CLINICAL STUDY PROTOCOL

A Pilot Safety and Pharmacokinetic Study of MB-102 versus Iohexol and the Use of the Non-invasive Optical Renal Function Monitor (ORFM) device, in Subjects with Normal and Impaired Renal Function and a Range of Skin Color Types

ClinicalTrials.gov NCT02772276

Protocol Number:	ORFM Pilot 2
Investigational Product:	MB-102 / Optical Renal Function Monitor (ORFM) Prototypes: QuantumLeap, Radiance, and Brilliance
Phase:	Pilot (2)
Sponsor:	MediBeacon Inc. 1100 Corporate Square Drive St. Louis, MO 63132 USA
Date of Protocol:	18 June 2021
Version of Protocol:	13.0 (Amendment 12)

Statement of Compliance

The study will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements including: The Code of Federal Regulations Title 21 CFR Parts 812, 11, 50, 54 and 56 and ISO 14155: 2011(E) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice

1 Synopsis

Protocol Number:	ORFM Pilot 2
Title:	A Pilot Safety and Pharmacokinetic Study of MB-102 versus Iohexol and the Use of the Non-invasive Optical Renal Function Monitor (ORFM) device, in Subjects with Normal and Impaired Renal Function and a Range of Skin Color Types
Investigational Product:	MB-102 ORFM Prototypes QuantumLeap, Radiance and Brilliance *Since the initiation of this protocol, the name of the investigational device has been changed to the Transdermal GFR Measurement System (TGFR) which consists of MB-102, the system monitor, and the prototype sensors QuantumLeap, Radiance and Brilliance. Supporting documentation may refer to ORFM or TGFR. Both names refer to the same investigational device.*
Number of Study Sites:	This study will take place at up to 4 investigational sites in the US.
Phase:	Pilot 2
Objectives:	• To evaluate the safety and tolerability of single dose and multiple doses of MB-102 in subjects with normal and impaired kidney function • To determine plasma pharmacokinetics of MB-102 compared to the pharmacokinetics of iohexol in subjects with normal and impaired renal function • To show that the MB-102 transdermal fluorescence measured GFR using the ORFM Brilliance device aligns with the measured MB-102 plasma GFR (Group 3) • To evaluate the safety and effectiveness of the ORFM investigational medical device prototypes QuantumLeap, Radiance and Brilliance for the non-invasive transdermal fluorescent detection of MB-102 in subjects with a range of skin color types • To determine the optimum dose of MB-102 for non-invasive measurement
Study Design:	Pilot, non-randomized, stratified open-label study.
Number of Treated Subjects:	Up to 261 subjects are intended to be enrolled across 3 Groups stratified by cohorts: **Group 1**: Approximately 60 subjects will be enrolled: Cohort 1: 30 subjects with normal to CKD Stage 2 renal function; and Cohort 2: 30 subjects with impaired renal function [CKD stage 3 – 4]). Fluorescence will be measured by the QuantumLeap ORFM Device. **Group 2**: Up to 60 subjects will be enrolled: Cohort 3: 20 subjects with normal to CKD Stage 2 renal function, Cohort 4: 40 subjects with impaired renal function [CKD stage 3-5]. Fluorescence will be measured by the Radiance ORFM Device. Approximately 10 subjects from Cohort 4 will undergo extended PK collection (out to 48 hours). Group 1 and Group 2 have been Completed

Group 3: Up to 141 subjects will be enrolled:

- **Cohort 5**: 8 subjects with normal to CKD stage 2 renal function,
- **Cohort 6**: 8 subjects with impaired renal function [CKD stage 3-5].

Fluorescence will be measured by the Brilliance ORFM Device and algorithm optimization will be performed.

Sensor Optimization Group (SOG)
In order to further optimize the sensor device, a Sensor Optimization Group (SOG) will be enrolled and consist of 18 healthy subjects with normal to CKD stage 2 renal function. An additional group of 9 healthy subjects may be enrolled into the SOG. Therefore, this cohort of subjects may range from a minimum of 9 subjects up to 27 subjects. SOG subjects will be followed for 12 hours.

Sensor Verification Group (SeVG)
A Sensor Verification Group (SeVG) will consist of up to 50 subjects to validate the Brilliance sensor. Sites will enroll subjects with normal renal function to Stage 5 CKD. Subjects with normal to stage 2 CKD will be considered the "SeVG-1" group and subject to specific eligibility. Subjects who have impaired renal function (CKD Stage 3-5) will be considered the "SeVG-2" group and subject to specific eligibility requirements.
A subset of subjects (up to 20) who weigh greater than 110 lbs (50 kg) will receive a fixed dose of 7 mL (130 mg).

A study interim analysis will be performed after completion of the SeVG cohort of all previously collected subject data (Groups 1, 2 and 3 through the SevG enrollment). This analysis will be performed to summarize clinical data in support of pivotal trial regulatory discussions. It is not the intention to stop the study early or revamp sample size for the remaining cohorts.

Cohorts 7 and 8

An additional 48 subjects may be enrolled to test the optimized algorithm and final device design:

Cohort 7: up to 24 subjects with normal to CKD stage 2 renal function. A subset of Cohort 7 subjects will have 2 doses of MB-102 and will be followed for 24 hours. Single dosed cohort 7 subjects will be followed for 12 hours.

Sites enrolling subjects into Cohort 7 (multiple dose group only for Protocol Version 11.0, 12.0 and 13.0) should strive to recruit subjects with a baseline eGFR $\geq$ 90 ml/min/1.73m^2 if feasible. The intent to enroll more normal subjects is to ensure clearance of MB-102 prior to the second dose in order to establish re-dose timelines for future subjects. In addition, subjects enrolled into the subsets of cohort 7 and 8 (Protocol Version 12.0) should strive to enroll subjects at the extremes of the Fitzpatrick Skin Scale (I and II and V and VI). Finally, subjects enrolled into Cohort 7A and 7B will an eGFR between 90 and 120 ml/min/1.73m^2. In addition, subjects in Cohort 7B will have a 24 hour period between doses (for a total post dose follow-up period of 36 + hours).

Cohort 8: up to 24 subjects with impaired renal function [CKD stage 3-5] will be followed for 48 hours.

Cohorts 7 and 8 will each enroll a set of subjects first to test the algorithm and

	then may be repeated if additional testing is determined to be required. *A subset of subjects in Cohort 7 and 8 (Cohorts 7A, 8A and 8B) will have a second sensor type placed on the pectoralis or sternum. This sensor (the 2-Part Brilliance Sensor) is being tested to evaluate a removable adhesive ring that would allow future re-use of the sensor portion.*
Treatment:	Eligible subjects will receive a single dose of MB-102 followed by a single dose of iohexol (Groups 1 and 2). Group 3, Cohorts 5, 6, SOG, SeVG-1, SeVG-2 and Cohort 8 will only receive a single dose of MB-102 and will not receive iohexol. A subset of subjects in Group 3, Cohort 7 will receive 2 doses of MB-102. Blood draws will be taken at pre-defined timepoints and the Optical Renal Function Monitor (ORFM) fluorescent measurements will be collected over an 8 - 12 hour period or up to 24-48 hours in certain cohorts. Group 1, Cohort 1 subjects may receive a range of doses of MB-102. Assessments of coefficient of variation will determine dose optimization. Remaining Group 1 subjects and Group 2 subjects will receive the optimized dose. Group 3 subjects (cohorts 5, 6, SOG and over half the subjects in the SeVG cohort will receive a single dose of 4 µmol/kg. A subset of the SeVG cohort (approximately 20 subjects who weigh greater than 110 lbs (50 kg) will receive a fixed dose of 7 mL (130 mg) MB-102. Cohorts 7 and 8 (regardless of weight) will all receive a fixed dose of 130 mg (7 mL). A subset of Group 3 subjects in Cohort 7 will receive 2 doses of MB-102 (fixed dose of 7 mL (130 mg). The 2nd dose will be administered 12 hours after the first dose. For Cohort 7B, subjects will receive their 2nd dose 24 hours after the first dose. Sensor placement in all subjects from Groups 1 and 2 will be in two different locations. All Group 1 and 2 subjects will have a single sensor placed on the sternum. A second location will be assigned to determine additional sites for fluorescent measurements. Group 3 subjects may have 2-3 different sensors located on different parts of the body. At least one sensor will be on the sternum or pectoralis major. • Group 1 subjects will have fluorescent measurements performed by the Prototype QuantumLeap device. • Group 2 subjects will have fluorescent measurements performed by the Prototype Radiance device. • Group 3 subjects will have fluorescent measurements performed by the Prototype Brilliance device. o A subset of subjects in Group 3 will also have a 2-part Brilliance sensor placed (cohort 7A, 7B, 8A and 8B)
Study Duration per Subject:	Screening period: up to 40 days prior to dosing; dosing day, and a follow-up visit within 7+/-3 days of dosing.
Study Population:	**Main Criteria for Inclusion (Group 1 and Group 2):** • Age ≥ 22 years – male or female

	○ Eligible female non-pregnant subjects who are either not of child-bearing potential or willing to use adequate contraception during the trial ○ Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose • Subjects willing to comply with study requirements • Subjects who have signed an informed consent form • Normal or non-clinically significant screening and baseline 12 lead ECG in the opinion of the PI • Adequate venous access sufficient to allow blood sampling per protocol requirements **Main Criteria for Inclusion (Group 3)** • Age ≥ 18 years – male or female ○ Eligible female non-pregnant subjects who are either not of child-bearing potential or willing to use adequate contraception during the trial ○ Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose • Subjects willing to comply with study requirements • Subjects who have signed an informed consent form • Normal or non-clinically significant screening and baseline 12 lead ECG in the opinion of the PI • Adequate venous access sufficient to allow blood sampling per protocol requirements ***Group 1 Cohort 1; Group 2 Cohort 3; and Group 3 Cohort 5, SOG, SeVG-1 Cohort and Cohort 7*** • Are healthy as determined by medical history, with no clinically significant findings on screening and baseline physical exams, vital signs and clinical laboratory panels or conditions that could adversely impact the subject's participation or safety, conduct of the study or interfere with study assessments • Have eGFR (CKD-EPI equation) of ≥60 ml/min/1.73m^2 (normal to Stage 2 CKD) at the time of screening Approximately half of the patients enrolled in each cohort to have Fitzpatrick Scale Type I, II or III skin color type. Approximately half of the patients enrolled in each cohort to have Fitzpatrick Type IV, V or VI skin color type. ***Group 1 Cohort 2*** • Possess stable renal function in the opinion of the PI • Have eGFR (CKD-EPI equation) of 15 – 59 mL/min/1.73m^2 at the time of screening • Stable use of immunosuppressant medications (when applicable) ~15 subjects per cohort to have Fitzpatrick Type I, II or III skin color type ~15 subjects per cohort to have Fitzpatrick Type IV, V or VI skin color type ***Group 2 Cohort 4, and Group 3 Cohorts 6, SeVG-2, and 8***

	• Possess stable renal function as defined as the most recent historical (within 3 months) eGFR and screening eGFR differing by ≤20%. • Have eGFR (CKD-EPI equation) of <59 mL/min/1.73m^2 based on a historical value collected within 3 months or from the screening serum creatinine • Stable use of immunosuppressant medications (when applicable) defined as no changes in the last 30 days or expected through the follow up visits, and a prednisone dose of <20 mg/day (or another steroid's equivalent dose). Approximately half of the subjects in each cohort to have Fitzpatrick Type I, II or III skin color type Approximately half of the subjects in each cohort enrolled to have Fitzpatrick Type IV, V or VI skin color type **Main Criteria for Exclusion (Group 1)** • Women who are pregnant, lactating or planning to become pregnant during the study, or women who are of childbearing potential unwilling to use a barrier method of birth control • Intolerant to venipuncture • Recent donation or loss of blood or plasma: 100 mL to 499 mL within 30 days prior to the initial dose of the study medication; or more than 499 mL within 56 days prior to the initial dose of study medication • Participation in another interventional trial within 30 days of screening or concurrently enrolled in any other medical research study which could impact the results of the study • History of drug or alcohol abuse within the past year • History of allergy or hypersensitivity to MB-102 or iohexol, or other related (iodinated contrast media) products, or any of the inactive ingredients • History of skin sensitivity to adhesives (e.g. Band-Aids, surgical tape) • Any food allergy, intolerance, restriction or special diet that, in the opinion of the Principal Investigator, could contraindicate the subject's participation in this study • Subjects who have allergies to 2 or more classes of drugs. (*Intolerance to a drug is not considered a drug allergy)* • Stable use (no changes within 30 days) of prescription or OTC medications • NSAID use within 2 days of dosing day • History of coagulation disorders or bleeding disorders that in the judgement of the investigator places the subject at undue risks for study related procedures • Are homozygous for sickle cell disease • Have a known thyroid disorder • Have pheochromocytoma • Currently on Coumadin (warfarin) who have an INR>4 at Screening • Current history of AIDS or HIV • Hepatitis B antigen positive, or C antibody positive • Site personnel immediately associated with the study or their immediate

	family members • Any characteristics which, in the opinion of the investigator, makes the subject a poor candidate for participation in the clinical trial • Prior enrollment and dosing in this Pilot 2 study • Significant scaring, tattoos or alterations in pigmentation on the sternum that would alter sensor readings versus other areas of the skin ***Additional Exclusion: Group 1 Cohort 1*** • History of significant cardiovascular disease, heart failure, myocardial infarction in the past 3 months, pulmonary, hematologic, endocrine, hepatobiliary, nephrologic, immunologic, dermatologic, neurologic (including any history of stroke and/or seizure disorder), psychological, musculoskeletal disease, diagnosis of cancer with the past 2 years or deemed clinically significant or unstable by the Principal Investigator; Note: history of gallstones or kidney stones are not excluded so long as the condition is not acute within 30 days of dosing. ***Additional Exclusion: Group 1 Cohort 2*** • Stage 5 CKD at the time of screening • Recent (within 3 months) significant medical condition or surgical procedure including myocardial infarction, laparoscopic procedures, or other medical inventions • Doses of prednisone greater than 10 mg/day within the last 90 days **Main Criteria for Exclusion: (Group 2)** • Women who are pregnant, lactating or planning to become pregnant during the study, or women who are of childbearing potential unwilling to use a barrier method of birth control o Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose • Unable to have venous access placed in both arms • Recent donation or loss of blood or plasma: 100 mL to 499 mL within 30 days prior to the initial dose of the study medication; or more than 499 mL within 56 days prior to the initial dose of study medication • Participation in another interventional trial within 30 days of dosing or concurrently enrolled in any other medical research study which could impact the results of the study • History of drug or alcohol abuse within the past year • History of skin sensitivity to adhesives (e.g. Band-Aids, surgical tape) • History of severe allergic hypersensitivity reactions (unacceptable adverse events) or anaphylactoid reaction to any allergen including drugs, MB-102 and iohexol or other related (iodinated contrast media) products (*intolerance to a drug is not considered a drug allergy*). • NSAID use within 2 days of dosing day • History of coagulation disorders or bleeding disorders that in the judgement of the investigator places the subject at undue risks for study related procedures • Are homozygous for sickle cell disease • Have hyperthyroidism or current thyroid cancer • Have pheochromocytoma

	• Currently on Coumadin (warfarin) who have an INR>4 at Screening • Current history of AIDS or HIV • Current evidence of an active Hepatitis B or C infection. *If the subject is Hepatitis C antibody positive, but the hepatitis C RNA is below the level of detection, they are considered immune and may be eligible for enrollment.* • Site personnel immediately associated with the study or their immediate family members • Any characteristics which, in the opinion of the investigator, makes the subject a poor candidate for participation in the clinical trial • Prior exposure to MB-102 • Significant scaring, tattoos or alterations in pigmentation on the sternum that would alter sensor readings versus other areas of the skin **Main Criteria for Exclusion: (Group 3)** • Women who are pregnant, lactating or planning to become pregnant during the study, or women who are of childbearing potential unwilling to use a barrier method of birth control o Males must be unwilling to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose • Unable to have venous access • Recent donation or loss of blood or plasma: 100 mL to 499 mL within 30 days prior to the initial dose of the study medication; or more than 499 mL within 56 days prior to the initial dose of study medication • Participation in another interventional trial within 30 days of dosing or concurrently enrolled in any other medical research study which could impact the results of the study • History of drug or alcohol abuse within the past year • History of skin sensitivity to adhesives (e.g. Band-Aids, surgical tape) • History of severe allergic hypersensitivity reactions (unacceptable adverse events) or anaphylactoid reaction to any allergen including drugs, or MB-102 (*intolerance to a drug is not considered a drug allergy*). • NSAID use within 2 days of dosing day • History of coagulation disorders or bleeding disorders that in the judgement of the investigator places the subject at undue risks for study related procedures • Currently on Coumadin (warfarin) who have an INR>4 at Screening • Current history of AIDS or HIV • Current evidence of an active Hepatitis B or C infection. *If the subject is Hepatitis C antibody positive, but the hepatitis C RNA is below the level of detection, they are considered immune and are be eligible for enrollment.* • Site personnel immediately associated with the study or their immediate family members • Any characteristics which, in the opinion of the investigator, makes the subject a poor candidate for participation in the clinical trial • Significant scaring, tattoos or alterations in pigmentation on the sternum that would alter sensor readings versus other areas of the skin ***Additional Exclusion: Group 2 Cohort 3, and Group 3 Cohorts 5, SOG, SeVG-1 and Cohort 7***

