TITLE: First-in-Human Study of ^{111}In-XYIMSR-01 SPECT/CT in Patients with Metastatic Clear Cell Renal Cell Carcinoma

Johns Hopkins University

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^{111}In-XYIMSR-01 FDA IND#: 153295

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1. BACKGROUND

1.1 Study Disease(s)

Renal cell carcinoma (RCC) & Carbonic Anhydrase IX (CAIX): Renal cell carcinoma (RCC) is the most common neoplasm of the kidney [1], with an estimated 60,000 patients diagnosed annually in the United States [2]. Among cases of RCC, the clear cell subtype (ccRCC) is the most prevalent, accounting for up to 70% of RCCs [3–5]. Common to ccRCC is loss of the Von Hippel-Lindau (*VHL*) tumor suppressor gene [6]. Loss of *VHL* in turn leads to over-expression of carbonic anhydrase IX (CAIX) [7], a membrane-associated enzyme responsible for catalyzing the reversible hydration of carbon dioxide to a bicarbonate anion and a proton [8, 9]. Overexpression of CAIX is known to be presented in approximately 95% of ccRCC tumor specimens [10–12], making it a useful biomarker for this disease.

CAIX has limited expression in normal tissues with the exception of the gastrointestinal tract, gallbladder and pancreatic ducts [8, 9, 13–15]. Feasibility for the non-invasive detection of ccRCC based on CAIX expression has been proved with the radiolabeled antibody G250 [16] and its potential clinical applications has been reviewed previously [17]. However, antibodies as molecular imaging agents suffer from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2–5 days or longer) and non-specific organ uptake. Low molecular weight agents demonstrate faster pharmacokinetics and higher specific signal within clinically convenient times after administration. Low molecular weight agents can also be synthesized in radiolabeled form more easily, and may offer a shorter path to regulatory approval [18].

Targeting CAIX with small molecule inhibitors has proved challenging in part because there exists fifteen human isoforms of carbonic anhydrase. These isoforms share common structural features, including a zinc-containing catalytic site, a central twisted β-sheet surrounded by helical connections, and additional β-strands. The isoforms, however, vary widely in terms of intracellular location, expression levels, and tissue distribution [8, 9]. Significant effort has been expended on the development of sulfonamides and other low molecular wright CAIX ligands for nuclear imaging, but most reported agents have been fraught with low tumor uptake and significant off-target accumulation [19–24]

^{111}In-XYIMSR-01. In 2015 Wichert and co-workers identified a promising dual-motif inhibitor of CAIX from a DNA-encoded chemical [25]. We subsequently improved upon this agent by replacing the IRDye750 portion of their molecule with the hydrophilic species 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which enables convenient radiolabeling with metal isotopes for positron emission tomography (PET), single photon emission computed tomography (SPECT), and radiopharmaceutical therapy [26, 27]. We have termed this agent XYIMSR-01 have previously reported our pre-clinical experience with an indium-111 labeled (^{111}In) version of the molecule [27]. SPECT imaging of immunocompromised mice bearing CAIX-expressing SK-RC-52 tumors revealed radiotracer uptake in tumor as early as 1 hour post-injection. Biodistribution studies demonstrated 26% injected dose per gram of radioactivity within tumor at 1 hour. At 24 hours post-injection, Tumor-to- blood, muscle, and kidney, ratios were 178.1 ± 145.4, 68.4 ± 29.0 and 1.7 ± 1.2, respectively. Retention of radioactivity was exclusively

observed in tumors by 48 hours, the latest time point evaluated. In total, imaging with ^{111}In-XYIMSR-01 enabled specific detection of ccRCC in this xenograft model, with pharmacokinetics surpassing those of previously described radionuclide-based probes against CAIX.

Dosimetry. Using the biodistribution data generated in the paper by Yang et al. we have estimated the human dosimetry for ^{111}In-XYIMSR-01 agent.

