tsai LL et al. First-in-Human Intrathoracic Implantation of Multidrug-Eluting Microdevices for In Situ Chemotherapeutic Sensitivity Testing as Proof of Concept in Nonsmall Cell Lung Cancer. *Ann Surg* 2023;277(5):e1143-e1149.)

2. STUDY RATIONALE

Studying the microdevice in patients with atopic dermatitis or psoriasis addresses challenges in assessing local cutaneous responses to treatments without systemic toxicities. Given that moderate-to-severe rash affected patients fail to adequately respond to targeted therapies ~20-40% of the time, this novel approach aims to predict individual patient responses and personalize treatment strategies. If this approach is successful, it would decrease costs (biologic targeted therapies average ~$30,000-40,000/year) and minimize systemic adverse effects that occur with immunosuppression, as well as decrease the time until a patient achieves successful response to skin therapy. This information is crucial for advancing personalized therapies and understanding the correlation between local drug responses and clinical outcomes in these inflammatory conditions.

2.1 Risk / Benefit Assessment

Risks associated with the microdevice will be mitigated through minimally invasive procedures, careful localization, and local anesthesia. The potential benefits, including personalized treatment insights without systemic toxicities, outweigh procedural risks. The study builds on successful trials and ongoing safety assessments, justifying the manageable risks for valuable contributions to treatment strategies.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objectives are to evaluate the safety of microdevice placement and removal based on assessment of adverse events, and to determine the feasibility of microdevice analysis based on the ability to place and retrieve the device with sufficient tissue, of sufficient quality, for downstream histopathology analysis and interpretation of at least 80% of the device reservoirs.

3.2 Secondary Objectives

The secondary objectives are to test feasibility of utilizing quantitative histopathologic assessment and/or transcriptional profiling to determine whether there is local improvement in lesional rash-affected skin with clinically relevant skin inflammation treating agents.

4. STUDY DESIGN

4.1 Study Overview

This is prospective pilot study evaluating the safety and feasibility of an investigational microdevice for in situ drug testing in patients with atopic dermatitis and psoriasis. The pilot study will determine the feasibility of using an *in situ* microdevice to measure local lesional rash-affected skin response to FDA-approved treatments used for atopic dermatitis and psoriasis. The microdevice is a drug delivery chamber smaller than a grain of rice with reservoirs that delivers up to 20 drugs of any class (small molecules and monoclonal antibodies) into spatially distinct regions of a rash, matching intra-lesional skin concentrations to those from systemic dosing. This allows for direct assessment of local cutaneous responses. It is delivered percutaneously and retrieved 72 hours after implantation by excising the device along with surrounding tissue through use of a standard 6 mm skin punch biopsy tool. This device allows testing of a range of relevant drugs directly inside the actual rash-affected skin, preserving the native rash physiology and, importantly, avoiding systemic toxicities. This study will aim to establish the feasibility of clinical application of an *in situ* candidate drug screening microdevice in atopic dermatitis and psoriasis, and the potential ability of the device to predict cutaneous response to standard of care.

The primary objectives are to evaluate the safety of microdevice placement and removal based on assessment of adverse events, and to determine the feasibility of microdevice analysis based on the ability to place and retrieve the device with sufficient tissue, of sufficient quality, for downstream histopathology analysis and interpretation of at least 80% of the device reservoirs. The secondary objectives are to test feasibility of utilizing quantitative histopathologic assessment and/or transcriptional profiling to determine whether there is local improvement in lesional rash-affected skin with clinically relevant skin inflammation treating agents. The study aims to establish the potential clinical application of the microdevice in predicting systemic responses to standard-of-care therapies.

Device placement:

The small size of the microdevice enables its placement via a percutaneous approach using an 18-gauge needle, a fraction of the size compared to standard punch tools for skin biopsies. For more information, please see Notes Section 2.

After placement, the microdevice will dwell in the tissue for approximately ~72 hours, enabling micro-doses of drugs to be released from the reservoirs and elicit local inflammatory responses.