	• History of significant cardiovascular disease, heart failure, myocardial infarction in the past 3 months, or NYHA class III or IV HF • Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, or psychiatric condition that in the opinion of the investigator would limit the subjects' ability to complete study requirements or may put the subject at increased risk or compromise interpretability of study results. *Note: a history of gallstones or kidney stones are not excluded so long as the condition is not acute within 30 days of dosing.* ***Additional Exclusion: Group 2 Cohort, 4 and Group 3 Cohorts 6, SeVG-2, and 8*** • Recent (within 3 months) significant medical condition or surgical procedure including myocardial infarction, thoracic laparoscopic procedures, or other significant medical inventions • Received >20 mg/day of prednisone or an equivalent dose of glucocorticoid for more than 7 days in the last 90 days prior to dosing day for an acute or chronic disorder • Currently receiving dialysis • Currently anuric
Primary Endpoint:	• Determine plasma pharmacokinetics of MB-102 compared to the pharmacokinetics of iohexol in subjects with normal and impaired renal function and a range of skin color types (Groups 1 and 2) • To show that the MB-102 transdermal fluorescence measured GFR using the ORFM Brilliance device matches the measured MB-102 plasma GFR (Group 3)
Secondary Endpoints:	• Evaluate the safety and tolerance of MB-102 • Evaluate the safety of the ORFM devices for the noninvasive transdermal fluorescent detection of MB-102 • Evaluate the effectiveness of the ORFM devices (QuantumLeap, Radiance and Brilliance) through the comparison of fluorescent measurements versus MB-102 across the three groups of subjects • Determine the optimum dose of MB-102 for noninvasive measurement
Primary Safety Endpoint:	• Adverse events (AEs and serious AEs [SAEs], UADEs)
Statistical Methods and Sample Size Calculations	As this is a Pilot Study, no formal calculation of sample size was conducted. Safety will be evaluated as the incidence of AEs and SAEs/UADEs. These will be summarized by cohort and overall.
Time Schedule:	Planned Start of Study: April 2016 Planned End of Study: Sep 2021

Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease – epidemiology collaboration
CO_2	Carbon dioxide
CRF	Case report form
Cl	Chloride
Cr	Creatinine
CrCl	Creatinine clearance
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FS	Fitzpatrick Scale
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human chorionic gonadotropin
HCT	Hematocrit
HDL	High density lipoprotein
HEENT	Head, Ears, Eyes, Neck, Throat
HIV	Human immunodeficiency virus
I	Iodine
IB	Investigators Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational Product
ISO	International Organization for Standardization
IV	Intravenous
K	Potassium
K_2EDTA	Potassium ethylenediaminetetraacetic acid
LDL	Low density lipoprotein
MedDRA	*Medical Dictionary for Regulatory Activities*
NIH	National Institute of Health
NSAID	Non-steroidal anti-inflammatory drug
OM	Operational Manual
ORFM	Optical Renal Function Monitor

OTC	Over the counter
PA	Physical Assessment (limited)
PE	Physical exam (full)
PI	Principal Investigator
PK	pharmacokinetic
POC	Point of care
PP	Per Protocol
RBC	Red blood cell
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCr	Serum creatinine
SeVG	Sensor Verification Group
SOG	Sensor Optimization Group
SNR	Signal to Noise Ratio
TGFR	MediBeacon Transdermal Glomerular Filtration Measurement System
tGFR	Transdermal Glomerular Filtration Rate
Tc-DTPA	Technetium diethylene triamine - pentaacetate
TEAE	treatment-emergent adverse event
UADE	Unanticipated Adverse Device Effect
Vd	Volume of Distribution
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

3 Introduction

3.1 Background

Therapeutic interventions for acute kidney injury (AKI) patients are delayed due to current clinical practice of reliance on a serum creatinine blood test (SCr) for an estimation of glomerular filtration rate (GFR). Typically, 24-72 hours elapse from onset of a kidney injury event to a SCr indicating a non-normal level (Stevens et al, 2006). Since AKI affects upwards of 20% of hospitalized patients and 70% of critically ill patients in the intensive care unit (ICU), this contributes to high mortality rates (approaching 60% for those requiring renal replacement therapy [Endre at al., 2011]), development of chronic kidney disease (affecting an estimated 27 million Americans, accounting for ~ 24% of Medicare costs [NIH 2008]), and consequent progression to end stage renal disease (with an estimated 400,000 Americans on dialysis [Kidney Disease Statistics for the US]).

Glomerular filtration rate (GFR) is widely accepted as the best indicator of kidney function and is a key component of the diagnosis and management of renal impairment. A simple, accurate, and point-of-care (POC) method for determining GFR is needed, as current methods for determining GFR are either: 1) practical but lack accuracy, or 2) accurate but prohibitively complex, especially for frequent and recurrent measurements.

Current medical practice for general renal function assessment relies on estimated GFR (eGFR). This involves estimation using equations based on a single serum creatinine (SCr) measurement, or a measurement of creatinine clearance (CrCl) based on a 24-hour collection of urine plus measurement of a single SCr concentration. Although readily available and convenient, measurement of SCr as an indicator of renal function is problematic because it is a lagging indicator of current renal function, lacks sensitivity, and may be misleading because it is affected by age, state of hydration, renal perfusion, muscle mass, dietary intake, and many other anthropometric and clinical variables (Agarwal, 2003 and Verhave et al., 2005). CrCl estimation using timed urine collections can be more accurate, but problems with completeness of 24-hour urine collection often result in under or over estimation of CrCl.

Measuring GFR using urinary or plasma clearance of exogenous filtration markers is the accepted standard for evaluation of kidney function. In the past three decades, renally filtered exogenous agents such as inulin, iohexol, ^{125}Iodine-iothalamate (^{125}I-iothalamate), and technetium-99m-diethylene triamine - pentaacetate (^{99m}Tc-DTPA) have all been used to determine GFR (Stevens et al., 2006). From both a safety and effectiveness standpoint, these agents are acceptable, although they contain iodine, which can cause anaphylactoid reactions, and they can be nephrotoxic when very high volumes are used. However, they are not used routinely to determine GFR because the protocols are time-consuming, complex, and expensive, which make their repeated use impractical in many clinical settings, and they may require imaging equipment and administration of radioactive agents (Stevens and Levey, 2009). Accurate measurement of GFR at the patient's bedside is highly desirable in order to assess the patient's renal function. There is a significant need to develop a simple, accurate, and POC method for measuring GFR (Erley et al., 2001).

To address this unmet clinical need, MediBeacon is developing a combination product that requires the administration of a fluorescent tracer agent designated MB-102 (formerly known as MP-3180) that will be detected transdermally by a sensor which is attached to a device console.

MB-102 has been engineered to be excreted from the body by the renal system, and specifically by the GFR mechanism. Normal functioning kidneys will remove this agent from the body with an approximate 2 hour half-life. Impaired functioning kidneys will take longer to excrete the agent and hence result in a longer half-life. An algorithm will be developed from the Group 1 data to convert the half-life data to GFR. Group 2 will test the algorithm for efficacy and robustness, as well as add to the algorithm database. Group 3 will focus on sensor optimization and provide data on the final iteration of the device.

The sensor contains the light source for excitation of the tracer agent and has a peak wavelength of 440 nm. The detector is able to acquire the emission of the tracer agent, which has a peak wavelength of 560 nm. The sensor used for QuantumLeap contains the processing electronics within the sensor itself, making it a desktop mouse sized device that is then connected to the console. The sensor for the Brilliance device is significantly smaller and limited to the materials necessary for excitation and acquisition, and collection and processing of the data is conducted within the console.

The device console is a laptop computer for the QuantumLeap device. The Radiance device will have a similar format but will possess updated software and processing algorithms based on Group 1 data analysis. The Brilliance device will be a tablet console and represents the prototype developed for the market.

This clinical trial will utilize a commonly available x-ray contrast agent, iohexol (5 mL administration of Omnipaque™ 300) as a GFR comparator in Groups 1 and 2.

A subset of subjects in Group 3 (Cohorts 7A, 8A, and 8B) will have a second sensor type placed. This sensor is a two-part design where the adhesive ring is removable (and discardable) from the sensor itself.

Since the initiation of this protocol, the name of the investigational device has been changed to the Transdermal GFR Measurement System (TGFR) which consists of MB-102, the system monitor, and the prototype sensors QuantumLeap, Radiance and Brilliance. Supporting documentation may refer to ORFM or Transdermal GFR Measurement System (TGFR). Both names refer to the same investigational device.

3.2 Nonclinical Data

Available nonclinical study data on MB-102 support that the chemistry of the drug substance/drug product, and the manufacturing of the drug substance/drug product does not present a risk to human subjects. **Table 1** summarizes the nonclinical safety studies conducted to date.

Table 1 Summary of Nonclinical Safety Studies Conducted on MB-102

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
Pharmacology/ Pharmacokinetic	CYP-450 enzyme screen [Study No. 1116783]	30Apr09	NA	NA	Negative
Pharmacology	Effect of MP-3180 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells [Study Number 130308.SJD]	23Aug13	10 and 300 µM	NA	Negligible hERG inhibition
Pharmacology	Single Intravenous Dose CNS Safety Pharmacology Study in Rats (Rat Irwin Study) [Study Number 030739-1]	5Sep13	0, 180, 600, or 1200 µmol/kg	10M, 10F	NOEL >1200 µmol/kg
Pharmacology	Single Intravenous Dose Respiratory Function Safety Pharmacology Study in Rats (Respiratory Study in Conscious Rats) [Study Number 030741-1]	26Aug 13	0, 180, 600, 1200 µmol/kg	4M	NOEL >1200 µmol/kg
Pharmacology	Single Intravenous Dose Cardiovascular Safety Pharmacology Study in Female Beagle Dogs [Study Number 030740]	30Sep13	0, 60, 200, 600 µmol/kg	4F	NOEL 200 µmol/kg (74.4 mg/kg) No toxicologic effects on cardiac rhythm or ECG morphology
Toxicology	Single Dose Expanded IV Bolus Toxicity and Toxicokinetic Study in Rats [Study No. 8202289]	10Sep09	180, 600, 1200 µmol/kg	Tox: 10M, 10F TK: 9M, 9F	[1]NOAEL 1200 µmol/kg
Toxicology	Single Dose Expanded IV Bolus Toxicity and Toxicokinetic Study in Beagles [Study No. 8202286]	26Aug09	60, 200, 600 µmol/kg	4M, 4F	[1]NOAEL 600 µmol/kg
Toxicology	Hemolytic Potential and Blood Compatibility in Human Blood and Plasma [Study No. 8202288]	16Jun09	25, 50, 100 mM	NA	Negative
Toxicology	Bacterial Reverse Mutation Assay with Confirmation [Study No. 8202287]	19Aug09	5 mg / plate	NA	Negative
Toxicology	Chromosomal Aberration Assay in Cultured Human Peripheral Blood Lymphocytes [Study No. 8202290]	18Aug09	10mM and lower	NA	Negative
Toxicology	Intravenous and Perivenous Local Tolerance Study with MB-102 in New	21Jan16	18.6 mg/mL	3 IV (1 mL) 3 PV (.25 mL)	MB-102 was well tolerated in male rabbits IV or PV

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
	Zealand White Rabbits [Study Number 8330229]				and did not cause adverse inflammation or irritation at the injection site
Toxicology	MB-102: Rat Bone Marrow Micronucleus Assay [Study Number 8330227]	19Jan16	112.5 mg/kg/day 225 mg/kg/day 450 mg/kg day	6M	No evidence of MB-102 related bone marrow toxicity
Toxicology	Neutral Red Uptake Phototoxity Assay of MB-102 in BALB/c 3T3 Mouse Fibroblasts [Study Number 20103140]	17Jan17	100 µg /mL MB-102	NA	An IC_{50} could not be calculated for either the +UVR or –UVR exposure conditions, and the MPE value is well within the "not phototoxic" range. No cytotoxity or phototoxity potential for MB-102 was noted.
Toxicology	2-Week Toxicity and Toxicokinetic Study in Rats with a 1-Week Recovery [Study Number 8371969]	12Feb18	0, 9, 90, 225 mg/kg/day	71M, 71F	Daily iv administration was well tolerated at dose levels up to 225 mg/kg/day (rats) and 75 mg/kg/day (dogs). Non adverse MB-102 related clinical observations were restricted to yellow discoloration of the skin, haircoat or urine at several dose levels. These observations were attributed to the colored nature of the test article.
Toxicology	2-Week Toxicity and Toxicokinetic Study in Beagle dogs with a 1-Week Recovery [Study Number 8371970]	8Feb18	3, 30, 75 mg/kg/day	16M, 16F	
Toxicology	2-Week Repeat Oral (Once-Daily) Toxicity and Toxicokinetic Study in Rats with a 1-Week Recovery Phase [Study Number GLP-2018-0403]	Mar19	0, 9, 90 mg/kg/dose	Group 1: 6M, 6F Group 2: 12M, 12F Group 3: 12M, 12F	Administration of MB-102, via oral gavage for 14 consecutive days in a Sprague- Dawley rat model evaluated at 14 days (main study) or following a 1-week recovery period (Day 21±1, recovery) produced

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					no morphological changes that were considered to be related to the test article. There were no clinical pathology findings that were considered test article-related. There is no clear evidence to suggest that the test article at up to a 10-fold the planned human equivalent dose produced any systemic toxicity over the 14-day exposure period, and there was no evidence of persistent or delayed effects of the test article after a 1-week recovery period of non-treatment. The NOAEL in this study was the high dose of 90 mg/kg bw in both genders.
Toxicology – Developmental and Reproductive Toxicology	Intravenous (bolus) Injection Dose Range-Finding Embryo-Fetal Developmental and Toxicokinetic Study with MB-102 in Pregnant Rabbits [Study Number 8401985]	21Jun2019	0, 4.5, 45,113 mg/kg/day GD 7-19	6	No MB-102-related effects on mean body weight or body weight gain, mean food consumption, macroscopic observations, reproductive performance, cesarean section parameters, or fetal external variations or malformations were noted. On GD 19, for MB-102, the area under the concentration-time curve from 0 to the time of the last measurable concentration

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					(AUC_{0-6}) was 28.9, 225.0, or 546.0 (h*mg/mL) in animals administered 4.5, 45.0, or 113.0 mg/kg/day, respectively
Toxicology – Developmental and Reproductive Toxicology	Intravenous (bolus) Injection Embryo-Fetal Developmental and Toxicokinetic Study with MB-102 in Pregnant Rabbits [Study Number 8401986]	29Jun2020	0, 4.5, 45,113 mg/kg/day GD 7-19	22	Administration of MB-102 was not associated with any test article related effects on mortality, food consumption macroscopic observations, or developmental toxicity. Based on these data, the no observed advese-effect level (NOAELS) for maternal and fetal toxicity was 112 µg/kg/day (GD 7 C_{max} and AUC_{0-6} values of 1780 µM and 2050 h*µM, respectively; GD 19 C_{max} and AUC_{0-6} values of 1860 µM and 1839 h*µM, respectively
Toxicology – Developmental and Reproductive Toxicology	Intravenous (bolus) injection Embryo-Fetal Development and Toxicokinetics Study with MB-102 in Pregnant Rats [Study Number 8401987]	02Jul2020	0, 9, 90, 225 mg/kg/day GD 6-17	Toxicity animals 22 per group Toxicokinetic animals 3 control, 6 for all other groups	Administration of MB-102 was not associated with any test article-related effects on mortality, mean food consumption or body weight values, cesarean section parameters, macroscopic observations, or developmental toxicity, including the teratogenic

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					potential. Based on these data, the no observed adverse-effect level (NOAEL) for maternal and fetal toxicity was 225 mg/kg/day (GD 6 Cmax and AUC0-6 values of 1460 µM and 1350 h*µM, respectively; GD 17 Cmax and AUC0-6 values of 1590 µM and 1640 h*µM, respectively).
Pharmacokinetics	Pharmacokinetic Interaction of MB-102 and Iohexol administered as Crossover Intravenous Injections in Non-naïve Male Beagle Dogs [Study Number SW15-2375]	8Jan16	Iohexol: 647 mg/kg[2] MB-102: 3.2 mg/kg Combined: 647 iohexol and 3.2 MB-102 mg/kg	3 per group	Co-administration of MB-102 and iohexol did not alter the PK parameters measured for either agent
Pharmacokinetics	*In Vitro* ADME Report: SW15-2569. Determination of the *in vitro* binding of MB-102 and Iohexol to Male Human Plasma Proteins [Study Number SW15-2569]	7Jan16	MB-102: 1.15 mg/mL stock: spike solution: 300 µM. Iohexol: 647.1 mg/mL stock: spike solution: 17.50 µM	NA	MB-102 and Iohexol are both minimally bound to human plasma proteins. Percent bound for MB-102 and iohexol are 4 ± 2 % and 6 ± 1 %, respectively.
Pharmacokinetics	*In Vitro* ADME Report: SW15-2374. Determination of the *in vitro* Blood to Plasma Ratio of MB-102 in Male Human Blood [Study Number SW15-2374]	7Jan16	MB-102: 1.15 mg/mL stock: spike solution: 300 µM.	NA	MB-102 minimally distributes to blood cells with a mean blood to plasma ratio of 0.590 ± 0.003.
Pharmacokinetics	Fluorescence Biodistribution of MB-102 Administered as a Single IV Injection in Male NU-*Foxn1nu* Nude Mice [Study Number SW15-2426]	15Jan16	2 mM MB-102	1 M in Group 1, 2 and 6; 3M in Group 3, 2M in Group 4, 15M in Group 5	Two separate imaging studies demonstrate that when MB-102 is injected in vivo, the agent distributes quickly throughout the test subject, then rapidly clears from the body and does not preferentially localize in any

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					tissue or organ with the exception of the bladder which is consistent with a known GFR agent
Pharmacokinetics	ADME-TOX Drug Transporter Study, [Study No. 100044128]	05Nov18	NA	NA	No significant activity in any of the drug transporter assays

[1]*Eventual limit is higher than reported number, this was the highest concentration employed; could not administer higher concentration due to volume consideration.*
[2]*Iohexol dose contained 300 mg/mL organic iodine*

For more detailed information on each of the nonclinical studies, please see the Investigator's Brochure.

3.3 Clinical Data

A total of 234 subjects have been treated with an IV administration of MB-102 across the three pilot studies (Pilot 1A, Pilot 1B and Pilot 2 Groups 1, 2 and 3. The Pilot 1 studies enrolled subjects with an eGFR indicating normal renal function. The Pilot 2 study enrolled subjects with normal renal function and those with renal function in the CKD stage 1-5 range. In addition, a total of 11 subjects (6 healthy volunteers and 5 Crohn's patients) have received a 4 or 8 μmol/kg oral dose of MB-102 in a study evaluating the use of MB-102 in the evaluation of gut permeability (MediBeacon Protocol 300-01). The total population exposure to MB-102 as of this IB version is 245 subjects. A total of 43 subjects (17.6% of the total population across 4 studies) were reported to have adverse events (AE). All reported events were mild or moderate in severity. No severe events have been reported, nor have any serious adverse events been reported.