Target Organs	Organ Dose (rem/mCi)	Organ Dose (mSv/MBq)
Adrenals	1.60E-01	4.31E-02
Brain	3.82E-02	1.03E-02
Breasts	6.07E-02	1.64E-02
Gallbladder Wall	1.54E-01	4.15E-02
Lower Large Intestine	1.24E-01	3.36E-02
Small Intestine	1.38E-01	3.73E-02
Stomach Wall	1.47E-01	3.97E-02
Upper Large Intestine	1.21E-01	3.28E-02
Heart Wall	1.38E-01	3.74E-02
Kidneys	4.74E-01	1.28E-01
Liver	1.79E-01	4.84E-02
Lungs	3.43E-01	9.28E-02
Muscle	1.67E-01	4.51E-02
Ovaries	1.39E-01	3.74E-02
Pancreas	1.72E-01	4.65E-02
Red Marrow	1.00E-01	2.71E-02
Osteogenic Cells	1.47E-01	3.98E-02
Skin	6.19E-02	1.67E-02
Spleen	1.59E-01	4.30E-02
Testes	9.07E-02	2.45E-02
Thymus	1.23E-01	3.32E-02
Thyroid	1.14E-01	3.08E-02
Urinary Bladder Wall	1.29E-01	3.49E-02
Uterus	1.35E-01	3.66E-02
Total Body	1.34E-01	3.63E-02

Based on the presented data, we have determined the kidneys to be dose limiting at 0.474 rem/mCi. In accordance with the guidance found in 21 CFR 361.1, 10.55 mCi may be administered to patients in this study.

Toxicology. The toxicology of cold $^{113/115}$In-XYIMSR-01 has been studied. Administration of $^{113/115}$In-XYIMSR-01 at doses of 11 and 55 µg/kg was well tolerated by male and female Sprague-Dawley rats. No consistent or treatment-related effects were observed with respect to the following endpoints: survival; clinical signs; body weight; clinical chemistry, hematology,

and urinalysis parameters; absolute or relative organ weights; or histopathology. These data support the safety of administering ^{111}In-XYIMSR-01 to human subjection.

2. OBJECTIVES

2.1 Primary Objectives:

The primary objective of this study is to evaluate the safety, tolerability, and feasibility of ^{111}In-XYIMSR-01 SPECT/CT in patients with metastatic ccRCC.

2.2 Secondary Objectives:

- To determine the biodistribution and radiation dosimetry of ^{111}In-XYIMSR-01.
- To characterize the pharmokinetics of ^{111}In-XYIMSR-01.
- To assess the concordance of findings on ^{111}In-XYIMSR-01 SPECT/CT with conventional imaging.

3. STUDY DESIGN AND SUBJECT POPULATION

3.1 Study design

The study is phase I, open label, single-arm study designed to evaluate the safety, tolerability, and feasibility of ^{111}In-XYIMSR-01 SPECT/CT in patients with metastatic ccRCC.

3.2 Eligibility Criteria

Inclusion Criteria:

1. Males or female sex
2. ≥18 years of age
3. Willingness to provide signed informed consent and comply with all protocol requirements
4. Histological confirmation of RCC with a clear cell component
5. 2-10 sites of disease measuring ≥1.5 cm on contrast-enhanced CT and/or MRI imaging of the chest, abdomen and pelvis performed ≤60 days prior to the date of study enrollment
6. Screening clinical laboratory values as specified below:
    - Serum bilirubin ≤ 1.5 times the upper limit of normal. For patients with known Gilbert's syndrome, ≤3 × ULN is permitted
    - ALT ≤ 3 times the upper limits of normal
    - AST ≤ 3 times the upper limits of normal
    - Creatinine clearance ≥50 mL/min based on Cockcroft-Gault formula
    - Absolute neutrophil count ≥ 1,500 /mm^3
    - Platelets ≥100,000/mm^3
    - Hemoglobin ≥ 9.0 g/dL
    - White blood cell count ≥ 2,000/mm^3

Exclusion criteria:

- Systemic therapy for the treatment of ccRCC within 12 months of study enrollment.
- Subjects administered any radioisotope within five physical half-lives prior to study drug injection.
- Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise obtaining reliable data, achieving study objectives, or completion.
- Women of child-bearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the imaging day.
- Women must not be breastfeeding.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. This study will not select subjects based on sex/gender and racial/ethnic group members.