Device retrieval:

To analyze the effects on the tissue, the microdevice will be removed along with a rim of intact surrounding tissue. Microdevice retrieval can be achieved through two approaches,

using dermatologic procedural techniques, similar to obtaining a skin punch biopsy, or surgical excision (as a backup). Given the straightforward nature and minimal risk involved in utilizing a 6 mm punch biopsy tool, this technique will be employed for microdevice retrieval. In the event the punch biopsy tool cannot retrieve the microdevice in totality, participants may undergo surgical excision of skin with embedded microdevice. For more information, please see Notes Section 2.

5. CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint is the evaluation of the safety and feasibility of the microdevice, specifically assessing adverse events associated with device placement and removal. This endpoint will be assessed from baseline to the completion of the microdevice retrieval, which occurs approximately 72 +/- 24 hours after implantation. This endpoint is appropriate as it directly addresses the study's primary objective of evaluating the safety of microdevice placement and removal based on assessment of adverse events, and to determine the feasibility of microdevice analysis based on the ability to place and retrieve the device with sufficient tissue, of sufficient quality, for downstream histopathology analysis and interpretation of at least 80% of the device reservoirs.

5.2 Secondary Efficacy Endpoints

The secondary endpoint is the evaluation of local improvement in lesional rash-affected skin with clinically relevant skin inflammation treating agents using quantitative histopathologic assessment, immunofluorescence, and/or transcriptional profiling of skin tissue. This endpoint is appropriate as it directly addresses the study’s eventual goal of measuring local improvement in lesional rash-affected skin.

5.3 Safety Evaluations

The safety evaluations in the study include:

1. Adverse Events Assessment:

   - Monitor and record adverse events associated with microdevice placement and retrieval procedures.

2. Technical Challenges or Complications:

   - Document any technical challenges or complications during the device retrieval process.

3. Logistical or Workflow Challenges:

   - Assess any logistical or workflow challenges related to the device retrieval procedure.

4. Complications of Microdevice Placement:

   - Evaluate for any complications arising from the microdevice placement, as assessed by a dermatologist.

5. Interim Adverse Events Monitoring:

- Monitor for any intercurrent adverse events following microdevice placement and record them.

Rationale: These safety evaluations aim to comprehensively assess the safety profile of the microdevice, covering adverse events, technical aspects, and logistical considerations associated with both placement and retrieval procedures.

Importantly, drug amounts per reservoir are typically less than 1/100,000 of the systemic dose given for each drug and therefore the risk of systemic toxicity is negligible (Notes Section 3). Thus, it is not necessary to evaluate the safety of each drug or biologic individually.

6. SUBJECT SELECTION

6.1 Study Population

The subject population consists of 20 individuals diagnosed with atopic dermatitis or psoriasis who are over the age of 18, with considerations for the suitability of skin lesions for microdevice placement. Exclusion criteria may apply for safety and feasibility reasons.

6.2 Inclusion Criteria

A confirmed diagnosis of atopic dermatitis or psoriasis, and the presence of suitable skin lesions for microdevice placement. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

7. CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

All

7.2 Prohibited Medications and Treatments

None

8. STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

There is only one treatment group.

8.2 Blinding

There is no blinding or need for blinding in this study.

8.3 Formulation of Test and Control Products

See Notes Section 3 and below for more details.

8.3.1 Formulation of Test Product

For this pilot study, the drugs used in the study will include standard medications used for treatment of atopic dermatitis and psoriasis. All the drugs are FDA approved for use in patients. The in situ microdevice will contain a subset of the following: Triamcinolone, 5-fluorouracil, Calcipotriene, Tapinarof, Crisaborole, Tacrolimus, Adalimumab, Etanercept, Certolizumab, Infliximab, Secukinumab, Ixekizumab, Apremilast, Risankizumab, Ustekinumab, Hydroxychloroquine, Methotrexate, Mycophenolate, Azathioprine, Chloroquine, Cyclosporine, Tofacitinib, Deucravacitinib, Dupilumab, Tralokinumab, Guselkumab, Tildrakizumab, Baractinib, Abrocitinib, Upadacitinib, Lebrikizumab, Nemolizumab, Ruxolitinib, Bimekizumab, Roflumilast.