There have been no clinically significant findings with regard to vital signs, physical exams or ECGs. Overall MB-102 dosed at 4 μmol/kg followed by a 5 mL dose of iohexol (Omnipaque™ 300) was well tolerated and safe in this population. Adverse events related to the device itself were due to the adhesive materials used to hold the ORFM (Optical Renal Function Monitor) sensor in place. All device related events were considered mild or moderate in severity. For more information, please see the Investigator's Brochure.

MB-102 equilibrates between the vasculature and tissues post intravenous (IV) administration. The plasma pharmacokinetics show a peak concentration at the first sample time point. In Pilot 1A, the first sample time point taken was approximately 5 minutes post administration; in Pilot 1B the first sample time point taken was approximately 30 minutes post administration. The fluorescence pharmacokinetics, reflecting the agent concentration in the tissue, has a peak fluorescence intensity in the range of 30 - 90 minutes, depending on the subject. MB-102 concentration equilibration between the vasculature and the tissue occurs approximately in this same timeframe.

In the Pilot 2 Groups 1 and 2, the first blood draw was taken at 5 minutes post administration of MB-102, and the last at 12 hours post administration. The transdermal fluorescence was measured at the sternum and one other location for each subject using the prototype device QuantumLeap and Radiance. For all 120 subjects over the wide range of GFR values, the following were observed:

- A two compartment plasma pharmacokinetic profile
- A high correlation between the MB-102 and iohexol plasma derived GFR values
- A high correlation between the MB-102 plasma and transdermal fluorescence pharmacokinetics

3.4 Study Rationale

This clinical study is the first to assess pharmacokinetics (PK) and function of the ORFM device in subjects with impaired kidney function. In addition, it will evaluate the impact of different skin color types on readouts by the ORFM prototype devices QuantumLeap, Radiance and Brilliance. These data will be used to further refine the algorithms used in the ORFM device for the pivotal trial and commercial development. Safety and tolerance of MB-102 will also be assessed in a larger population of subjects.

4 Study Objectives

The objectives of this pilot study are:

- To evaluate the safety and tolerability of single dose and multiple doses of MB-102 in subjects with normal and impaired kidney function
- To determine plasma pharmacokinetics of MB-102 compared to the pharmacokinetics of iohexol in subjects with normal and impaired renal function (Groups 1 and 2)
- To show that the MB-102 transdermal fluorescence measured GFR using the ORFM Brilliance device aligns with the measured MB-102 plasma GFR (Group 3)
- To evaluate the safety and effectiveness of the ORFM investigational medical device prototypes QuantumLeap, Radiance and Brilliance for the non-invasive transdermal fluorescent detection of MB-102 on subjects with a range of skin color types
- To determine the optimum dose of MB-102 for non-invasive measurement

5 Investigational Plan

5.1 Overall Study Design and Plan

Protocol ORFM Pilot 2 is a pilot, safety and pharmacokinetic study of MB-102 versus iohexol (Groups 1 and 2) and the use of the non-invasive ORFM device in normal and compromised renal function subjects with different skin color types.

Up to 261 subjects are intended to be enrolled across 3 Groups stratified by cohorts:

Group 1: Approximately 60 subjects will be enrolled:

- Cohort 1: 30 subjects with normal to CKD Stage 2 renal function
- Cohort 2: 30 subjects with impaired renal function (CKD stage 3-4).

Fluorescence will be measured by the QuantumLeap ORFM Device.

Data from Group 1 subjects will be used to determine dose optimization. In addition, Group 1 data will be analysed in order to modify the sensor algorithm for use in Group 2 subjects. These updates will then be implemented prior to initiation of Group 2 enrollment.

Group 2: Up to 60 subjects will be enrolled:

- Cohort 3: 20 subjects with normal to CKD Stage 2 renal function
- Cohort 4: 40 subjects with impaired renal function (CKD stage 3-5)
    - Approximately 10 subjects in Cohort 4 will have extended PK collections (out to 48 hours)

Fluorescence will be measured by the Radiance ORFM Device.

Group 3: Up to 141 subjects to be enrolled:

- Cohort 5: 8 subjects to have normal to CKD Stage 2 renal function
- Cohort 6: 8 subjects with impaired renal function (CKD stage 3-5)
- Sensor Optimization Group (SOG): 18 subjects with normal to CKD Stage 2 renal function; if optimization still requires additional work; a third and final group of 9 subjects will be enrolled to finalize the device and algorithm design.
- Sensor Validation Group (SeVG): up to 50 subjects will be enrolled who have normal renal function to Stage 5 CKD. A subset of subjects (approximately 20) who weigh greater than 110 lbs (50 kg) will receive a fixed dose of 7 mL (130 mg). Subjects receiving the fixed dose may be normal or renally compromised.

A study interim analysis will be performed after completion of the SeVG cohort of all previously collected subject data (Groups 1, 2 and 3 through the SevG enrollment). This analysis will be performed to summarize clinical data in support of pivotal product development and regulatory submissions. It is not the intention to stop the study early or revamp sample size for the remaining cohorts.

The final algorithm and sensor will be further tested in up to 48 additional subjects:

- Cohort 7: up to 24 subjects to have normal to CKD Stage 2 renal function
  - A subset of cohort 7 subjects will have 2 doses of MB-102; the 2nd dose of MB-102 will be administered 12 hours after the first dose (original Cohort 7, 7A)
  - A subset of subjects (Cohort 7B) will have 2 doses of MB-102; the 2nd dose of MB-102 will be administered 24 hours after the first dose
- Cohort 8: up to 24 subjects with impaired renal function (CKD stage 3-5) and followed for 24-48 hours
- All cohort 7 and 8 subjects will receive the fixed dose of 130 mg (7 mL).

Cohorts 7 and 8 will be divided into the following subsets in order to test additional sensor types in development. These subsets are outlined in **Table 2**.

Table 2 Cohort 7 and 8 Subsets

Cohort Subgroups	Dosing	Follow-up (Hrs)	Sensors	Enrollment
Cohort 7	Single or 2 doses	12 - 24 hours	Brilliance (1-2 sensors/subject)	Up to 24 subjects
Cohort 7A	Single or 2 doses	12 - 24 hours	Brilliance (1-2 sensors/subject) and Brilliance 2-part sensor	
Cohort 7B	2 doses	36 hours	Brilliance (1-2 sensors/subject) and Brilliance 2-part sensor	
Cohort 8	Single dose	48 hours	Brilliance (1-2 sensors/subject)	Up to 16 subjects
Cohort 8A	Single dose	48 hours	Brilliance (1-2 sensors/subject) and Brilliance 2-part sensor	
Cohort 8B	Single dose	24 hours	Brilliance (1-2 sensors/subject) and Brilliance 2-part sensor	Up to 8 subjects
Total cohort 7 and 8 Enrollment:				Up to 48

Fluorescence will be measured by the Brilliance ORFM Device and some subjects will be exposed to a 2-Part Brilliance sensor.

All Cohorts will enroll approximately half their subjects with Fitzpatrick Scale (FS) Type I, II or III, and half with Type IV, V and VI skin color type (Fitzpatrick, 1975) (**Appendix A Fitzpatrick Scale**).

5.2 Dose Optimization

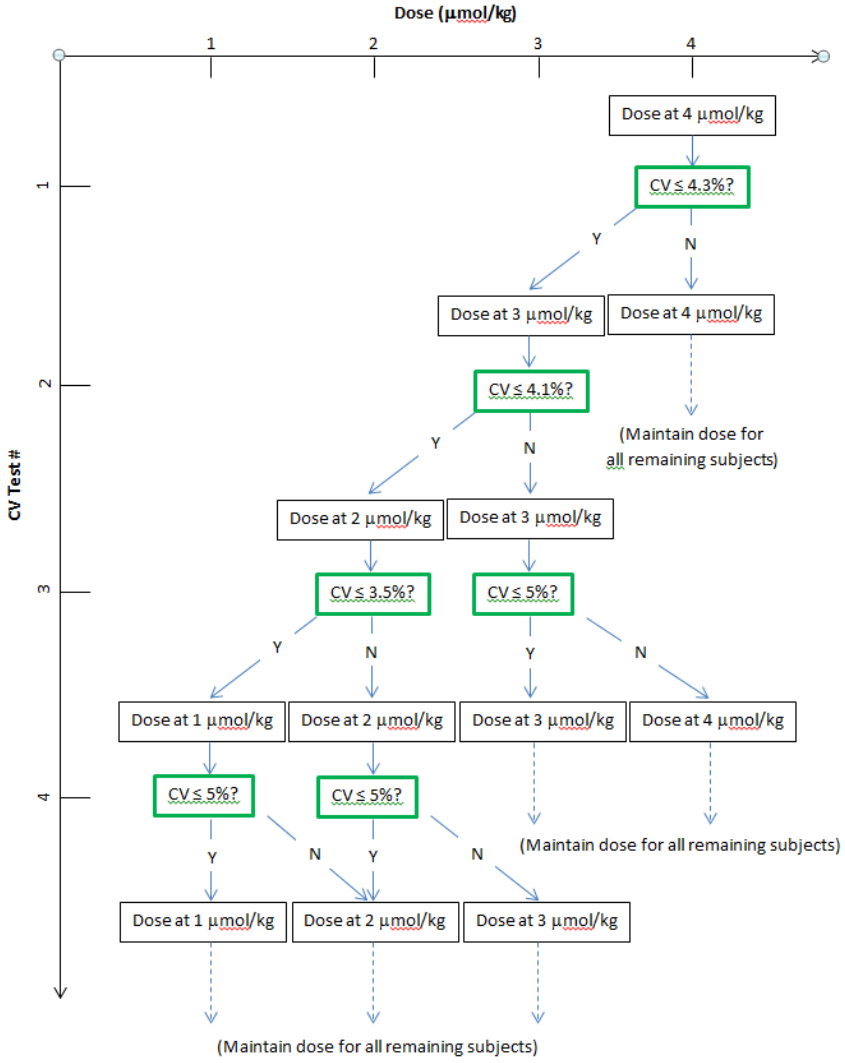
In order to determine the optimal dose of MB-102, Group 1 subjects may receive different doses of Investigational Product (IP). The maximum dose of 4 µmol/kg has already been tested in 8 subjects in a prior clinical study (Pilot 1B) and found to be safe and well tolerated.

Coefficient of Variation (CV) will be used as the criterion for selecting dose. CV is defined here as the standard deviation divided by the mean (expressed as a percentage) of the time constants from multiple single exponential fits to the trans-cutaneous fluorescence emission decay over non-overlapping 15 minute time windows between 2 and 4 hours after IP dosing. The CVs will

be separately averaged across 2 subjects within FS I, II and III skin color types and 2 subjects within FS IV, V, and VI skin color types.

The initial dose will be 4 µmol/kg, and the target CV will be 5%. Dose de-escalation will only be performed if the resulting average CVs for both skin type groups are below the maximum stated requirements. As shown in **Figure 1**, the CV thresholds for dose de-escalation from 4 to 3 µmol/kg, 3 to 2 µmol/kg, and 2 to 1 µmol/kg are 4.3%, 4.1%, 3.5%, respectively. These dose scaling targets assume that the CV has a square root dependence on the signal size (i.e. "Poisson" noise distribution), but after dose de-escalation, a second CV determination will be made to ensure the target CV of 5% has been achieved. Details on the methods and analysis of dose selection will be available in a separate MediBeacon Experimental Protocol.

Figure 1 Dose Optimization Schema



5.2.1 Group 2 Dosing

Subjects enrolled in Group 2 will receive a dose of 4 µmol/kg of MB-102. No dose optimization work will be conducted.

5.2.2 Group 3 Dosing

Subjects enrolled in Group 3, Cohorts 5, 6, SOG and part of the SeVG group will receive a dose of 4 µmol/kg of MB-102. No dose optimization work will be conducted.

A subset of SeVG subjects (up to 20 subjects who weigh greater than 110 lbs [50 kg]) and all subjects in cohorts 7 and 8 will receive a fixed dose of 7 mL (130 mg). This dose is equivalent to what a 191 lb subject would receive if dosed at the standard 4 µmol/kg dose level. This dose change is within the safety margin of previously performed non-clinical studies. The purpose of testing a fixed dose level is to determine if such a dose will be adequate across a variety of subject weights and still remain an accurate measurement of tGFR. A fixed dose level would simplify dose preparation when the product goes to market.

A subset of subjects enrolled into Cohort 7 will receive 2 doses of MB-102 (both doses will at the fixed dose level of 7 mL or 130 mg). The 2nd dose of MB-102 will be administered either 12 hours or 24 hours (Cohort 7B) after the first dose.

5.3 Overview of Study Procedures

5.3.1 Groups 1 and 2

Potential subjects will be screened for eligibility within 40 days prior to planned dosing. Following pre-dose procedures to ensure eligibility, two ORFM sensors will be affixed to the subjects in Groups 1 and 2; one on the sternum (all subjects) and a second one on an alternative location which may include the forehead, occipital triangle, pectoralis major, lower hip, upper hip, lower sternum or chin. The subject will then receive MB-102 and iohexol injections. MB-102 will be administered by IV injection over 30 seconds, followed by a 10 mL saline flush IV over 30 seconds. Iohexol will be administered to each subject following the MB-102 administration by IV injection over 30 seconds, followed by a 10 mL saline flush IV over 30 seconds.

PK sampling will be collected pre-dose and at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 480, 600 and 720 minutes post-dose.

For the subgroup in Cohort 4 who consent to have extended PK collection, additional PK samples will occur at 960 (16 hours), 1440 minutes (24 hours), 1920 minutes (32 hours), 2400 minutes (40 hours) and 2880 minutes (48 hours) post-dose.

Urine will be collected pre-dose and for the 12 hour duration of PK sampling (and extended out to 48 hours for subjects in the extended PK subgroup) for all subjects in Groups 1 and 2. Aliquots of urine will be collected during each void, and the total volume excreted during the 12 or 48 hour post-dose period will be recorded.

Safety assessments in the form of clinical labs, vital signs, ECGs and adverse event collection will occur during the dosing day.

Within 7 +/- 3 days of dosing, subjects will return to the study center for additional safety follow-up assessments.

5.3.2 Group 3

Potential subjects will be screened for eligibility within 40 days prior to planned dosing. Following pre-dose procedures to ensure eligibility, one ORFM sensor will be affixed to the subject and (in certain subjects) a 2nd sensor (connected to a separate device) may be attached to a 2nd location. Sensor placement locations include: the sternum, the forehead, occipital triangle (side of neck), pectoralis major, lower hip, upper hip, lower sternum or chin. A dose of 4 µmol/kg MB-102 will be administered by IV injection over 30 seconds, followed by a 10 mL saline flush IV over 30 seconds.

PK sampling in cohort 5 will be collected pre-dose and at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, and 480 minutes post-dose (8 hour collection period).

PK sampling in cohorts 6, 7 (single dose subjects), the SOG cohort, SeVG-1 and SeVG-2 will be collected pre-dose and at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 480, 600 and 720 minutes post-dose (12 hour collection period).

PK sampling in cohort 7 [including 7A and 7B] (multiple dose subjects) will be collected at the following timepoints: pre-dose and 5, (±1 min), 120, 180, 240, 300 (±5 min), 360, 480 and 600 (±10 min). In addition, a PK sample will be drawn at 720 minutes after the first dose administered in Cohort 7B. Prior to the 2nd dose, a pre-second dose draw will be performed. Blood draws will re-start after the administration of the 2nd dose and be collected at the following timepoints: 5 (±1 min), 120, 180, 240, 300 (±5 min), 360, 480, and 600 (±10 min). It is anticipated that this subset of subjects will remain at the study center for 24 – 36+ hours. As of Amendment 11, PK sampling for multiple dose subjects will have an additional PK blood draw at 60 minutes (±5 min).

PK sampling in cohort 8, and 8A will be collected pre-dose and at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720 minutes (12 hours); 960 (16 hours), 1440 (24 hours), 1920 (32 hours), 2400 (40 hours) and 2880 minutes (48 hours).

PK sampling in cohort 8B will be collected at collected pre-dose and at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720 minutes (12 hours); 960 (16 hours), and 1440 (24 hours).

Urine will not be collected in Group 3.

Safety assessments in the form of clinical labs, vital signs, ECGs and adverse event collection will occur during the dosing day.

Prior to sensor placement, and each time a sensor is removed (or a sensor replaced) melanin and erythema will be measured using a Mexameter® MX18. Photographs of the sensor once affixed to a subject may also be taken in order to assess the utility of the adhesive. No subject identifying features will be included in the photographs.

Within 7 +/- 3 days of dosing, subjects will return to the study center for additional safety follow-up assessments.

5.4 Discussion of Study Design

This pilot study is designed to provide safety and pharmacokinetic data as well as ORFM data that will be used for the design of future studies.

5.5 Selection of Study Population

5.5.1 Number of Planned Subjects

Up to 261 subjects divided into 3 enrollment Groups with normal or impaired renal function who meet all of the eligibility criteria will be enrolled. An effort will be made to ensure both men and women are enrolled across all cohorts.

No sample size calculation was made to determine the number of planned subjects. This is a hypothesis generating study to optimize the device and algorithm and is not intended to meet statistical significance for this purpose.

5.5.2 Inclusion Criteria

To be eligible for study entry, all subjects must satisfy all of the following criteria:

Main Criteria for Inclusion (Group 1 and Group 2):

- Age $\geq$ 22 years – male or female
  - Eligible female non-pregnant subjects who are either not of child-bearing potential or willing to use adequate contraception during the trial
  - Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose
- Subjects willing to comply with study requirements
- Subjects who have signed an informed consent form
- Normal or non-clinically significant screening and baseline 12 lead ECG in the opinion of the PI
- Adequate venous access sufficient to allow blood sampling per protocol requirements

Main Criteria for Inclusion (Group 3):

- Age $\geq$ 18 years – male or female
  - Eligible female non-pregnant subjects who are either not of child-bearing potential or willing to use adequate contraception during the trial
  - Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose

- Subjects willing to comply with study requirements
- Subjects who have signed an informed consent form
- Normal or non-clinically significant screening and baseline 12 lead ECG in the opinion of the PI
- Adequate venous access sufficient to allow blood sampling per protocol requirements

Group 1 Cohort 1 (30 subjects), Group 2 Cohort 3 (20 subjects) and Group 3: Cohorts 5 (8 subjects), SOG Cohort (up to 27 subjects), SeVG-1 (up to 25 subjects) and Cohort 7 (up to 16 subjects)

- Are healthy as determined by medical history, with no clinically significant findings on screening and baseline physical exams, vital signs and clinical laboratory panels or conditions that could adversely impact the subject's participation or safety, conduct of the study or interfere with study assessments
- Have eGFR (CKD-EPI equation) of ≥60 ml/min/1.73m^2 (normal to Stage 2 CKD) at the time of screening

Approximately half of the patients enrolled in each cohort will have Fitzpatrick Scale Type I, II or III skin color type and the other half will have Fitzpatrick scale Type IV, V or VI skin color type.