4. STUDY PROCEDURES

	Screening/ Baseline[9]	^{111}In-XYIMSR-01 Dosing and SPECT/CT Imaging	^{111}In-XYIMSR-01 SPECT/CT	Follow-Up visit
	Day-30 to Day 1	Day 1	Day 2, and Day 3 post-injection (24± 1 hour, and 48± 1 hour post-injection)	Within 7 Days from ^{111}In-XYIMSR-01 Administration
Informed Consent & Eligibility	X			
Demographics (date of birth, race, ethnicity)	X			
Medical History	X			
Vital Signs (Blood Pressure, Heart Rate, Temperature)[1]	X	X[1]	X	
Height and weight	X	X	X	
Clinical Labs (Hematology, Chemistry)[2]	X	X	X[10]	
Urinalysis	X			
Pregnancy test[3]	X	X		
Study Sample Collection[4]		X		
12-Lead Electrocardiogram (ECG)	X	X[5]	X[11]	
^{111}In-XYIMSR-01 Administration[6]		X		
SPECT/CT[7]		X	X	
Adverse Events		X	X	X
Concomitant Medications	X	X	X	X
Standard-of-care Conventional Imaging Review	X			X
Standard-of-care Archived Tumor Tissue or Recent Tumor Biopsy	X			
Follow-Up phone call[8]				X

[1] On Day 1 Vital Signs (Blood Pressure, Heart Rate, Temperature) will be performed before ^{111}In-XYIMSR-01 Administration injection and at the end of ^{111}In-XYIMSR-01 SPECT/CT

[2]Standard of care comprehensive metabolic panel to include measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase.
Standard of care CBC: WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), WBC count, RBC count, Hematocrit, Hemoglobin, Platelets.

[3] For females of childbearing potential, a negative serum or urine pregnancy test will be obtained within a 24-hour period prior to SPECT/CT study.

[4] Blood samples will be collected at the following time points: pre-dose, 5±2 minutes, 10±2 minutes, 20±5 minutes, 30±5 minutes, 1±0.25 hour, 1.5±0.25 hour, and 24 hours ± 1 hour, post-injection to estimate elimination half-life. About 5 mL of blood will be collected in a heparinized tube at each time point via a peripheral vein.
[5] A 12-lead electrocardiogram will be performed just prior to ^{111}In-XYIMSR-01 administration and immediately following SPECT/CT imaging
[6]Patients will receive 10.5±1 mCi of radiotracer via an intravenous catheter placed in an antecubital vein or an equivalent venous access.
[7] SPECT/CT will be acquired at 2-4, 24± 1 hour, and 48± 1 hour post-injection. For the first three enrolled patients, a total of three fields of view will be acquired and for the remaining 7 patients two fields of view will be acquired. Each SPECT acquisition will be acquired over a 20-30 minute period.
[8] A safety phone call will also occur 7(±3) days post-dosing. Ongoing adverse events thought to be related to ^{111}In-XYIMSR-01 will be followed until resolution of the adverse event, until an alternate cause has been identified, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that ^{111}In-XYIMSR-01 is not the cause of the adverse event.
[9] In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person research study visits or portions of research study visits where determined to be appropriate and where determined by the investigator not to increase the participants' risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.
[10] Safety blood tests: comprehensive metabolic panel to monitor blood chemistries, including kidney and liver function, and blood cell count will be collected at the end of 48 hour SPECT/CT imaging.
[11] A 12-lead electrocardiogram will be conducted at the end of 48 hour SPECT/CT imaging.

Pharmacokinetics & Imaging Timepoints:

Procedure	Pre-dose	0 hour	5± 2min.	10± 2 min.	20± 2 min.	30± 5 min.	60± 25 min.	90± 25 min.	2-4 hour	24± 1 hour	48± 1 hour
^{111}In-XYIMSR-01 Administration		X									
Blood & Plasma Collection	X		X	X	X	X	X	X		X	
^{111}In-XYIMSR-01 SPECT/CT Imaging									X	X	X

5. CRITERIA FOR DISCONTINUATION: CANCELLATION/WITHDRAWL PROCEDURES AND EARLY STOPPING RULES.

5.1 Cancellation Guidelines

If a participant does not receive an injection of the radiotracer, the participant may be canceled. Reasons for cancellation must be documented. Note: A patient may only be canceled if no investigational drug is administered.

5.2 Withdrawal of Consent

Participants may voluntarily withdraw consent at any time or for any reason during the study without effect on their further management/treatment.

5.3 Withdrawal of a Participant by the Investigator

Reasons for withdrawal might include:

- Participants may be withdrawn from the study, prior to any imaging studies, by the investigator if deemed medically necessary.
- Inter-current illness, abnormal laboratory values, and/or adverse events that precludes further study participation.
- Significant protocol violation or noncompliance.
- The study is terminated.