See Notes Section 3 for further details.

8.3.2 Formulation of Control Product

Pure PEG (polyethylene glycol) will be used as a control.

8.3.3 Packaging and Labeling

Each microdevice will harbor up to 19 FDA-approved drugs relevant to the treatment of atopic dermatitis and psoriasis, including those that are standard-of-care. Each drug or drug combination will be released from multiple, separate reservoirs. One reservoir will harbor a drug vehicle (PEG) only. For this pilot study, the drugs used in the study will include standard agents used for treatment of atopic dermatitis and psoriasis. All the drugs must be FDA approved for use in patients. In future studies, additional investigational drugs may be added via appropriate procedures.

8.4 Supply of Study Drug at the Site

Drugs will be paid for by the study and will be purchased through the research pharmacy. There will be no charge to patients for the drugs used in this study.

8.4.1 Dosage/Dosage Regimen

Microdevice Description: The microdevice is a small construct measuring 750μm in diameter and 5mm in length (Notes Section 1, Figure 1). It contains up to 20 reservoirs, each loaded with a unique drug or combination of drugs. The drugs are released into small, non-overlapping regions.

8.4.2 Dispensing

Drug Delivery: The microdevice is placed percutaneously using an 18-gauge needle. Once placed, it remains in the tissue for approximately 72 +/- 24 hours, allowing microdoses of drugs to be released from the reservoirs and elicit local responses.

8.4.3 Administration Instructions

The device and medication will be administered by the investigators. See Notes Section 3 for further details.

8.4.4 Storage

Loaded Microdevice will be stored at 4ºC in either UCSF research pharmacy or DFCI pharmacy.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

9. STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A skin examination will be performed by either the investigator or a sub investigator who is a physician at Screening.

9.1.5 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

10. EVALUATIONS BY VISIT

10.1 Visit 1. Screening Visit and Device Placement: **For more information on device placement, please see Notes Section 2**

1. Identification of eligible patients with confirmed atopic dermatitis or psoriasis.
2. Review the study with the subject (or subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
3. Assign the subject a unique screening number.
4. Record demographics data.
5. Record medical history, including history of rash, diagnosis date, and prior treatments.
6. Record concomitant medications.
7. Perform a skin examination.
8. Percutaneous placement of microdevices (1 each in 2 separate skin lesions, totaling 2 microdevices per patient) with local anesthesia (1% lidocaine with 1:100,000 epinephrine) administered intra-dermally, careful taping of the guidewire to the skin, covered with a sterile bandage to prevent dislodgement.
9. Monitoring of the patient for a short time (15 minutes) after device placement.
10. Patients will be provided with verbal and written instructions and a phone number to call with questions after discharge. Female patients of childbearing age will be instructed that they should continue current oral contraceptive pills or intrauterine device for 30 days after the device retrieval visit.

10.2 Visit 2. Device Retrieval Visit: (Approximately 72 +/- 24 hours after device implantation) **For more information on device retrieval, please see Notes Section 2**

1. Scheduled for approximately 72 +/- 24 hours after device implantation.
2. Evaluation by a dermatologist to assess adverse events.
3. Percutaneous retrieval of microdevices using a 6 mm skin biopsy punch tool.
4. Clean skin. Local anesthesia (1% lidocaine with 1:100,000 epinephrine) delivered in a ring block via a 30-gauge needle.

5. Take sample(s), place suture. Patient will be offered either absorbable sutures (does not require follow up visit), offered a suture removal kit (to remove stiches at home by themselves), or have a follow up visit lasting for a few minutes to remove sutures.
6. If retrieval via punch biopsy tool is unsuccessful, patients may undergo surgical excision. In patients needing surgical excision, the procedure will be scheduled to occur within 14 days of the implantation.
7. Post-retrieval assessment of adverse events.
8. Discharge instructions for home care.