Group 1 Cohort 2 (30 subjects)

- Possess stable renal function in the opinion of the PI
- Have eGFR (CKD-EPI equation) of 15 – 59 mL/min/1.73m^2 at the time of screening
- Stable use of immunosuppressant medications (when applicable)

~15 subjects per cohort to have Fitzpatrick Type I, II or III skin color type
~15 subjects per cohort to have Fitzpatrick Type IV, V or VI skin color type

Group 2 Cohort 4 (40 subjects) and Group 3 Cohorts 6 (8 subjects), SeVG-2 (up to 25 subjects) and Cohort 8 (up to 16 subjects)

- Possess stable renal function as defined as the most recent historical (within 3 months) eGFR and screening eGFR differing by ≤20%.
- Have eGFR (CKD-EPI equation) of <59 mL/min/1.73m^2 based on a historical value collected within 3 months or from the screening serum creatinine
- Stable use of immunosuppressant medications (when applicable) defined as no changes in the last 30 days or expected through the follow up visits, and a prednisone dose of <20 mg/day (or another steroid's equivalent dose) (see **Section 5.10.2** and **Table 3**).

Approximately half of the subjects per Cohort to have Fitzpatrick Type I, II or III skin color type
Approximately half of the subjects per Cohort to have Fitzpatrick Type IV, V or VI skin color type.

5.5.3 Main Criteria for Exclusion (Group 1):

- Women who are pregnant, lactating or planning to become pregnant during the study, or women who are of childbearing potential unwilling to use a barrier method of birth

control
- Intolerant to venipuncture
- Recent donation or loss of blood or plasma: 100 mL to 499 mL within 30 days prior to the initial dose of the study medication; or more than 499 mL within 56 days prior to the initial dose of study medication
- Participation in another interventional trial within 30 days of screening or concurrently enrolled in any other medical research study which could impact the results of the study
- History of drug or alcohol abuse within the past year
- History of allergy or hypersensitivity to MB-102 or iohexol, or other related (iodinated contrast media) products, or any of the inactive ingredients
- History of skin sensitivity to adhesives (e.g. Band-Aids, surgical tape)
- Any food allergy, intolerance, restriction or special diet that, in the opinion of the Principal Investigator, could contraindicate the subject's participation in this study
- Subjects who have allergies to 2 or more classes of drugs. (*Intolerance to a drug is not considered a drug allergy)*
- Stable use (no changes within 30 days) of prescription or OTC medications
- NSAID use within 2 days of dosing day
- History of coagulation disorders or bleeding disorders that in the judgement of the investigator places the subject at undue risks for study related procedures
- Are homozygous for sickle cell disease
- Have a known thyroid disorder
- Have pheochromocytoma
- Currently on Coumadin (warfarin) who have an INR>4 at Screening
- Current history of AIDS or HIV
- Hepatitis B antigen positive, or C antibody positive
- Site personnel immediately associated with the study or their immediate family members
- Any characteristics which, in the opinion of the investigator, makes the subject a poor candidate for participation in the clinical trial
- Prior enrollment and dosing in this Pilot 2 study
- Significant scaring, tattoos or alterations in pigmentation on the sternum that would alter sensor readings versus other areas of the skin

Additional Exclusion: Group 1 Cohort 1:

- Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered medical exam or psychiatric condition that in the opinion of the investigator would limit the subjects' ability to complete study requirements or increase risk to the subject or interpretability of the study results.
- Note: history of gallstones or kidney stones are not excluded so long as the condition is not acute within 30 days of dosing.

Additional Exclusion: Group 1 Cohort 2

- Stage 5 CKD at the time of screening
- Recent (within 3 months) significant medical condition or surgical procedure including myocardial infarction, laparoscopic procedures, or other medical inventions
- Doses of prednisone greater than 10 mg/day within the last 90 days

5.5.4 Main Criteria for Exclusion: (Group 2)

- Women who are pregnant, lactating or planning to become pregnant during the study, or women who are of childbearing potential unwilling to use a barrier method of birth control
    - Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose
- Unable to have venous access placed in both arms
- Recent donation or loss of blood or plasma: 100 mL to 499 mL within 30 days prior to the initial dose of the study medication; or more than 499 mL within 56 days prior to the initial dose of study medication
- Participation in another interventional trial within 30 days of treatment or concurrently enrolled in any other medical research study which could impact the results of the study
- History of drug or alcohol abuse within the past year
- History of skin sensitivity to adhesives (e.g. Band-Aids, surgical tape)
- History of severe allergic hypersensitivity reactions (unacceptable adverse events) or anaphylactoid reaction to any allergen including drugs, MB-102, iohexol or other related (iodinated contrast media) products (*Intolerance to a drug is not considered a drug allergy)*
- NSAID use within 2 days of dosing day
- History of coagulation disorders or bleeding disorders that in the judgement of the investigator places the subject at undue risks for study related procedures
- Are homozygous for sickle cell disease
- Have hyperthyroidism or current thyroid cancer
- Have pheochromocytoma
- Currently on Coumadin (warfarin) who have an INR>4 at Screening
- Current history of AIDS or HIV
- Current evidence of an active Hepatitis B or C infection. *(If the subject is Hepatitis C antibody positive, but the Hepatitis C RNA is below the level of detection, they are considered immune and may be eligible).*
- Site personnel immediately associated with the study or their immediate family members
- Any characteristics which, in the opinion of the investigator, makes the subject a poor candidate for participation in the clinical trial
- Prior exposure to MB-102
- Significant scarring, tattoos or alterations in pigmentation on the sternum that would alter sensor readings versus other areas of the skin

5.5.5 Main Criteria for Exclusion: (Group 3)

- Women who are pregnant, lactating or planning to become pregnant during the study, or women who are of childbearing potential unwilling to use a barrier method of birth control

    - Males must be willing to practice abstinence or utilize adequate contraception from dosing day to at least 7 days post dose
- Unable to have venous access
- Recent donation or loss of blood or plasma: 100 mL to 499 mL within 30 days prior to the initial dose of the study medication; or more than 499 mL within 56 days prior to the initial dose of study medication
- Participation in another interventional trial within 30 days of treatment or concurrently enrolled in any other medical research study which could impact the results of the study
- History of drug or alcohol abuse within the past year
- History of skin sensitivity to adhesives (e.g. Band-Aids, surgical tape)
- History of severe allergic hypersensitivity reactions (unacceptable adverse events) or anaphylactoid reaction to any allergen including drugs, and MB-102 (*Intolerance to a drug is not considered a drug allergy)*
- NSAID use within 2 days of dosing day
- History of coagulation disorders or bleeding disorders that in the judgement of the investigator places the subject at undue risks for study related procedures
- Currently on Coumadin (warfarin) who have an INR>4 at Screening
- Current history of AIDS or HIV
- Current evidence of an active Hepatitis B or C infection. *(If the subject is Hepatitis C antibody positive, but the Hepatitis C RNA is below the level of detection, they are considered immune and may be eligible).*
- Site personnel immediately associated with the study or their immediate family members
- Any characteristics which, in the opinion of the investigator, makes the subject a poor candidate for participation in the clinical trial
- Significant scarring, tattoos or alterations in pigmentation on the sternum that would alter sensor readings versus other areas of the skin

Additional Exclusion: Group 2 Cohort 3 and Group 3 Cohorts 5, SOG Cohort, SeVG-1 and Cohort 7

- History of significant cardiovascular disease, heart failure, myocardial infarction in the past 3 months, or NYHA class 3 or 4 HF
- Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, or psychiatric condition that in the opinion of the investigator would limit the subjects' ability to complete study requirements or may put the subject at increased risk or compromise interpretability of study results. *Note: a history of gallstones or kidney stones are not excluded so long as the condition is not acute within 30 days of dosing.*

Sites enrolling subjects into Cohort 7 (multiple dose group only for Protocol Versions 11.0 and 12.0) should strive to recruit subjects with a baseline eGFR > 90 ml/min/1.73m^2 if feasible. The intent to enroll more normal subjects is to ensure clearance of MB-102 prior to the second dose in order to establish re-dose timelines for future subjects. In addition, subjects enrolled into the subsets of cohort 7 and 8 (Protocol Version 12.0) should strive to enroll subjects at the extremes of the Fitzpatrick Skin Scale (I and II and V and VI). Finally, subjects enrolled into Cohort 7A

and 7B will an eGFR between 90 and 120 ml/min/1.73m^2. In addition, subjects in Cohort 7B will have a 24 hour period between doses (for a total post dose follow-up period of 36 + hours).

Additional Exclusion: Group 2 Cohort 4 and Group 3 Cohorts 6, SeVG-2, and 8

- Recent (within 3 months) significant medical condition or surgical procedure including myocardial infarction, thoracic laparoscopic procedures, or other significant medical inventions
- Received >20 mg/day of prednisone or an equivalent dose of glucocorticoid for more than 7 days in the last 90 days prior to dosing day for an acute or chronic disorder
- Currently receiving dialysis
- Currently anuric

5.5.6 Removal of Subjects from Therapy or Assessments

In accordance with applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution where the subject's care is provided.

Reasons for withdrawal from the study may include 1 or more of the following:

- Withdrawal of consent
- Administrative decision by the PI or MediBeacon
- Adverse event requiring removal from the study
- Physician prescribes a treatment that would conflict with the subject's continued participation in the study

Subjects withdrawing from the study will be encouraged to complete the follow-up study visit including all safety evaluations. The reason(s) for withdrawal will be documented.

Reasonable efforts will be made to contact subjects who are lost to follow-up. All attempts and contacts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time due to a safety issue or if special circumstances arise making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

5.5.7 Replacement of Subjects

Should a subject meet eligibility, but is unable to be dosed, that subject may be replaced.

Subjects will not be replaced if they are dosed but unable to complete study assessments.

5.6 Investigational Device

The Optical Renal Function Monitor (ORFM) investigational device is intended to measure the

Glomerular Filtration Rate (GFR) in patients with normal or impaired renal function by noninvasively monitoring fluorescent light emission from an exogenous tracer agent (MB-102) over time. The devices utilized in this protocol are ORFM Prototypes QuantumLeap, and Radiance as next generation from the ORFM prototype 1 used in Pilot 1B. The Brilliance device being evaluated in Group 3 will be a prototype of the final device used for the pivotal trial and future marketing.

Subjects in Group 1 will be evaluated using ORFM prototype QuantumLeap, and subjects enrolled into Group 2 will be evaluated using ORFM prototype Radiance. Subjects in Group 3 will be evaluated using the ORFM prototype Brilliance. The primary difference in the prototypes is the sensor—prototype QuantumLeap and Radiance used with Group 1 and 2 subjects will have a "mouse" sized probe that incorporates all the electronics into the sensor itself. Prototype Brilliance used with Group 3 subjects will have a smaller sized probe where the majority of the electronics are found in a tablet connected to the probe. Design change controls and design verification according to 21 CFR 820.30 will be fully applied and documented prior to use in the study.

The study device QuantumLeap (used in Group 1) and the Radiance device (used in Group 2) will be operated solely by the Sponsor. Both devices will be set-up and run in accordance with the applicable ORFM Operator's Manual (OM). The sponsor will also provide oversight of the use of the Brilliance device.

Site staff will place and affix the ORFM device sensors for all enrolled subjects. For subjects in Groups 1 and 2, two separate sensors will be attached via standard adhesive pads to two locations on each subject: sternum and one of the following positions: forehead, occipital triangle, pectoralis major, upper hip, lower hip, chin, and lower sternum. If one location is determined to not be feasible, it may be eliminated from use with future enrolled subjects. In addition, if another location is deemed feasible for testing, it may be selected for use in future study subjects. In Group 3, some subjects may be connected to two Brilliance devices and have a sensor on more than one location.

In Group 3, cohorts 7A, 7B, 8A and 8B, the Brilliance 2-Part Sensor will be placed on subjects in addition to the 1-2 standard Brilliance sensors. The additional sensors will be placed on the sternum or the pectoralis major.

The only parts of the investigational device component (ORFM) that come into contact with the subject is the single-use adhesive pad attached to the sensors. This provides a smooth, surface, which is affixed to the subject's skin. The sensors remain in contact with the skin and are held in place by means of a self-adhesive pad, typical of those used for disposable ECG patches. Sensors placed on the forehead (for Groups 1 and 2) may require an additional head strap in order to maintain the position. The sensors remain affixed to the patient for approximately 9 - 12.5 hours. This may be increased in the extended PK group for up to 16 hours, out to 24 hours for the Cohort 7 multiple dose group and Cohort 8B, and out to 48 hours for Cohort 4 extended PK subjects and Cohort 8 and 8A.

As of amendment 10 (protocol version 11) dated 18 Nov 2020; subjects will also be exposed to a commercially available skin adhesive clip that will attach to the sensor cable. The purpose of this clip is to secure the sensor cable to allow for subject movements. It will be tested in cohorts 7 and 8 only and used in all subset cohorts.

5.6.1 Identity of Investigational Device

The ORMF is manufactured by MediBeacon Inc. (St. Louis, MO, USA). All packaging and labeling operations will be performed according to current Good Manufacturing Practice (GMP), ISO 13485 and the relevant regulatory requirements.

5.6.2 Labeling

Each device will be clearly labelled with a Serial Number. The Brilliance Device will be labelled "CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use" Per 21 CFR 812.5(a).

5.6.3 Storage, Supply and Return/Destruction

Multiple investigational devices (consoles and sensors in Groups 1 and 2) (which will be re-used across study subjects) will be provided to the clinical site. Disposable items (adhesive pads) will be single-subject use only. Devices and disposable materials must be stored in a secure location and are only for use during the clinical trial. All devices will be returned to the Sponsor at the conclusion of the trial. For Group 3, sensors will be single use.

All parts coming in contact with the subject's skin are disposable (adhesive pads).

5.6.4 Device Accountability

All inventory received for clinical trial use will be tracked. Unused inventory will be returned to MediBeacon or disposed of following instructions from the Sponsor. An investigational device accountability record will be kept current and will contain:

- Subject ID (screening number)
- Device(s) console serial number used
- Sensor serial number
- Date of dosing
- Any observations noted during the use of the device on a subject

5.7 Investigational Drug

MB-102 is a bis-serine aminopyrazine that will be used as an exogenous fluorescent Glomerular Filtration Rate (GFR) agent. This agent is excited by blue light and emits green light.

MB-102 has the following characteristics:

- Produces fluorescence in vivo when excited by blue light, which can be reliably detected

by transdermal measurement when MB-102 is injected intravenously
- Has elimination kinetics that allows determination of GFR from fluorescence measurement within a clinically useful timeframe
- Is filtered by the kidney
- Is not protein bound
- Is not expected to undergo secretion or tubular reabsorption
- Is not expected to be metabolized by the liver or other organs
- Is not expected to affect kidney function
- Has been shown to be safe in animal models, in therapeutic dose range
- Is photostable in its administration form and during sample handling and analysis
- Has been shown to be a reasonable GFR tracer agent in nonclinical animal models

A sixty (60) month stability-testing program conducted under Good Manufacturing Practices (GMP) for the Active Pharmaceutical Ingredient (API) Lot # 07-130227-02/02-43-01 used in the Pilot 2 studies was completed. Results show negligible change with respect to the zero time parameters at 60 months.

A sixty (60) month stability-testing program conducted under GMP for our latest manufactured API Lot # 2337-1706-00256 was initiated. Results show negligible change with respect to the zero time parameters at the two year time point.

A 24 month stability-testing program for the GMP formulated product Batch P03915, which is being used for Groups 1 and 2 in this Pilot 2 study, has been completed. Results show negligible change with respect to the zero time parameters.

Formulated product with designation Batch P04517 was manufactured under GMP conditions by AMRI using API Lot # 2337-1706-00256. This batch was placed on stability at 2 - 8°C for a three year period. At the 24 month time point, there is negligible degradation in purity and essentially no change in the total impurity amount.

5.7.1 Identity of Investigational Drug

MB-102 is packaged in amber vials at a concentration of 18.6 mg/mL in a 3 mL volume. MB-102 in formulation includes the following: sodium dihydrogen phosphate monohydrate, sodium hydroxide, sodium chloride, water for injection. Instructions for preparation of MB-102 for investigational use will be included in the Study Procedure Manual.

5.7.2 Investigational Drug Labeling

MB-102 drug labels include the following information:

MP-3180 (MB-102)
18.6 mg/mL solution for injection
3mL of MP-3180 (MB-102) in formulation
Product for IV use only

Lot No: XXXXX Mfg Date: XX/XXX/XXXX

Caution: New Drug-Limited by Federal (or United States) law to investigational use.
Manufactured by:
AMRI (Glasgow) Limited
Todd Campus, West of Scotland Science Park
Acre Road, Glasgow, G20 OXA, UK

5.7.3 Investigational Drug Storage, Supply, Return/Destruction

MB-102 vials should be stored at 2°C – 8°C in a secure location. Records of temperature will be maintained by the clinical site.

Adequate supply from manufacturing lots (batch numbers P03915/1 and P04517-1) will be provided to the investigational site.

All study medications will be stored, reconciled and either returned to the sponsor or destroyed according to applicable regulations following authorization by MediBeacon or designee.

5.7.4 Investigational Drug Accountability

Drug accountability will be maintained by the clinical site and will be reviewed during the study and 100% reconciled at the conclusion of the trial.

Drug accountability documentation may include, but may not be limited to, the following information:

- Receipt date
- Lot
- Expiry and/or manufacture date
- Dispensing information

5.8 Reference Drug

Iohexol (Omnipaque™ 300) is an FDA approved iodinated contrast media used to enhance x-ray or CT imaging tests. It has minimal protein binding and approximately 80-90% is excreted in the urine.

Omnipaque™ is provided as a sterile, pyrogen-free, colorless to pale-yellow solution. The concentration used as the reference standard in this trial is 647 mg/mL. Five millilters (5 mL) will be administered therefore the total dose received will be 3,235 mg. *Note: typical doses administered in accordance with the Package Insert for Omnipaque™ 300 for imaging procedures range from 50 – 200 mL (32.4 – 129.0 g).*

Each milliliter of iohexol contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide.