Reason for discontinuation from the study should be adequately documented. Data will be collected for all withdrawn subjects up until the time of discontinuation.

5.4 Early Stopping Rules

The safety and tolerability will be assessed on an ongoing basis during the course of the study. The study will be halted and safety and dosing will be further evaluated if any single patient experiences a grade 3-5 toxicity that is believed to be related to radiotracer administration

6. PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

6.1 ^{111}In-XYIMSR-01 Investigational Product:

6.1.1 Drug Substance

Common Name: ^{111}In-XYIMSR-01

Unite Dose: 10.5±1 mCi of ^{111}In-XYIMSR-01 followed by SPECT/CT imaging

Route of administration: Intravenous catheter placed in an antecubital vein or an equivalent venous access

6.1.2 ^{111}In-XYIMSR-01 Manufacturer

The radiotracer will be manufactured at the Center for Translational Molecular Imaging located

at 5510 Nathan Shock Dr., Baltimore, MD, 21224.

7. ANALYSIS PLAN AND STATISTICAL CONSIDERATIONS

7.1 Primary Objective

The primary objective of this study is to evaluate the safety, tolerability, and feasibility of SPECT/CT imaging with ^{111}In-XYIMSR-01. All adverse events (AEs) will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The principal investigator or designee will determine if an observed adverse event is attributable to radiotracer administration. Based on our experience with similarly dosed radiotracers, we do not expect any grade 3-5 radiotracer-related adverse events. If the observed rate is indeed 0%, then a sample size of 10 patients will allow for 90% confidence that the actual toxicity of the radiotracer is in the range of 0% to 25%.

7.2 Secondary Objectives

Biodistribution and Radiation Dosimetry: A secondary objective of this study is to determine the biodistribution and radiation dosimetry of ^{111}In-XYIMSR-01. To allow for this, SPECT/CT images will be acquired at 2-4, 24 ± 1 hour, and 48 ± 1 hour post-injection. For the first three patients a total of three fields of view will be acquired and for the remaining 7 patients two fields of view will be acquired. Each SPECT acquisition will be acquired over a 20-30 minute period. The first time point acquisition for each field of view will include a high resolution CT. All other time points will be acquired with a low-dose CT.
The acquired PECT/CT images will be used to perform the biodistribution and radiation dosimetry calculations. Time-activity curves (TACs) demonstrating radiotracer activity as a function of time post injection (minutes) will be drawn for the whole body and the following organs: brain, breast, gallbladder, stomach, pancreas, heart wall, lung, liver, bladder, muscle, pancreas, red marrow, spleen, adrenals, upper large intestine, lower large intestine, small intestine, thymus, thyroid, testes and ovaries. Individual organ residence times will be calculated by fitting an exponential function to the TAC data and analytically integrating the fitted functions from zero to infinity. Organ specific mean radiation-absorbed dose estimates for ^{111}In-XYIMSR-01 will be calculated from the individual organ residence times. Reference organ mass values will be adjusted based on actual organ masses. The OLINDA software package will be used to determine the absorbed dose [28].

Characterization of Pharmokinetics: The pharmacokinetic profile of ^{111}In-XYIMSR-01 will be determined as a secondary endpoint of the study. ~5 mL of blood will be collected in heparinized tubes at pre-dose, 5±2 minutes, 10±2 minutes, 20±5 minutes, 30±5 minutes, 1±0.25 hour, 1.5±0.25 hour, and 24 hours ± 1 hour, post-injection to estimate elimination half-life. The collected blood will be evaluated for total radioractictity, the ratio of free versus protein-bound radiotracer, and measurement of the relative percentage of radiotracer and its metabolites.

Comparison with Anatomical Imaging: As an initial assessment of the diagnostic performance of ^{111}In-XYIMSR-01 SPECT/CT, findings on this novel imaging test will be compared to those on conventional imaging (CT and/or MRI). Using descriptive statistics we plan to summarize the number of lesions that are detected with all imaging modalities, the number of lesions detected

with ^{111}In-XYIMSR-01 SPECT/CT but not with conventional imaging, and the number of lesions detected with conventional imaging but not by ^{111}In-XYIMSR-01 SPECT/CT.