Optional: Visit 3 (~2 weeks after Visit #2)

1. Remove suture.

2. Inspect biopsy site(s) to rule out infection.

3. Record any adverse experiences

4. Alternatively, this visit can be skipped, and the patient will be provided with a suture removal kit and can self-remove sutures (this is an option that we provide to patients in clinical practice to minimize inconvenience of a return visit for suture removal only)

11. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Dr. Raymond J. Cho should be contacted directly at this number to report medical concerns or questions regarding safety. Phone: (650)520-0208.

12. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Device

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Subjects who discontinue study treatment early should still be offered a visit for suture removal.

12.3 Replacement of Subjects

Subjects who withdraw from the study will be replaced.

13. PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary

endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Failure to comply with Good Clinical Practice (GCP) guidelines

The investigator Raymond Cho will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

14. STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who consent to the study and have a skin sample taken will have data analyzed.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, rash type and biopsy site.

14.3 Analysis of Primary Endpoint

Safety and tolerability data will be summarized. Postoperative follow up for each patient will be performed, and adverse events associated with device placement and removal will be tabulated and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study device. This endpoint will be assessed from baseline to the completion of the microdevice retrieval, which occurs approximately 72 +/- 24 hours after implantation.

14.4 Analysis of Secondary Endpoints

Histopathologic assessment will measure local cutaneous response to anti-inflammatory agents using histopathologic assessment. We will perform concomitant genomic, immunofluorescence, and transcriptomic analysis with assessment of local drug response to explore whether the skin/microdevice samples provide adequate tissue of sufficient quality for these types of analyses.

Devices left in place longer than 104 hours will not be included in the data analysis but may be removed with subsequent surgical procedures (up to 14 days later), although the biomaterials of the microdevice are acceptable from a safety standpoint for long-term dwelling in tissue.

14.5 Sample Size and Randomization

There will be 20 patients. This is a non-randomized study.

15. DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the investigator but will be identified by deidentified subject number. If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Study funder (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

Leftover biological specimens may be saved for future research with optional ICF patient consent.

15.4 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation submitted to the Study funder. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement. Study funder will only receive deidentified data.

16. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol, and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to Study funder prior to the shipment of study supplies to

the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SCHEDULE OF STUDY VISITS

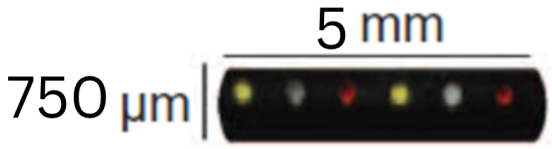
	VISIT 1 **Screening Visit and Device Placement**	**VISIT 2** **Device Retrieval Visit** **(72 +/- 24 hours after device placement)**	**VISIT 3** **Optional Suture Removal Visit** **(~2 weeks after Visit 2)**
Informed Consent	**X**		
Demographics Data	**X**		
Medical History	**X**		
Concomitant Medications	**X**		
Skin Examination	**X**	**X**	
Placement of Microdevices	**X**		
Monitoring (15 minutes)	**X**		
Adverse Experiences		**X**	
Skin Biopsy		**X**	
Retrieval of Microdevices		**X**	
Provide Verbal and Written Discharge Instructions	**X**	**X**	
(If applicable) Schedule surgical excision procedure within 14 days of implantation		**X**	
Suture removal and biopsy site check			**X**

NOTES:

Section 1: Concept for in-vivo drug sensitivity assay and description of device

The microdevice is a drug delivery chamber smaller than a grain of rice with reservoirs that delivers up to 20 drugs of any class (small molecules and monoclonal antibodies) into spatially distinct regions of a rash, matching intra-lesional skin concentrations to those from systemic dosing. This allows for direct assessment of local cutaneous responses. During implantation, drugs diffuse into confined regions. Each such region can be assayed independently to assess the specific response of a given drug. Following incubation, a second biopsy procedure is administered in which a coring needle selectively retrieves a small column of tissue that immediately surrounds the device. This tissue contains the regions of drug diffusion and is sufficient for determination of efficacy of drugs. Adapted from Jonas, O., Landry, H. M., Fuller, J. E., Santini, J. T., Jr, Baselga, J., Tepper, R. I., Cima, M. J., & Langer, R. (2015). An implantable microdevice to perform high-throughput in vivo drug sensitivity testing in tumors. *Science translational medicine*, *7*(284), 284ra57. https://doi.org/10.1126/scitranslmed.3010564.

Figure 1. Representative depiction of in situ microdevice



Section 2: Percutaneous device placement and retrieval

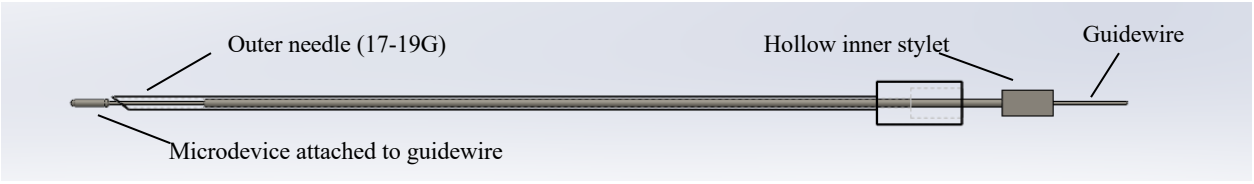
Device Delivery:

The small size of the microdevice enables its placement via a percutaneous approach using an 18-gauge needle, a fraction of the size compared to standard punch tools for skin biopsies.

In the current study, a coaxial system comprising a 18G metal outer needle and an inner hollow needle stylet will be used for microdevice delivery (see below figure). The microdevice is placed at the tip of the delivery needle and the guide wire is coaxially placed inside the inner stylet. Bone wax is placed at the tip of the needle, keeping the microdevice from prematurely advancing beyond the needle tip. The entire coaxial delivery needle is guided to the desired depth determined by markings on the delivery needle, which will be no more than 5-6mm deep. Once satisfactory location of the needle is clinically assessed by visual examination, the inner stylet is advanced at least 5mm to deploy/release the microdevice. The needle and inner stylet is then removed over the guidewire, leaving

the microdevice and guidewire in place. The external portion of the guidewire is secured to the participant's skin using a sterile adhesive cover to prevent dislodgement.

Figure 2.



Microdevice implantation apparatus: An outer needle houses an inner hollow stylet and an innermost guidewire with microdevice at its tip. The microdevice attached to the end of the guidewire is deployed into tissue by advancing the inner stylet. This is similar to the mechanism used for deploying fiducial markers and brachytherapy seeds.

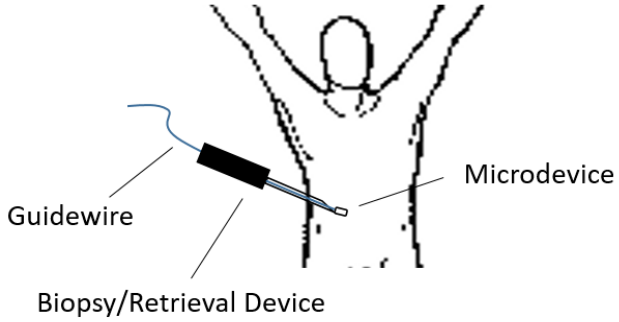
After placement, the microdevice will dwell in the tissue for approximately 72 +/- 24 hours, enabling micro-doses of drugs to be released from the reservoirs and elicit local inflammatory responses.