The Package Insert for Omnipaque™ is provided as **Appendix B: Package Insert for Omnipaque™ 300**.

5.9 Contact Procedures for Medical Issues Requiring Immediate Attention

Any medical-related issues or questions requiring immediate resolution or direction should be directed to the Sponsor medical monitor using the contact information listed below:

[redacted]

5.10 Prior and Concomitant Therapy

Throughout the study, investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate care, with the exception of other investigational agents or drugs that may alter renal function. All attempts should be made to maintain the subjects on a stable dosing regimen of medications from screening through the duration of the study.

Concomitant medication information will be collected for all subjects within 7 days of dosing through the follow-up visit. Additionally, use of any non-drug procedural therapies will be recorded for each subject including the nature of the therapy, the date/time of the procedure, and the reason for the therapy. Concomitant medication information taken at the time of an SAE will also be collected during the safety data follow-up.

5.10.1 Prohibited Concomitant Medications

The use of NSAIDs are prohibited 2 days prior to dosing for all subjects.

5.10.2 Stable Use of Immunosuppressive Medications

The protocol currently allows for subjects on immunosuppressant medications. This is due to the fact that these medications are common to this subject population and that iohexol serves as a "within subject" control for any changes in eGFR over time that may be associated with this group of medications. **Table 3** lists those medications that fall into this category and outlines timelines around stability of those medications required for enrollment.

Table 3 Dose Stability Timelines for Subjects on Immunosuppressive Agents

Immunosuppressive Agent	Dose Stability Timeframe
Antithymocyte Globulin (rabbit)	No changes within 90 days
Basiliximab	No changes within 90 days
Infliximab	No changes within 90 days
Antithymocyte Globulin (equine)	No changes within 90 days
Rituximab	No changes within 90 days
Cyclosporine	No changes within 30 days
Tacrolimus	No changes within 30 days

6 Study Procedures

6.1 Schedule of Assessments and Procedures

The schedule of planned study assessments is shown in **Table 4** for Groups 1 and 2 and in **Table 5** for Group 3 Cohort 5 only, **Table 6** for Group 3: SOG, SeVG-1 and 2, Cohort 6, Cohorts 7 (Single Dose) and 8; and **Table 7** for Cohort 7 (multiple dose subjects).

Table 4 ORFM Pilot 2 Study Schedule (Groups 1 and 2)

Period	Screening	Dosing Day	Dosing Day	Dosing Day	Follow-up Visit
	≤40 days to day -2 prior to Dosing	*Pre-dose*	*Dosing*	*Post-dose*	*7 days +/- 3 days*
Informed Consent[a]	X				
Inclusion / Exclusion	X	X			
Demographics	X				
Medical History	X	X			
Pregnancy Test for WOCBP[b]	X	X			X
PE or Limited PA[c]	X	X			X
Vital Signs[d]	X	X		X	X
Height and Weight[e]	X	X			
Clinical Labs[f]	X	X		X	X
ORFM Data Collection[g]		X	X	X	
Administration of MB-102[h]			X		
Administration of iohexol[h]			X		
PK blood collection[i]		X		X	
Urine collection[j]		X		X	
ECG[k]	X	X		X	
Hep B/C Testing	X				
Water / Food[l]		X		X	
Concomitant Therapies[m]	X	X		X	X
Adverse Events[n]			X	X	X
Document Fitzpatrick Skin Color Type	X				

Groups 1 and 2 Table Legend

a. Consent is prior to any study related procedures being conducted.
b. Negative pregnancy serum human chorionic gonadotropin (hCG) test at screening for women of childbearing potential (WOCBP) is required for eligibility and at the follow-up visit. On dosing day, a urine pregnancy test will be conducted for WOCBP
c. A full physical examination (PE) is required at the screening visit. A full PE or limited physical assessment (PA) may be conducted prior to dosing and (if symptoms direct) within the last 2 hours of PK assessments (Limited PA includes assessments of HEENT, cardiovascular, abdominal systems). A full or limited exam may be conducted at the follow-up visit.
d. Vital signs include blood pressure (BP), respiration rate, heart rate and temperature. Note: temperature is collected at screening, pre-dose, at the conclusion of dosing day (and at the 24 and 48 hour vital sign collection for the extended PK subgroup) and at the follow-up visit (and not during multiple timepoints on dosing day). Whenever possible, the subject should be seated and resting for approximately 5 minutes prior to all measurements. Vital signs will be collected at screening, pre-dose and at the following post-dose timepoints: [6, 11, 16 min (±1 min)]; [35, 65, 95, 125 min (±5 min)]; [185, 245, 305, 365, 485, 605, 725 min (±10 min)]. The extended PK group will have additional vital signs measured at [965 (±10 min)] and [1445, 1925, 2405, 2885 min (±30 min)].
e. Height and Weight should be measured at screening and weight only verified on dosing day
f. Clinical laboratory assessments will be analyzed by a central laboratory and consist of the measurements noted in **Table 8**. Coagulation panel will be conducted at Screening, pre-dose, and as part of the post-dose draw clinical labs at 720 min.
g. ORFM data collection will commence prior to dose administration. At least 15 minutes prior to dosing, sensors should be placed on the subject and the ORFM device started. Data collection will continue through 12 hours of PK sampling and up to 16 hours in the extended PK group.
h. MB-102 will be administered via IV bolus injection over a 30 second injection period. This will be followed by a 10 mL saline flush over 30 seconds. Time of administration will be recorded. Iohexol will be administered after completion of the saline flush following MB-102 administration. Iohexol should also be injected IV over 30 seconds followed by a 10 mL saline flush over 30 seconds.
i. PK blood draws will be collected at the following timepoints: pre-dose and 5, 10, 15; (± 1 or 2 min), 30, 60, 90, 120, 180, 240, 300 (±5 min), 360, 480, 600 and 720 (±10 min) minutes post dose. Blood draws should be via a venous catheter and will be processed in accordance with instructions available in the Study Procedure Manual. Subjects enrolled in the extended PK subgroup will have additional PK sampling at [960 (16 hours), 1440 min (24 hours), 1920 min (32 hours) and 2400 (40 hours) 2880 min (48 hours) (±30 min)].
j. Urine collection will occur pre-dose, and whenever urination occurs. The time of collection will be obtained, and a sample collected in accordance with the instructions in the Study Procedure Manual. The total volume of urine excreted during the pre-dose through the 12 or 48 hour extended PK period will be recorded.
k. A 12 lead electrocardiogram (ECG) will be performed at Screening, Pre-dose, and at the following post-dose time-points: 55 min (± 5 min), 115 min (± 5 min), 235 min (±5 min) and 740 min (±10 min). In addition, subjects in the extended PK group will have an ECG collected at 1420 min (±30 min) and 2860 min (±30 min). Subjects should be resting quietly for 10-15 minutes prior to the ECG collection.
l. Subjects will be required to consume 240 mL of ambient temperature water approximately 1 hour prior to dosing and again at approximately 30 minutes prior to dosing. Following dosing, water consumption will be permitted *ab libitum.* A standard meal will be provided as a breakfast, lunch and dinner at appropriate times during the dosing day. Snacks and juice drinks may also be provided.
m. Concomitant medications administered within 7 days prior to baseline through the final follow-up visit will be recorded.
n. Adverse events are collected from the time of dosing through the follow-up visit.

Table 5 ORFM Pilot 2 Study Schedule: Group 3, Cohort 5 only

Period	Screening	Dosing Day	Dosing Day	Dosing Day	Follow-up Visit
	≤40 days to day -2 prior to Dosing	*Pre-dose*	*Dosing*	*Post-dose*	*7 days +/- 3 days*
Informed Consent[a]	X				
Inclusion / Exclusion	X	X			
Demographics	X				
Medical History	X	X			
Pregnancy Test for WOCBP[b]	X	X			X
PE or Limited PA[c]	X	X			X
Vital Signs[d]	X	X		X	X
Height and Weight[e]	X	X			
Clinical Labs[f]	X	X		X	X
Mexameter measurements[g]		X		X	
Sensor photographs[h]		X	X	X	
ORFM Data Collection[i]		X	X	X	
Administration of MB-102[j]			X		
PK blood collection[k]		X		X	
ECG[l]	X	X		X	
Hep B/C Testing	X				
Water / Food[m]		X		X	
Concomitant Therapies[n]	X	X		X	X
Adverse Events			X	X	X
Document Fitzpatrick Skin Color Type	X				

Group 3 Cohort 5 Table Legend

a. Consent is prior to any study related procedures being conducted.
b. Negative pregnancy serum human chorionic gonadotropin (hCG) test at screening for women of childbearing potential (WOCBP) is required for eligibility and at the follow-up visit. On dosing day, a urine pregnancy test will be conducted for WOCBP
c. A full physical examination (PE) is required at the screening visit. A full PE or limited physical assessment (PA) may be conducted prior to dosing and (if symptoms direct) within the last 2 hours of PK assessments (Limited PA includes assessments of HEENT, cardiovascular, abdominal systems). A full or limited exam may be conducted at the follow-up visit.
d. Vital signs include blood pressure, respiration rate, heart rate and temperature. Note: temperature is collected at screening, pre-dose, at the conclusion of dosing day and at the follow-up visit (and not during multiple timepoints on dosing day). Whenever possible, the subject should be resting for approximately 5 minutes prior to all measurements. Vital signs will be collected at screening, pre-dose and at the following post-dose timepoints: [6, 11, 16 min (±1 min)]; [35, 65, 95, 125, 185, 245, 305, 365, 485 min (±5 min)].
e. Height and Weight should be measured at screening and weight only verified on dosing day
f. Clinical laboratory assessments will be analyzed by a central laboratory and consist of the measurements noted in **Table 8**. Coagulation panel will be conducted at Screening, pre-dose, and as part of the post-dose draw clinical labs.
g. Measurements of melanin content and erythema in the skin will be taken prior to sensor placement at locations on the skin where the sensor(s) will be placed, each time a sensor is removed or becomes detached, and at the final removal
h. Photographs (digital) may be taken of the sensor once it is affixed to the skin. Subject faces or identifying features will not be included in the photographs.
i. ORFM data collection will commence prior to dose administration. At least 15 minutes prior to dosing, sensors should be placed on the subject and the ORFM device started. Data collection will continue through 8 hours of PK sampling.
j. MB-102 will be administered via IV bolus injection over a 30 second injection period. This will be followed by a 10 mL saline flush over 30 seconds. Time of administration will be recorded.
k. PK blood draws will be collected at the following timepoints: pre-dose and 5, 10, 15; (± 1 or 2 min), 30, 60, 90, 120, 180, 240, 300 (±5 min), 360, 480 (±10 min) minutes post dose. Blood draws should be via a venous catheter and will be processed in accordance with instructions available in the Study Procedure Manual.
l. A 12 lead ECG will be performed at Screening, Pre-dose, and at the following post-dose time-points: 55 min (± 5 min), 115 min (± 5 min), 235 min (±5 min) and 460 min (±10 min).
m. Subjects will be required to consume 240 mL of ambient temperature water approximately 1 hour prior to dosing and again at approximately 30 minutes prior to dosing. Following dosing, water consumption will be permitted *ab libitum.* A standard meal will be provided as a breakfast, lunch and dinner at appropriate times during the dosing day. Snacks and juice drinks may also be provided.
n. Concomitant medications administered within 7 days prior to baseline through the final follow-up visit will be recorded.

Table 6 ORFM Pilot 2 Study Schedule: Group 3, SOG SeVG-1, SeVG-2, Cohort 6, Cohort 7 (Single Dose Subjects) and 8, 8A and 8B

Period	Screening	Dosing Day	Dosing Day	Dosing Day	Follow-up Visit
	≤40 days to day -2 prior to Dosing	*Pre-dose*	*Dosing*	*Post-dose*	*7 days +/- 3 days*
Informed Consent[a]	X				
Inclusion / Exclusion	X	X			
Demographics	X				
Medical History	X	X			
Pregnancy Test for WOCBP[b]	X	X			X
PE or Limited PA[c]	X	X		X	X
Vital Signs[d]	X	X		X	X
Height and Weight[e]	X	X			
Clinical Labs[f]	X	X		X	X
Mexameter measurements[g]		X		X	
Sensor photographs[h]		X	X	X	
ORFM Data Collection[i]		X	X	X	
Administration of MB-102[j]			X		
PK blood collection[k]		X		X	
ECG[l]	X	X		X	
Hep B/C Testing	X				
Water / Food[m]		X		X	
Concomitant Therapies[n]	X	X		X	X
Adverse Events			X	X	X
Document Fitzpatrick Skin Color Type	X				

Table 5 Legend Group 3, SOG Cohort, SeVG-1, SeVG-2, Cohort 6, Cohort 7 (Single Dose Subjects) and Cohort 8, 8A and 8B

a. Consent is prior to any study related procedures being conducted.
b. Negative pregnancy serum human chorionic gonadotropin (hCG) test at screening for women of childbearing potential (WOCBP) is required for eligibility and at the follow-up visit. On dosing day, a urine pregnancy test will be conducted for WOCBP
c. A full physical examination (PE) is required at the screening visit. A full PE or limited physical assessment (PA) may be conducted prior to dosing and (if symptoms direct) within the last 2 hours of the first treatment day (Limited PA includes assessments of HEENT, cardiovascular, abdominal systems). A full or limited exam may be conducted at the follow-up visit.
d. Vital signs include blood pressure, respiration rate, heart rate and temperature. Note: temperature is collected at screening, pre-dose, at the conclusion of dosing day and at the follow-up visit (and not during multiple timepoints on dosing day). Whenever possible, the subject should be resting for approximately 5 minutes prior to all measurements. Vital signs will be collected at screening, pre-dose and at the following post-dose timepoints: [6, 11, 16 min (±1 min)]; [35, 65, 95, 125, 185, 245, 305 min (±5 min)]; 365, 485, 605 and 725 min (±10 min)]. Subjects enrolled in Cohort 8A will have additional vital signs measured at [965 (±10 min)] and [1445, 1925, 2405, 2885 min (incl. temp) (±30 min)]. Vital signs for subjects in Cohort 8B will stop at 24 hours.
e. Height and Weight should be measured at screening and weight only verified on dosing day
f. Clinical laboratory assessments will be analyzed by a central laboratory and consist of the measurements noted in **Table 8**. Coagulation panel will be conducted at Screening, pre-dose, and as part of the post-dose draw clinical labs (at the end of treatment day 1).
g. Measurements of melanin content and erythema in the skin will be taken prior to sensor placement at locations on the skin where the sensor(s) will be placed, each time a sensor is removed, replaced or becomes detached, and at the final removal
h. Photographs (digital) may be taken of the sensor once it is affixed to the skin. Subject faces or identifying features will not be included in the photographs.
i. ORFM data collection will commence prior to dose administration. At least 15 minutes prior to dosing, sensors, including an adhesive clip to secure the sensor cable [cohort 7 and 8 subjects enrolled under protocol version 11], should be placed on the subject and the ORFM device started. Data collection will continue through 12 hours (or 24 - 48 hours for Cohort 8, 8A or 8B) of PK sampling.
j. MB-102 will be administered via IV bolus injection over a 30 second injection period. This will be followed by a 10 mL saline flush over 30 seconds. Time of administration will be recorded. Subjects in Cohorts 7 and 8 (and a subset of the SeVG cohort) will receive a fixed dose of 7 mL (130 mg).
k. PK blood draws will be collected at the following timepoints: pre-dose and 5, 10, 15; (± 1 or 2 min), 30, 60, 90, 120, 180, 240, 300 (±5 min), 360, 480, 600 and 720 (±10 min) minutes post dose. Subjects enrolled in Cohort 8 and 8A will have additional PK sampling at [960 (16 hrs), 1440 min (24 hrs), 1920 min (32 hrs) and 2400 (40 hrs) 2880 min (48 hrs) (±30 min)]. Those in Cohort 8B will have draws stopping at 24 hours. Blood draws should be via a venous catheter and will be processed in accordance with instructions available in the SPM.
l. A 12 lead ECG will be performed at Screening, Pre-dose, and at the following post-dose time-points: 55 min (± 5 min), 115 min (± 5 min), 235 min (±5 min), and 740 min (±10 min). Subjects enrolled in Cohort 8 will have an ECG performed at 1420 min and 2860 min (±30 min)
m. Subjects will be required to consume 240 mL of ambient temperature water approximately 1 hour prior to dosing and again at approximately 30 minutes prior to dosing. Following dosing, water consumption will be permitted *ab libitum.* A standard meal will be provided as a breakfast, lunch and dinner at appropriate times during the dosing day. Snacks and juice drinks may also be provided.
n. Concomitant medications administered within 7 days prior to baseline through the final follow-up visit will be recorded.