7.3 Sample Size/Accrual Rate

We plan to enroll 10 patients diagnosed with Metastatic Clear Cell Renal Cell Carcinoma. We do not expect any severe radiotracer-related adverse events based on our experience with similar types of radiotracers. We will pause the accrual and re-evaluate safety if one or more patients experience grade 3-5 toxicity that is believed to be related to radiotracer administration.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Unanticipated problems or events and study deviations will be reported to the JHM-IRB and the FDA according to the currently published policies of these entities.
Information about radiotracer-related adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through laboratory test or other means, will be collected and recorded and followed as appropriate. Safety assessments will consist of monitoring and recording all adverse events (AEs), as per the FDA guidelines, IND application sponsors are required to notify FDA in a written safety report of:

- any adverse experience associated with the use of the drug that is both serious and unexpected or
- any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity.

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or suspected adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application.

Serious adverse event or suspected adverse reaction refers to an event or reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- in-patient hospitalization or prolongation of existing hospitalization,

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly or birth defect.

Life-threatening adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious.

Mandatory Safety Reporting

- **Initial reporting:** IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

Unexpected serious suspected adverse reactions suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within **15 calendar days** following the sponsor's initial receipt of the information.
Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

- **Follow-up reporting:** Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571.

The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

The report must be submitted to an appropriate Review division that has the responsibility to review the IND application under which the safety report is submitted. Each submission to this IND must be provided in triplicate (original plus two copies). Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1

5901-B Ammendale Road
Beltsville, MD 20705-1266

8.1 Potential Risks

- **Risk of [^{111}In]XYIMSR-01:** [^{111}In]XYIMSR-01 is investigational and only used for research purposes. There are no anticipated effects of this drug based on preclinical toxicology studies. Patients will be monitored closely as per the Study Calendar to assess for adverse events. The study will be halted and safety and dosing will be further evaluated if any single patient experiences a grade 3-5 toxicity that is believed to be related to radiotracer administration.

- **Risk of radiation:** During the course of this study patients will be exposed to approximately 3.8 rem of radiation (1.8 rem for a single dose of 10.5±1 mCi and 2 rem from the CT component of the SPECT/CT scans)

9. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

9.1 Data and Safety Monitoring Plan

Data and Safety Monitoring:
This is a DSMP Medium Risk study under the SKCCC Data and Safety Monitoring Plan (02/21/2019). Data Monitoring of this protocol will occur annually. The protocol will be monitored internally at SKCCC by the Principal Investigator and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.
Additionally, scheduled meetings will take place monthly and will include the protocol principal investigator, research team, and, when appropriate, the collaborators, subinvestigators, and biostatistician involved with the conduct of the protocol.

The PI, Dr. Yasser Ged, is responsible for monitoring and oversight of problem/events. Scheduled meetings will take place monthly and will include the protocol principal investigator, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.
During these meetings, the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for study objectives.

The PI is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial endpoints and to confirm that the safety outcomes favor continuation of the study.

The PI, Dr. Yasser Ged, will be the medical monitor for this study. The medical monitor will make an assessment regarding the safety of continuing or modifying the study.

9.2 Data Management

Imaging data will be stored on our university radiology archives system. Source documentation will be maintained by site study staff to support the patient research record.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Every effort will be made to maintain the anonymity and confidentiality of all patients during this clinical study. However, because of the experimental nature of this investigational product, the Investigator agrees to allow the IRB, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study site records of all participants enrolled into this study.

The Investigator will assure that each participant's anonymity will be strictly maintained and that each participant's identity is protected from unauthorized parties.
Participants will be assigned a numerical code by the study team. The code list is kept secure and confidential by the study team on physically secured servers. Sufficient information will be retained at the study site to permit sample data and data to be connected with the unique participant number assigned to each study participant.

Data security will be controlled through appropriate restriction of access to only individual users to accomplish their roles in the data management process.

9.3 Record Retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator should maintain all source documents, and study-related documents.
JHM Organization Requirements: The Organization requires that investigators maintain research records for approved human subjects research protocols in accordance with federal and Organization requirements. The data and other records stored must be kept in a secure, protected manner in accordance with Johns Hopkins policies. Original data must be retained for at least 5 years from the date of publication. Beyond that, where questions have been raised regarding the validity of the published data, investigators must preserve the original data until such questions have been resolved to the satisfaction of the Organization and any involved government agencies. The director or chair of each department or research unit must decide whether to preserve original data for a given number of additional years or for the life of the unit.

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