Device retrieval:

To analyze the effects on the tissue, the microdevice will be removed along with a rim of intact surrounding tissue. Microdevice retrieval can be achieved through two approaches, using dermatologic procedural techniques, similar to obtaining a skin punch biopsy or surgical excision. Given the straightforward nature and minimal risk involved in utilizing a punch biopsy tool this technique will be employed for microdevice retrieval. In the event the punch biopsy tool cannot retrieve the microdevice in totality, participants may undergo surgical excision of skin with embedded microdevice.

The retrieval procedure is as follows: The sterile adhesive covering is removed from the participant and the guidewire extending from the participant is straightened. The 6 mm skin biopsy punch tool is placed coaxially around the guidewire (see below figure). The biopsy tool is advanced to the hub of the tool, ensuring a full thickness biopsy from epidermis to subcutaneous fat. Following biopsy device advancement into the participant, the tissue to be removed is lift with the use of forceps or the guide wire and cut at the base in the subcutaneous fat, allowing sampling/cutting of the tissue surrounding the microdevice. The microdevice and tissue is submitted in formalin for histopathologic analysis.

Figure 3.



Microdevice retrieval: Biopsy

The retrieval device is guided to the edge of the microdevice over the guidewire (image not to scale). After satisfactory position of the biopsy device, it will be inserted into the skin to the subcutaneous fat around the microdevice to the cut surrounding tissue, and the tissue/microdevice is removed from the participant.

Section 3: Description, Form, Storage and Stability, Compatibility

All agents used in this study are FDA approved for use in atopic dermatitis and psoriasis.

3.1 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, will undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

3.2 Availability

Drugs will be obtained directly from the DFCI (Dana Farber Cancer Institute) pharmacy. Drugs are commercially available agents available from various manufacturers. The specific manufacturer will be determined by the DFCI formulary.

3.3 Preparation

The drug will be prepared, mixed with polyethylene glycol matrix, and loaded into the microdevice in a sterile manner in the Jonas laboratory at BWH Harvard), using protocols developed with the FDA. Each step in the process will be monitored by a research pharmacist and recorded on a checklist. Of note, the volume of each reservoir is physically limited in capacity so there is a maximum amount of drug solution that can be added per reservoir. Pure PEG (polyethylene glycol) will be used in control conditions.

3.4 Administration

Drugs will be released from the microdevice into local tissues. The drug will be released from the microdevice via passive diffusion, as has been extensively characterized in pre-clinical studies. The drug will only penetrate the local cutaneous tissues. The duration of drug release will be for a period of 72 +/- 24 hours while the microdevice is in the skin prior to retrieval. The local tissue is retrieved along with the microdevice, and no residual drug will remain.

The drug amounts released from a given reservoir on the microdevice into the skin are approximately 1 microgram which is on the order of one-millionth of the systemic dose. The FDA defines "micro-doses as <1% of the total systemic dose" and provides streamlined approval for human testing of compounds at these doses. The doses released from the microdevices are less than a thousandth of what the FDA terms a microdose. Additionally, per the microdevice structure and preliminary data, the drugs will only be released 300-400 micrometers into the local tissue area. This region containing virtually all of the drug is then removed from the body during microdevice retrieval. Nonetheless, even if the entire contents of drug in the device were to reach the systemic circulation in some manner, they would be many thousands of times less than a physiologically relevant dose and therefore would have a minimal impact on the patient.

The microdevice will only remain in place for 72 +/- 24 hours until its removal at surgery.

3.5 Ordering

Drugs will be obtained from the DFCI pharmacy or directly from manufacturers.

3.6 Accountability

All drugs will be dispensed from the DFCI pharmacy using standard procedures. Drugs will be loaded into the microdevice and tracked in detail under the supervision of a research pharmacy. The microdevices containing drug will be tracked during sterilization, transfer, and storage until implanted and retrieved from patients. The investigator and clinical research team will be responsible for maintaining records of the inventory using standard drug accountability forms.

3.7 Destruction and Return

Any excess drug at the time of microdevice loading will be disposed of in the research pharmacy per standard procedures. Any unused microdevices will be destroyed following proper procedures for disposal of biohazardous materials.