Table 7 Group 3 Cohort 7 (Multiple Dose Subjects)

Period	Screening	Dosing Day	Dosing Day	Dosing Day	Dosing Day	Dosing Day	Dosing Day	Follow-up Visit
	≤40 days to day -2 prior to Dosing	*Pre-dose 1*	*Dosing 1st Dose*	*Post-dose 1*	*Pre-dose 2*	*Dosing 2nd dose*	*Post-dose 2*	*7 days +/- 3 days*
Informed Consent[a]	X							
Inclusion / Exclusion	X	X						
Demographics	X							
Medical History	X	X						
Pregnancy Test for WOCBP[b]	X	X						X
PE or Limited PA[c]	X	X						X
Vital Signs[d]	X	X		X	X		X	X
Height and Weight[e]	X	X						
Clinical Labs[f]	X	X		X			X	X
Mexameter measurement		X		X	X		X	
Sensor Photographs[h]		X	X	X	X	X	X	
Transdermal Data Collection[g]		X	X	X	X	X		
Administration of MB-102[h]			X			X		
PK blood collection[i]		X		X	X		X	
ECG[j]	X	X		X	X		X	
Hep B/C Testing	X							
Water / Food[k]		X		X	X		X	
Concomitant Therapies[l]		X	X	X	X	X	X	X
Adverse Events[m]			X	X	X	X	X	X
Document Fitzpatrick Skin Color Type	X							

Table Legend for Group 3 Cohort 7 (including subsets 7A and 7B) (Multiple Dose Subjects with 24/36 hour follow-up)

a. Consent is prior to any study related procedures being conducted.
b. Negative pregnancy serum human chorionic gonadotropin (hCG) test at screening for women of childbearing potential (WOCBP) is required for eligibility and at the follow-up visit. On dosing day, a urine pregnancy test will be conducted for WOCBP who agree to use an acceptable method of birth control
c. A full physical examination (PE) is required at the screening visit. A full PE or limited physical assessment (PA) may be conducted prior to dosing on each day and within 2 hours of completion of the dosing day (if symptoms direct). (Limited PA includes assessments of HEENT, cardiovascular, abdominal systems). A full or limited exam may be conducted at the follow-up visit.
d. Vital signs include blood pressure, respiration rate, heart rate and temperature. Note: temperature is collected at screening, pre-dose (for both doses), at the conclusion of dosing day and at the follow-up visit (and not during multiple timepoints on dosing day). Whenever possible, the subject should be resting for approximately 5 minutes prior to all measurements. Vital signs will be collected at screening, pre-dose and at the following post-dose timepoints: [6, 11, 16 min (±1 min)]; [35, 65, 95, 125, 185, 245, 305 min (±5 min)]; 365, 485, 605, 725 min (±10 minutes). Additional vital signs will be collected prior to the 2nd dose being administered. Vital signs will be collected at the following timepoints after the 2nd dose is given: [6, 11, 16 min (±1 min)]; [35, 65, 95, 125, 185, 245, 305 min (±5 min)]; 365, 485, and 605 (±10 min). Note: for Cohort 7 and 7A, the 2nd dose is administered 12 hours after the first; for cohort 7B, the 2nd dose is administered 24 hours after the first dose.
e. Height and Weight should be measured at screening and weight only verified on dosing day. For Cohort 7A (enrolled under Amendment 12) and Cohort 7B, weight will also be recorded on dosing day.
f. Clinical laboratory assessments will be analyzed by a central laboratory and consist of standard chemistry, hematology and urinalysis parameters (**Table 8)**. Coagulation panel will be conducted at Screening only, pre-dose and as part of the follow-up labs on dosing day. Labs will be drawn pre-dose and at 720 minutes (± 10 minutes) post dose 1.
g. ORFM data collection will commence prior to dose administration. At least 15 minutes prior to dosing, sensors, including an adhesive clip to secure the sensor cable [cohort 7 subjects enrolled under protocol version 11], should be placed on the subject and the ORFM started. Data collection will continue through the duration of PK sampling out to 10 hours even if the device indicates transdermal MB-102 can no longer be detected.
h. MB-102 will be administered as a fixed dose of 7 mL (130 mg) via IV bolus injection over a 30 second period. This will be followed by a 10 mL saline flush over 30 seconds. Time of administration will be recorded. The 2nd dose administered will also be a fixed dose of 7 mL (130 mg) delivered as described above. All subjects in Cohort 7/7A will have a 2 hour wash-out period after the 10 hour PK mark; subjects in Cohort 7B will have a 12 hour wash-out period after the final dose 1 PK collection. Preparation of the subject for the 2nd dose should start at approximately 11.5 hours from the first dose for Cohort 7/7A. The original sensor will remain attached to the subject in Cohorts 7/7A.
i. PK blood draws will be collected at the following timepoints: pre-dose and 5, (±1 min), [for Cohort 7A and 7B, a 60 minute PK sample will also be collected], 120, 180, 240, 300, (±5 min), 360, 480 and 600 (±10 min). For Cohort 7B, a PK draw will also be performed at 720 min (±10 min). A pre-dose 2 blood draw will be collected prior to the 2nd dose. Blood draws will re-start after the administration of the 2nd dose and be collected at the following timepoints: 5, (±1 min), [for Cohorts 7A and 7B, a 60 minute PK sample will also be collected], 120, 180, 240, 300 (±5 min), 360, 480, 600 (±10 min)]. Blood draws should be via a venous catheter and will be processed in accordance with instructions available in the Study Procedure Manual.
j. A 12 lead ECG will be performed at Screening, Pre-dose, and at the following post-dose time-points: 55 min, 115 min, 235 min (±5 min) and at 730 min (± 10 min). After the 12 hour rest for Cohort 7B, a pre-2nd dose ECG will be performed. Post-2nd dose ECG collection will follow the same timepoints: 55 min, 115 min, 235 min (±5 min), and 610 (± 10 min). Subjects should be resting quietly for 10-15 minutes prior to the ECG

collection.

k. Concomitant medications administered within 7 days prior to baseline through the final follow-up visit will be recorded.
l. Adverse events are collected from the time of dosing through the follow-up visit.

6.2 Screening

Screening will occur within 40 days (but at least 2 days prior to) the baseline / dosing day and will comprise of the following:

- Obtain written informed consent before any study-specific assessments are performed
- Assess eligibility against the inclusion and exclusion criteria
- Collect demographic data and medical history
- Obtain screening non-fasting laboratory tests including chemistry, hematology, lipid and coagulation profile (See **Section 7.1.2.6** and **Table 8**. Test for Hepatitis B/C, perform serum pregnancy test in women of child-bearing potential and collect a urine sample for urinalysis.
- Based on the results of the screening creatinine, calculate eGFR using the CKD-EPI equation (Levey, et al., 2009); or (for Group 2 and 3) record a historical eGFR available within 40 days of screening
- Collect height and weight measurements
- Perform a full physical exam and collect vital signs including temperature (**Sections 7.1.2.7** and **7.1.2.8**)
- Perform a 12 lead ECG (**Section 7.1.2.9**)
- Review concomitant medications for exclusionary medications and stability of over the counter (OTC) and prescription drugs
- Document Fitzpatrick Skin Scale Color Type (**Appendix A Fitzpatrick Scale**)
- Subjects should be reminded to drink 240 mL of water approximately 1 hour prior to their scheduled dosing time (therefore subjects should be encouraged to drink this prior to coming to the study site on dosing day).

6.3 Dosing Day: Baseline Assessments

Baseline assessments will be performed prior to dosing. Some assessments (subject eligibility review, medical history update, concomitant medication review, ECG and physical exam) may be performed the night prior to dosing for subjects brought into the study centers overnight. Vitals must be recorded prior to MB-102 administration.

- Update medical history with any new information or issues occurring since the initial screening visit.
- Review subject eligibility

- For subjects enrolled in Cohort 7A (Protocol version 13.0) and Cohort 7B, a weight will be collected
- Confirm that the subject has consumed 240 mL of ambient water at least 1 hour prior to dosing time.
- A venous catheter should be placed in one arm for PK blood draws. A pre-dose baseline draw should be collected.
- A second catheter should be placed in the opposite arm for dosing of MB-102 and iohexol (Groups 1 and 2 only). Following dose completion, this catheter can be removed.
    - For Cohort 7A (enrolled under Protocol Version 13.0) and Cohort 7B, a butterfly catheter will be used for MB-102 dosing.
- Obtain baseline laboratory tests including chemistry, lipids, hematology, coagulation and urinalysis (**Section 7.1.2.6** and **Table 8**).
- Perform a limited physical assessment and collect vital signs (including temperature) (**Sections 7.1.2.7** and **7.1.2.8**). Ensure the subject's weight has remained consistent since screening.
- Record concomitant medications taken within 7 days of the baseline visit
- Perform a 12 lead ECG (**Section 7.1.2.9**)
- Prior to dosing, have the subject consume 240 mL of ambient water
- A pre-dose urine sample will be collected in accordance with the instructions in the Study Procedure Manual. The total volume of urine excreted from this sample until 12 hours post-dose will be recorded or out to 48 hours for the extended PK group. Urine PK sampling applies to Group 1 and 2 only (urine PK will not be performed for Group 3 subjects).
- For WOCBP, a urine pregnancy test will be performed
- *For Group 3 subjects only: Mexameter readings of melanin and erythema will be measured at the intended site of sensor placements.*
- Prior to dosing, the device sensors should be attached to the subject (one probe on the sternum, and for some subjects, a second on an assigned location) and ORFM data acquisition initiated.
    - For subjects in Cohort 7 and 8 subset cohorts (7A, 7B, 8A and 8B) the additional sensor will be placed (the 2-Part Brilliance Sensor) and data acquisition initiated

- Baseline data acquisition for subjects enrolled in Cohorts 7 and 8 may be collected for 20 – 90 minute period prior to MB-102 administration. During this period, no procedures or assessments should be performed, and subjects will be instructed to remain very still.

- *For Group 3 subjects only: photographs of the sensor placement may be collected. Photographs will not include any identifying features or the subject's face.*

6.4 MB-102 Dosing (All Groups)

The dose of MB-102 should be available and the dose prepared based on the subject's weight and assignment to dose strata and in accordance with instructions provided in the Study Procedure Manual with the exception of the subset of subjects who weigh greater than 110 lbs (50 kg) in SeVG cohort who will receive a fixed dose of 130 mg MB-102 (7 mL). In addition, all subjects (regardless of weight) in Cohorts 7 and 8 will receive the fixed dose of 130 mg. Final dose calculation should also be based on weight and not volume. The prepared syringe should be maintained at ambient temperature. MB-102 and iohexol dosing (when applicable) will be performed in the opposite arm from PK draws whenever feasible.

Administration of MB-102 will be through a catheter placed in the arm (typically the antecubital fossa though other locations are acceptable) of subjects for all cohorts with the exception of Cohort 7A (enrolled under Protocol Version 12.0) and Cohort 7B. Ideally, a 21-gauge needle and 10 mL syringe (for subjects receiving the fixed dose) should be used for administration. Subjects in Cohort 7A (under Protocol Version 12.0) and Cohort 7B will be dosed via direct IV injection through a butterfly catheter.

- Ensure Universal Standard precautions are taken with handwashing and gloving procedures; maintain aseptic technique when handling the prepared syringe
- The site should ensure patency of the catheter by initially flushing with saline or a heparin solution. Assessing patency of the placed catheters every 8 hours or so will also ensure ease of the PK draws. Any catheter that shows resistance to flush or if blood is unable to be drawn out should be replaced.
- Prior to MB-102 administration, ensure blood can be removed from the catheter. For Cohort 7A (under Protocol Version 12.0) and Cohort 7B subjects, a butterfly catheter will be used for MB-102 injection which will be removed from the arm after dosing.
- Administration of MB-102 should be via a steady bolus injection (without hard pressure) over 30 seconds
- Following MB-102, a 10 mL saline flush should be administered over 30 seconds
- The injection site should be observed for swelling or induration.
- For all 2nd dose administration for cohorts 7A and 7B, a different vein in the same arm will be used for dosing.

To avoid extravasation/infiltration:

- Ensure no dislodgement of the catheter or needle cannula during venipuncture
- Ensure the vein wall is not punctured during placement
- Ensure appropriately sized catheters are used for the vein size of the subject

- Avoid strong pressure on the syringe plunger during saline or MB-102 administration

It is particularly important for site teams to check the patency of catheters used for the second MB-102 administration in Cohort 7 subjects receiving a second dose of MB-102. If a catheter is determined to be compromised in anyway, another catheter may be placed for dosing in the same arm as the original catheter. Note: catheters used for MB-102 dosing should not be re-used for PK draws. Cohort 7A (under Protocol Version 12.0) and Cohort 7B subjects will be dosed directly via IV injection through a butterfly catheter.

The time noted at the completion of MB-102 injection is the start-time for the timing of the PK draws.

- Adverse event collection begins

6.5 Iohexol Dosing (Groups 1 and 2 only)

- 5 mL of iohexol will be administered as a bolus via IV over approximately 30 seconds
- 10 mL saline flush will be administered via IV over approximately 30 seconds

6.6 Post-dose Study Procedures

Post dose study procedures are outlined in **Section 13** for each of the various Groups and Cohorts:

- **13.1 Group 1 (Cohorts 1 and 2) and Group 2 (Cohorts 3 and 4 subset)**
- **13.2 Post-Dose Procedures: Group 2 (Cohort 4 Extended PK Subgroup only)**
- **13.3 Post-Dose Procedures: Group 3: Cohort 5**
- **13.4 Post-Dose Procedures: Group 3: SOG**
- **13.5 Post-Dose Procedures: Group 3: SeVG, Cohort 6 and 7, 7A: Single Dose Subgroup**
- **13.6 Post-Dose Procedures: Group 3: Cohort 7, 7A and 7B: Multiple Dose Subgroup**
- **13.7 Post-Dose Procedures: Group 3: Cohort 8 and 8A**
- **13.8 Post-Dose Procedures: Group 3: Cohort 8B**

6.7 Follow-up Visit

Subjects will return for a safety follow-up visit approximately 7 +/-3 days after dosing. The following assessments will be performed

- Obtain laboratory tests including chemistry, lipids, hematology and urinalysis [and pregnancy test for WOCBP], (**Section 7.1.2.6** and **Table 8**).
- Perform a full or limited physical exam and collect vital signs including temperature (**Sections 7.1.2.7** and **7.1.2.8**)
- Record concomitant medications
- Collect adverse events

6.8 Early Withdrawal / Unscheduled Visits

Any subjects that withdraws from the study early for any reason, or who needs to have an unscheduled visit performed to assess a safety issue, will have the following assessments performed:

- Obtain laboratory tests including chemistry, lipids, hematology, and urinalysis profile (**Section 7.1.2.6** and **Table 8**).
- Perform a full or limited physical exam and collect vital signs including temperature (**Sections 7.1.2.7** and **7.1.2.8**)
- Record concomitant medications
- Collect adverse events
- Record withdrawal date and reason for withdrawal, if appropriate

7 Efficacy and Safety Variables

7.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 4, Table 5, Table 6 and **Table 7** in **Section 6.1** shows the planned study assessments.

7.1.1 Efficacy Assessments

This pilot study is not designed to address treatment efficacy rather it is to evaluate the use of MB-102 and the ORFM device to provide a point of care (POC) means to collect GFR data.

7.1.2 Safety Assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit after screening. Planned safety assessments are detailed in the ORFM Pilot 2 Study Schedule (**Table 4, Table 5, Table 6** and **Table 7**). The investigators or site staff will be responsible for monitoring the safety of subjects who have entered this study and will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE). Significant findings that were noted to be

present at or prior to dosing must be included in the relevant medical history page of the eCRF. Significant new findings that begin or worsen after dosing must be recorded on the AE page of the eCRF. Subjects should be followed until the event is resolved or stabilized. AEs are collected from the time of dosing until the completion of the follow-up visit.

7.1.2.1 Adverse Events

Adverse Event Definition

An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, temporally associated with the use of a medicinal product, whether or not related to the investigational medical device or drug.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. For the purposes of this trial, the device is the ORFM and the sensor system including the adhesive pads for the attachment of the optical sensors to the body.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. The following data should be documented for each AE:

- Description/term of the symptom event (underlying diagnosis)
- Date of first occurrence and date of resolution (if applicable)
- Classification of "serious" or "not serious" (**Section 7.1.2.2**)
- Severity
- Causal relationship
- Action taken
- Outcome of event

For abnormal clinically significant laboratory findings, the clinical manifestation (diagnosis) should be noted as an adverse event (e.g. anemia instead of low hemoglobin). Should a clinically significant lab abnormality occur that is not part of a diagnosis, the abnormality itself may be reported as an AE. Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to normal or an adequate explanation of the abnormality is determined. When an abnormal laboratory result corresponds to a sign/symptom of an already reported AE it is not necessary to separately record the lab result as an additional AE.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

- **Mild:** results in minimal transient impairment of a body function or damage to a body structure and/or does not require any intervention other than monitoring or OTC medication.

- **Moderate:** Results in moderate transient impairment of a body function or transient damage to a body structure and/or requires intervention, such as administration of medication or transfusion or laparoscopic or endoscopic procedure to prevent permanent impairment of a body function or damage to a body structure.

- **Severe:** An event which is life threatening, results in permanent impairment of a body function or permanent damage to a body structure or necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure.

The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as serious, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient‘s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

An event that changes in severity (gets worse or gets better) should be noted as its worst severity.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study device (and components), investigational drug or the reference standard (iohexol). Causality should be assessed using the categories presented below:

Unrelated	Clinical event with an incompatible time relationship to study device or study drug, and that could be explained by underlying disease or other drugs or is incontrovertibly not related to the study device.
Unlikely	Clinical event whose time relationship to study device investigational drug makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs.
Possible	Clinical event with a reasonable time relationship to study device or investigational drug, but that could also be explained by concurrent disease or other drugs.

Probable	Clinical event with a reasonable time relationship to study device or investigational drug, and is unlikely to be attributed to concurrent disease or other drugs.
Very Likely/Certain	Clinical event with plausible time relationship to study device or investigational drug, and that cannot be explained by concurrent disease or other drugs.

AEs that are deemed related should be further assessed to determine if a relationship to the investigational drug, device or reference standard can be elucidated.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Concomitant interventional treatment(s) administered (includes medications or procedures)
- Other, specify

Outcome of the Event

The investigator will describe the outcome of the event in the appropriate section of the eCRF, as follows:

- Unknown
- Resolved
- Ongoing
- Resolved with sequelae
- Death (with date and cause reported)

Follow-up of Adverse Events

Subjects with AEs should be followed until the event is resolved or until, in the opinion of the investigator and medical monitor, the event is stabilized or determined to be chronic.

7.1.2.2 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any AE from this study that results in one of the following outcomes:

An adverse event that:
a) led to death;
b) led to serious deterioration in the health or the subject, that either resulted in:

1) a life threatening illness or injury or
2) a permanent impairment of a body structure or a body function, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;

c) led to fetal distress, fetal death or a congenital abnormality or birth defect

Reporting requirements for all SAEs is detailed in **Section 7.1.2.3**.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a serious adverse event.

7.1.2.3 Reporting of Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study whether or not the event is considered to be related to the ORFM device, investigational drug or reference standard. All serious adverse events must be reported by the Investigator (or designee) by submitting the Serious Adverse Event Report Form to the Sponsor or designee, within 24 hours of learning of the adverse event.

The Sponsor, or their designee, in cooperation with the Investigator, will assess all serious adverse events considered device-related for potential reportability to regulatory authorities and ethical committees as an Unanticipated Adverse Device Effect (UADE) or as an expedited serious adverse event.

Note: It is also the responsibility of the Investigator to inform their Independent Ethics Committee (IEC) of other serious adverse events (i.e. non-UADEs) as required by their IEC procedures and in conformance with regulations.

SAEs must be reported on an SAE Report Form via email within 24 hours of site knowledge to: CLINCALSTUDIES@MEDIBEACON.COM

The investigator should not wait to receive additional information to document fully the event before notification to the Sponsor of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time and linked by the investigator to this study, should be reported to MediBeacon.

The sponsor or designee will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the IEC approval/favorable opinion of the study. In addition, the sponsor, will expedite the reporting to all concerned investigators, to the IECs, and to the regulatory authorities of all adverse device reactions that are both serious and unanticipated.

7.1.2.4 Pregnancies

Testing for pregnancy for a female study subject with childbearing potential must be conducted at screening (or within 7 days of dosing). Subjects who are pregnant or intend to become pregnant during the study should be excluded. Should a pregnancy occur with a study subject, the pregnancy should be reported to MediBeacon within 24 hours of the site's knowledge on the appropriate form in the Study Procedure Manual. All pregnancies will be followed to term, delivery or premature termination. Additional follow-up will occur for 3 months post-partum.

Pregnancies should be reported via email to: **CLINCALSTUDIES@MEDIBEACON.COM**

7.1.2.5 Device Observations / Malfunctions

All device observations, malfunctions or failures of the ORFM device will be documented in the eCRF.

7.1.2.6 Clinical Laboratory Evaluation

All clinical laboratory assessments will be performed by a central lab. Reference ranges will be provided to the site and used by the investigator to assess the laboratory data for clinical significance and pathological changes relative to baseline measurements. The following laboratory tests will be performed as indicated in **Table 8** at timepoints outlined in **Table 4, Table 5, Table 6** and **Table 7.**

Table 8 Summary of Clinical Safety Laboratory Assessments

All lab tests are non-fasting.

Chemistry Panel	**Hematology**	**Other required lab tests**
• Alkaline Phosphatase • Alanine Aminotransferase (ALT) • Albumin • Aspartate Aminotransferase (AST) • Bilirubin (total and direct) • Blood Urea Nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (C) • Creatinine (SCr) • Glucose • Phosphorus • Potassium • Sodium • Total Protein • Uric acid • BUN/Creatinine ratio **Lipids** • Cholesterol • Triglycerides	• Hematocrit • Hemoglobin • WBC • RBC • Platelets Differentials • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	*For WOCBP* • Serum pregnancy test (screening and a urine dipstick on day of doing; and serum at the follow-up visit **Urinalysis** • Protein • Glucose • Acetone • Hemoglobin (blood) • Bilirubin • Urobilinogen • Acetone • Nitrite • Leucocytes • pH • Specific gravity • Color • Bacteria (when indicated) If abnormalities are seen, then microscopic examination will be performed

Chemistry Panel	Hematology	Other required lab tests
		Coagulation Parameters *Only performed at screening and on dosing day* • PT • INR • aPTT

7.1.2.7 Vital Signs

Vital signs (including blood pressure, heart rate, respiration, and temperature) will be measured at screening, at multiple timepoints on dosing day (see **Section 13)**, and at the follow-up visit. Vital signs should be collected while the subject is in a seated position and after resting for approximately 5 minutes for all measurements. Temperature is only collected at screening, pre-dose, and the completion of the dosing day, and at the follow-up visit. In the extended PK group (Group 2) and Cohort 8 (Group 3), temperature is also taken at 1445 minutes (after the 24 hour PK collections).

7.1.2.8 Physical Examinations or Limited Physical Assessments

Physical examinations (when conducted by a physician) or limited physical assessments (when conducted by a nurse or other qualified personnel) should include at a minimum an assessment of the head, ears, eyes, nose, throat (HEENT), respiratory, cardiovascular, and gastrointestinal systems. It is preferred that the same medical professional perform the baseline and post dosing assessments. Significant findings that were present prior to dosing must be included in the Medical History eCRF page. Significant new findings that begin or worsen after dosing must be recorded on the AE page of the eCRF. Clinically significant abnormalities occurring post-dose should be evaluated by a physician and noted as AEs.

The study physician will assess the subject for the occurrence of clinically significant new findings that begin or worsen after dosing which must be recorded as an AE on the eCRF page. A full physical exam should be conducted at screening and limited physical assessments may be conducted at other time points and must also be inclusive of the relevant organ or body system of interest for assessing the AE

7.1.2.9 ECGs

Standard 12 lead ECGs will be collected at screening and various timepoints on dosing day (see (**Table 4, Table 5, Table 6** and **Table 7**) and during the 48 hour period for Extended PK group (Group 2) and Cohort 8 (Group 3). The following parameters will be assessed: interpretation, ventricular rate, PR interval, QRS duration, QT, and QTcF.

Subjects should be allowed to rest quietly approximately 10-15 minutes prior to their ECG. Post-dose ECGs are timed to allow for this. Additional ECGs may be collected if an issue or safety concern is noted.

An appropriately trained and experienced physician will interpret the ECGs. A subject with an

abnormal clinically significant ECG at baseline or prior to dosing does not qualify for the study. A subject with an abnormal not clinically significant ECG does not qualify without investigator comment on the ECG source document/eCRF.

For changes that are clinically significant, the investigator is to continue to monitor the subject until the change returns to normal, or until the investigator determines that follow-up is no longer medically necessary, or the subject is referred to his/her primary care physician. If the investigator determines the change is not clinically significant, the investigator's evaluation will be documented on the ECG source document and no further action is required. ECGs with clinically significant abnormalities will also be reviewed by a cardiologist.

7.1.2.10 PK Sample Collection

PK samples will be collected at the timepoints noted in **Section 13.** Recommendations for venous access and sample processing information is available in the Study Procedure Manual.

7.1.2.11 Urine Collection

The total volume of urine excreted from the time starting pre-dose through 12 hours (or 48 hours for the extended PK subgroup) will be recorded for subjects enrolled into Groups 1 and 2 only. A sample will also be collected in accordance with the instructions provided in the Study Procedure Manual.

8 Information for the Investigator: Potential Risks of the Device

Adverse events that may be anticipated in this clinical study are outlined for the Investigational Drug, the ORFM Device and the Reference Standard (iohexol).

8.1 Investigational Drug

Clinical data from the Pilot 1A and 1B studies (total n = 32 subjects) included the following adverse events:

- Pilot 1A
  - Vasovagal reaction (1 subject)
  - Dizziness (1 subject, 2 events)

These events occurred in fasting subjects shortly after dosing and resolved on that day. No other AEs, injection site reactions, clinically significant laboratory values or significant changes in vital signs were noted during this study.

- Pilot 1B
  - Headaches (56.3% of subjects)
  - Erythema (at the site of the adhesive) (100% of subjects)
  - Diarrhoea (1 subject)
  - Dizziness (occurring in 1 subject following release from the study center)

Erythema was thought to be related to the adhesive used to adhere the sensor to the skin. Headaches were deemed related to the head strap required to hold the forehead sensor in place.

MB-102 is excreted in the urine. Therefore, urine discoloration is expected but has not been considered an adverse event in prior studies.

In the ongoing Pilot 2 study, a total of 202 subjects with normal to compromised renal function have been exposed to MB-102. A total of 120 subjects received a dose of 4 µmol/kg followed by a 5 mL injection of iohexol. Seventy (70) subjects received a single dose only (no iohexol) of 4 µmol/kg of MB-102) and 12 have received a fixed dose of 130 mg (7 mL). All reported AEs were mild or moderate in severity and resolved without sequalae. Overall, MB-102 given in conjunction with or without iohexol was well tolerated in this subject population.

A total of 33 adverse events were reported in 22 treated subjects in Groups 1, 2 and 3 (Cohorts 5, 6 SOG and SeVG only) for an AE rate of 10.9% in the treated population. A total of 24 events in 19 subjects were considered mild and 9 moderate events occurred in 5 subjects (2.5% of the population). There were no severe events reported. There were no Serious Adverse Events (SAEs) reported during the study. There were no Unanticipated Adverse Device Effects (UADEs) reported during the study.

Four AEs, dyspepsia, chromaturia, hot flush and (facial) rash were considered related to investigational product (MB-102); all events resolved by study completion. Dyspepsia and chromaturia were also considered to be related to iohexol. Of note, chromaturia is an expected effect of MB-102 and expected in all subjects as the excretion of MB-102 will color the urine of subjects receiving the product. It is not a documented effect of iohexol (per the label).

Seven (7) AEs occurring in 7 subjects were considered related to the device (sensor attachment); these included application site erythema, dermatitis, and pruritus and were considered related to the adhesive material used to hold the sensor in place. Two events of application site discoloration (melanin spot at the sensor location) were noted in 2 subjects in the SOG cohort which resolved within 24 hours of removal of the sensor. Other reported AEs (conjunctivitis, nausea, vomiting, cardiac murmur, headache, anxiety, micturition urgency, pollakiuria, urine odor abnormal, peripheral oedema, fatigue, and a pruritis event [not at the sensor location] were considered not related to MB-102, the sensor device or iohexol. Injection site reactions (bruising, erythema, extravasation) were also not considered related to MB-102.

There may also be other risks that are unforeseen at this time. For additional information on the risk profile, please reference the current Investigator's Brochure.

8.2 ORFM Device

There are no direct risks associated with the ORFM device (console) as it does not contact the study subject. Adverse events observed from the sensors are with regard to the methods used to affix it to the study subject including head straps and adhesive tape (see **Section 8.1**).

8.2.1 Adhesive Clip

As with the adhesive used on the sensors, there is the chance of reaction to the adhesive used to attach the clip to the skin. Reactions could include redness, itchiness or other localized skin reactions.

8.2.2 2-Part Brilliance Sensor

The 2-Part Brilliance Sensor includes a removable adhesive ring that will allow re-use of the sensor itself. There are no direct risks associated with the 2-Part Brilliance Sensor. As with the other devices described above, skin reactions may be seen to the adhesive used to hold the sensor in place.

8.3 Reference Standard

Risks associated with the reference standard iohexol (Omnipaque™ 300 are detailed in the current version of the Package Insert (Appendix B).

It should be noted that the dose level of iohexol (5 mL) is significantly lower than the doses used for contrast imaging. A published study by Nilsson-Ehle in over 8000 patients using iohexol to measure kidney function reported “an extremely low toxicity” related to the small doses of iohexol administered. He reported very few adverse events compared to typical radiographic imaging studies (e.g. CT study, urography, angiography) where much larger volumes of iohexol may be used (i.e. 10-50 times). The author reported “no complications in 8000 investigations except for 2 patients who reported malaise and vomiting between 1 to 3 hours after injection of iohexol” and they concluded that they did not know if these adverse effects were related to their procedure.

8.4 Trial Procedures

The study will collect approximately 135 mL of blood on dosing day (PK draws and lab draws) for a standard subject in Group 1 and 2, and Group 3 Cohorts 6, SOG and Cohort 7 (Single Dose Subjects) and slightly less volume for Group 3 Cohort 5 subjects. Subjects in the extended PK subgroup (Group 2) will have approximately 165 mL of blood collected over a 48-hour period. Multiple dose subjects from Cohort 7 will have approximately 146 - 154 mL of blood collected (PK collection is reduced in this group). Blood collection may lead to light-headedness and dizziness in some study subjects. It is recommended to ensure subjects continue to hydrate and eat during dosing day to mitigate the effect of blood loss.

Bruising and pain at the site of the venous catheters may also be expected.

9 Statistical Methods

9.1 Statistical and Analytical Plans

9.1.1 Datasets or Populations Analyzed

Safety Analysis Set: The Safety Analysis Set (SAF) will consist of all subjects who sign the Informed Consent and receive study drug in the study. All safety analyses will be performed on the safety analysis set.

Per Protocol Set: The Per Protocol Set (PP) will consist of all subjects who receive the investigational drug and have no major protocol deviations. Demographic and Other Baseline Characteristics including Subject's age, race, sex, weight, body mass index (BMI), baseline CKD status, and medical history will be recorded at screening and summarized for the Safety and Per Protocol Sets.

9.1.2 Subject Disposition

The number and percentage of subjects who complete the study or who terminate early from the study and the reasons for early termination will be collected and reported. Subjects will be considered to have completed the study if they complete the dosing day.

The number and percentage of subjects in each analysis population will be presented. Percentages will be based on the number of subjects enrolled.

9.1.3 Pharmacokinetic Assessments

Pharmacokinetic parameters for MB-102 and iohexol will be calculated using both compartmental and non-compartmental techniques. Data from the patients in Cohort 1 that were used for dose ranging for MB-102 will have their data dose normalized to be consistent with the dose used for the remainder of the study. All pharmacokinetic assessments will be performed using Phoenix WinNonlin (and possibly Phoenix NLME) Build 6.4.0.768.

Non-compartmental analysis (NCA) will be performed on data for both MB-102 and iohexol. The following parameters will be determined:

- C_{max} – the maximum plasma concentration obtained during the sampling interval
- T_{max} - the time at which C_{max} occurred
- λ_z – the terminal rate constant will be determined by linear regression of the terminal linear phase of the log plasma concentration-time profile.
- AUC_{last} - Area under the plasma concentration-time curve from the time zero to the time of the last quantifiable concentration.
- AUC_∞ - Area under the plasma concentration-time curve from time zero to infinity. (AUC_∞) will be calculated as: $AUC_\infty = AUC_{last} + LQC/\lambda_z$ where LQC is the predicted concentration (based on the terminal regression) at the time of the last measurable

concentration.

- $t_{1/2}\,\lambda_z$ – the elimination half-life will be calculated as $t_{1/2}\,\lambda_z = \ln(2)/\lambda_z$.
- Clp – Total plasma clearance will be calculated as: Clp = Dose/ AUC_∞.
- CLr - Renal clearance will be calculated as: CLr = Ae/ AUC_{last}, where Ae is the cumulative amount of analyte excreted in urine over the sampling interval.

In addition to the NCA analysis described above, a compartmental analysis will be performed separately for each subject's profile. Based on prior data, it is expected that a two compartmental model will provide an adequate fit. In addition, a population fit may also be attempted.

Observed plasma and urine concentrations will be summarized descriptively by time point and agent (MB-102 or iohexol) for all subjects included in the pharmacokinetic analysis. In addition, plots of mean concentrations over time will be provided by agent, including standard error bars around the mean values.

All derived results for pharmacokinetic parameters will be summarized numerically by agent. For categorical variables, the frequency of subjects will be provided along with the percentage based on the number of subjects with available data. Summaries will be based on observed data (i.e., no missing data will be imputed) and will include all dosed subjects completing all aspects of the study.

An analysis of variance of estimated GFR will be performed taking into account the factors subjects, treatments (MB-102 and iohexol), CKD stage and skin color type.

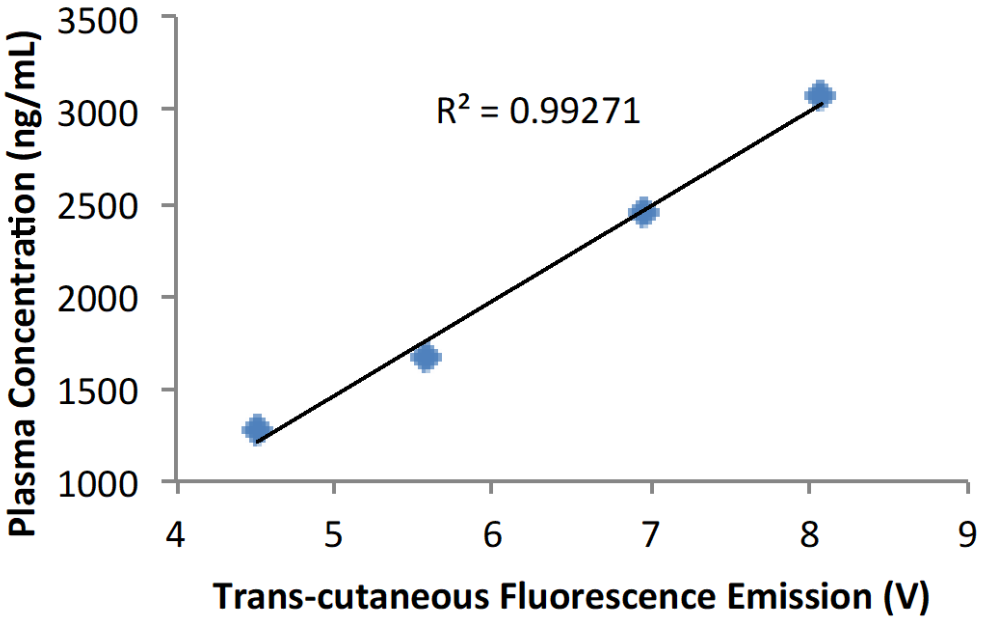
All plasma and urine concentrations will be provided in listings by subject and time point. Any blood measurements obtained outside of the defined windows around the scheduled time point will be identified as protocol deviations. Additionally, pharmacokinetic parameters will be provided in listings sorted by subject.

9.1.3.1 Analysis of ORFM Fluorescence Data (*t*GFR) vs PK Data for GFR Determination

A correlation between the fluorescence intensity and tracer concentration at each time point in the renal excretion phase will be performed to establish that the transdermal fluorescence pharmacokinetics matches the plasma pharmacokinetics. Summaries of the data will be performed to evaluate the effects of skin color and CKD stage on the correlation.

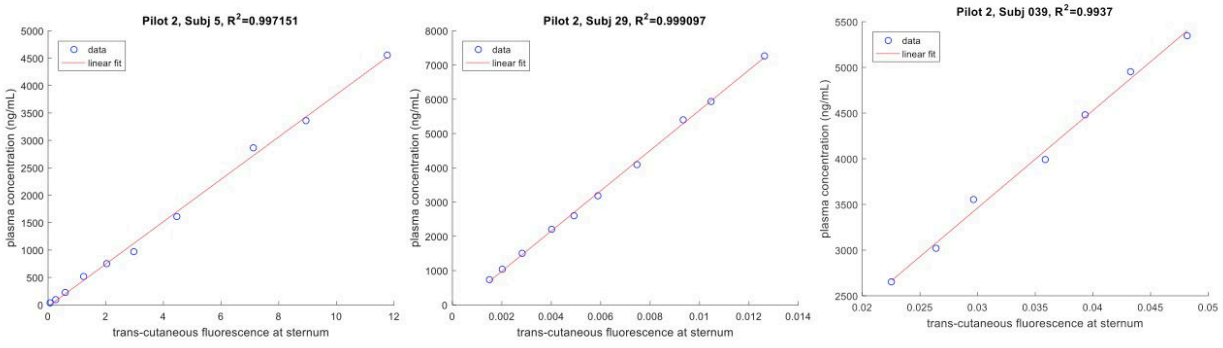
Data from a Pilot 1B study shows that plotting plasma concentration versus fluorescence intensity at the same time points in the renal excretion phase yields a tight correlation (**Figure 2**). The data shown in this correlation are from healthy subjects with normal renal function (measured by eGFR) who received a 4 µmol/kg dose.

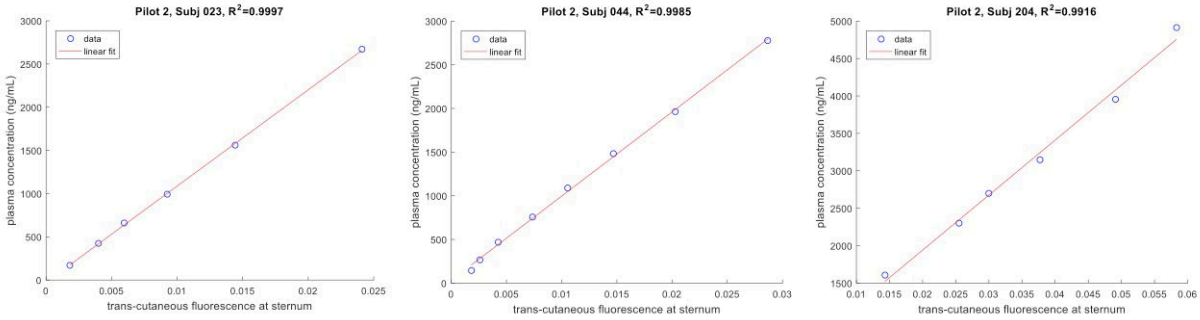
Figure 2 Correlation between Plasma Pharmacokinetics and Fluorescence Pharmacokinetics in Pilot 1B, Subject 12



In the Pilot 2 Group 1 clinical study, this type of correlation was observed across subjects with GFR values over the entire range. Examples are shown below (**Figure 3**):

Figure 3 Transdermal fluorescence correlates with plasma Pharmacokinetics over a range of GFR





mGFR ~ 131 mL/min mGFR ~ 64 mL/min mGFR ~ 50 mL/min

From the Pilot 2 Group 1 plasma measured GFR from MB-102 and the fluorescence decay constant from all subjects, a very preliminary correlation plot has been constructed (**Figure 4**), similar to the graph as done in Rabito et. al. 2010 (**Figure 5**).

Figure 4 Correlation between Plasma GFR and Trans-cutaneous Fluorescence Clearance Rate (with Volume of Distribution (VD) correction of GFR)

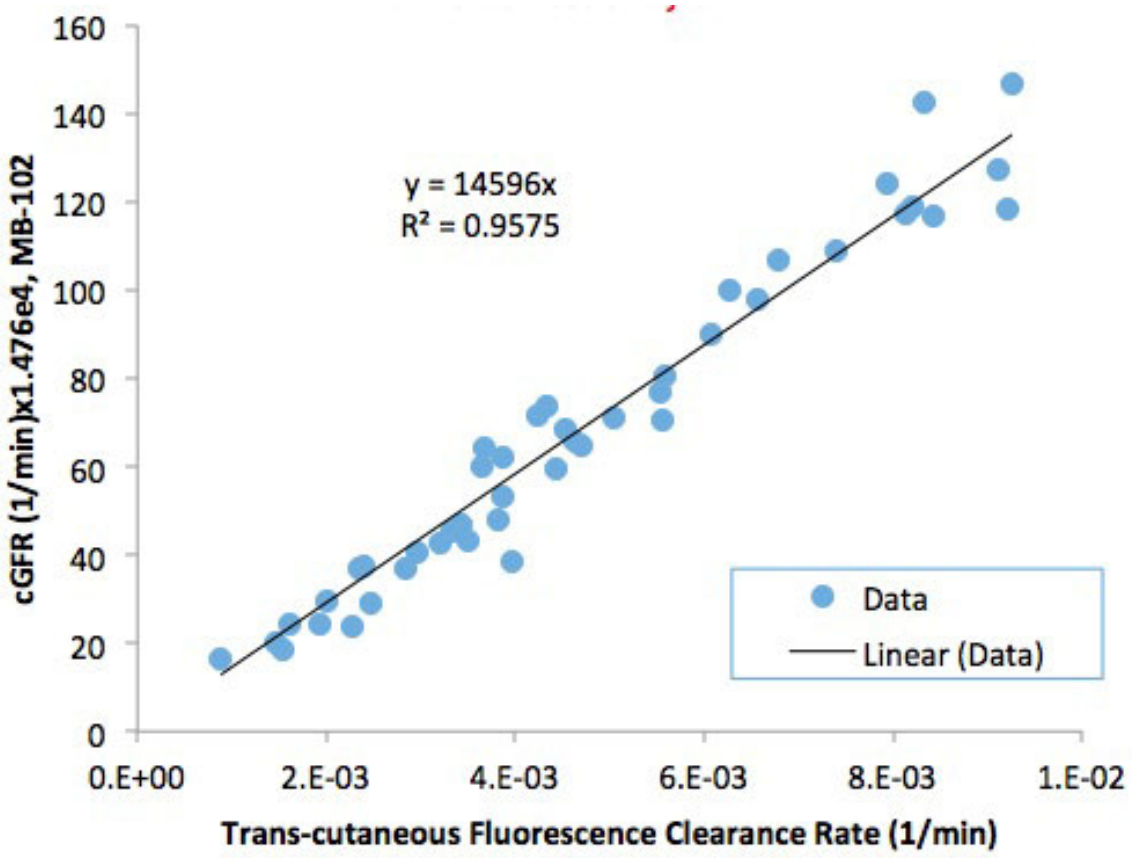
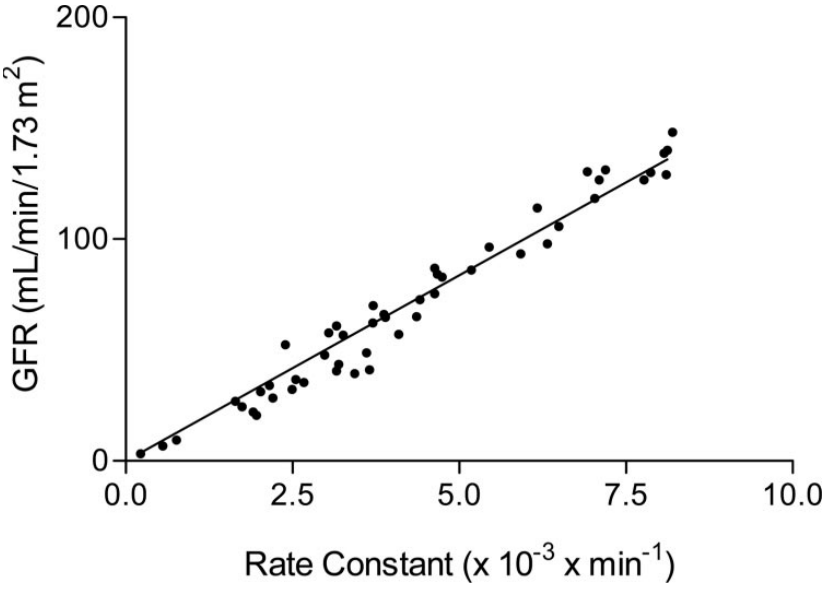


Figure 5 Correlation between GFR measured as renal clearance of 125I-iothalamate and the rate of clearance of 99mDTPA



Further analysis of the data will be done to determine the optimum data conversion using volume of distribution, body surface area, and possibly other factors.

For Pilot 2 Group 2 subjects, this type of graph will be used to convert the measured fluorescence time constant "fluorescence GFR" and then compare that value with the MB-102 plasma measured GFR from the same subjects. The database will also be updated with this new data to make the algorithm more robust for the pivotal studies to follow.

9.1.4 Safety Variables

The clinical safety measurements include AEs, physical exam findings, vital signs, ECG collection, and laboratory tests.

Treatment-Emergent Adverse Events

AEs will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA). The system organ class and preferred term for each AE will be available, along with the verbatim reported term, event start and stop dates/times, seriousness, severity, relationship to treatment/device, action taken, and event outcome. SAEs will also be documented in a case narrative format.

The overall numbers and percentages of subjects who experienced any treatment-emergent AE (TEAE), will be presented. AEs will be presented by system organ class, and preferred term.

Physical Examinations/Limited Physical Assessments

The results of physical examinations will be provided in subject data listings for Groups 1 and 2 and will be collected either as medical history or adverse events for Group 3. All clinically significant treatment-emergent abnormalities will be reported as AEs.

Clinical Laboratory Assessments

Clinical laboratory tests include clinical chemistry, hematology, urinalysis and coagulation parameters. Each parameter will be summarized using the most appropriate descriptive statistics. Details will be specified in the Statistical Analysis Plan (SAP). Also, individual subject results will be assessed against an appropriate reference range if available. The manifestation of any clinically significant abnormality that develops during the study will be reported as an AE.

Prior and Concomitant Therapies

Concomitant medications administered within 7 days prior to and through follow-up will be listed. Medications will be coded using the World Health Organization (WHO) drug dictionary. Data will be provided in one or more subject data listings. Concomitant non-drug therapies will be listed.

9.1.5 Study Interim Analysis

A study interim analysis will be performed after completion of the SeVG cohort of all previously collected subject data (Groups 1, 2 and 3 through the SevG enrollment). This analysis will be performed to summarize clinical data in support of pivotal regulatory discussions. It is not the intention to stop the study early or revise the sample size for the remaining cohorts.

9.1.6 Early Termination of the Study

MediBeacon may terminate this study early if safety considerations arise or for other reasons. In addition, if MediBeacon determines that adequate data are available to continue program development, early termination (prior to enrollment of all planned subjects in Group 3) may occur.

9.1.7 Determination of Sample Size

This is a pilot study therefore no formal calculation of sample size was performed.

9.1.8 Missing Data

Missing values will not be imputed. Additional data imputation rules may be specified in the Statistical Analysis Plan if needed.

10 Quality Assurance and Quality Control

10.1 Training

The clinical site will be trained on the protocol and study procedures. In addition, Sponsor representatives will be onsite during dosing procedures to operate the ORFM device.

10.2 Audit and Inspection

The study site and study documentation may be subject to quality assurance audits during the course of the study by the sponsor, or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

10.3 Monitoring

Data for each subject will be recorded in an electronic data capture (EDC) system. Data collection must be completed for each subject enrolled in the study.

In accordance with GCP and International Conference on Harmonization (ICH) guidelines, the study monitor will conduct monitoring visits at regular intervals. During the visits, the study monitor will perform the source document verification and verification that investigator's obligations and all applicable regulatory requirements are being fulfilled. The frequency of monitoring visits will be determined by the rate of subject recruitment.

The investigator must permit the monitor, the IEC, the sponsor's internal auditors and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records, including direct access to electronic medical records for confirmation of data contained within the EDC system. Subject confidentiality will be protected at all times.

10.4 Data Management and Coding

MediBeacon or designee will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant Standard Operating Procedures (SOPs) at MediBeacon or their designee.

Study sites will enter data into a 21 CRF Part 11 compliant electronic data capture (EDC) system via a secure internet connection. Data entered into the EDC system must be verifiable against source documents at the study site. Any changes to the data entered into EDC system will be recorded in the audit trail.

Missing or inconsistent data will be queried via the EDC system to the investigator for clarification. Subsequent modifications to the database will be documented.

10.5 Protocol Deviations

The Investigator will not deviate from the clinical protocol without the prior written approval of MediBeacon except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the study. In medical emergencies, prior written approval for protocol deviations will not be required, but MediBeacon or their designee must be notified via telephone within 24 hours of occurrence. Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) are not permitted.

Major Protocol Deviation is a significant deviation from the protocol that may impact subject safety and/or affect the integrity of clinical trial data. These may include, but are not limited to the following:

- Improper or inadequate informed consent procedures
- Subject did not meet eligibility criteria
- Subject received prohibited concomitant medication(s) at any time during the trial
- A significant protocol required assessment or procedure was not performed per protocol requirements
- Subject received incorrect study medications at any time during the trial
- Significant departure from protocol-required dosing
- Subject developed criteria that required withdrawal from study protocol but was not withdrawn

A Minor Protocol Deviation is a deviation that does not impact subject safety and/or compromise the integrity of the clinical trial data.

Deviations will be documented at the site and submitted to the IEC (as required) and the sponsor.

10.6 Device Accountability

ORFM devices and investigational drug MB-102 will be supplied to the clinical site. During the study, used vials of MB-102 should be maintained until reviewed by the clinical monitor. At the termination of the study, all devices will be returned to MediBeacon. Unused investigational drug may be returned or destroyed following authorization by the sponsor. The investigator must maintain records of receipt, use and disposition of the devices and of the drug as well as the reference standard. The following records will be kept:

- Records of devices received, including dates of receipt, quantity, serial number and the signature of the person in charge of device accountability.
- Records of device use, including the subject ID, date of use, and any specific data the sponsor requires collected on the device usage form.
- Records of storage of the investigational agent
- Records of receipt, use and destruction of the investigational agent
- Records of use of the reference standard (as applicable)

10.7 Direct Data Collection

Fluorescent measurements will be collected directly by the ORFM device prototypes and will not appear on any available source documentation. The ORFM computer system will be a closed system and direct data output to hard media will be used prior to upload to a secure server for analysis.

11 Records / Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. All study records will be available for inspection by the sponsor or its representatives, or a regulatory agency.

Investigator files containing all records and reports of the investigation should be retained for a minimum of two (2) years after the completion/ termination of the investigational study or the date that the records are no longer required for purposed of supporting a premarket approval application. The Sponsor will determine with the investigational site as to this exact date so that the minimum two-year record retention can be accomplished. Records may be discarded upon written notification by the Sponsor. To avoid error, the Principal Investigator should contact MediBeacon, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Trial Agreement, the Sponsor should be contacted if the Principal Investigator plans to leave the investigational site so that appropriate arrangements for file custodianship can be made.

The following records must be maintained in designated study administrative files:

- Clinical protocol and all amendments
- Signed Investigator Agreement
- Independent Ethics Committee Approval Letter(s) documenting review and approval of all protocols, amendments, IBs, ICFs, subject materials, etc.
- IEC-approved informed consent(s) (including any revisions)
- Current Curriculum Vitae for all Investigators and subinvestigators including evidence of current medical licensure
- Financial Disclosure Form for all Investigators
- Correspondence relating to this study
- Correspondence with the IEC
- IEC membership list and/or assurance
- Investigational site authorized study personnel signature list and delegation of authority
- Device Instructions for Use
- Lab certification, including a set of the lab’s normal range for tests performed

- EDC Completion Guidelines
- Subject Screening & Enrollment Log
- Site Visit Log (e.g. for Monitor sign-in)
- Site Training records
- Investigational Device and Drug Accountability Logs
- Reports (includes Adverse Event reports and final reports from Investigator and Sponsor)
- Copy of all EC approved subject-related materials and/or study advertising materials

The following records must be maintained for each subject enrolled in the study:

- Signed subject consent forms
- Electronic copy of final completed case reports (to be provided by the sponsor at the end of the study)
- All lab work and testing results
- Record of any complications, adverse events, device problems and/or malfunctions, with supporting documentation
- Procedure reports, progress notes, physician and/or nursing notes, and subject office files
- Records pertaining to subject deaths

12 Ethics

12.1 Independent Ethics Committee (IEC)

Before initiation of the study at each study site, the protocol, all protocol amendments, Investigators Brochure, the ICF, the subject information sheet and any other relevant study documentation will be submitted to the appropriate IEC. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the study device is released to the investigator. Any necessary extensions or renewals of IEC approval must be obtained, in particular, for changes to the study such as modification of the protocol, the ICF, the written information provided to subjects, and/or other procedures.

The investigator will report promptly to the IEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC annually, or more frequently if requested by the IEC. On completion of the study, the site will notify the IEC that the study has ended.

12.2 Ethical Conduct of the Study

The ICH guidelines for current GCP (ICH R2, 2016), The Code of Federal Regulations Title 21 CFR Parts 812, 11, 50, 54 and 56 and ISO 14155: 2011(E) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, as well as the ethical principles defined by the World Medical Association Declaration of Helsinki, and the requirements of national device and data protection laws and other applicable regulatory requirements will be followed.

12.3 Subject Information and Consent

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study. The written consent must be given by the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given time to consider the study, if this is required, or if the subject requests more time. Subjects and/or legally authorized representatives will be required to sign and date the ICF. After signatures are obtained, a copy will be provided to the subject, and a signed ICF will be kept and archived by the investigator in the investigator's study file for possible inspection by regulatory authorities, the IEC, or sponsor.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

12.4 Financing and Insurance

This clinical trial will be sponsored by MediBeacon and its conduct will be governed under an executed Clinical Trial Agreement that will define the coverage of costs associated with study implementation by the trial site. MediBeacon will maintain appropriate clinical trial insurance at limits agreed upon in the agreement.

12.5 Subject Confidentiality

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the ethics committees approving this research, and any other applicable regulatory agency(ies), will be granted direct access to the study subjects' original medical records (including electronic medical records) for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

12.6 Reporting and Publication, Including Archiving

Publication of all study results in the form of abstracts, manuscripts, presentations, posters, etc. will be developed in accordance with the Clinical Trial Agreement.

13 Post-Dose Procedures by Group and Cohort

13.1 Group 1 (Cohorts 1 and 2) and Group 2 (Cohorts 3 and 4 subset)

- Single dose
- Cohort 1 and 3: healthy to stage 2 CKD: enrolled 50 subjects
- Cohort 2 and 4: compromised renal function: enrolled 60 subjects
- 12 hour follow-up
- Iohexol administration
- Urine collection

Post-dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)

- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)
- Clinical laboratory (safety labs) draw at 720 minutes (±10 minutes) (chemistry, hematology, lipids, and coagulation). The venous catheter may be removed.
- Vital sign collection at 725 minutes (±5 minutes)
- 12 lead ECG will be conducted at approximately 740 minutes (±10 minutes)
- 5 mL urine samples will be collected each time the subject voids. The total volume of urine excreted will be recorded until 12 hours post-dose.
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

13.2 Post-Dose Procedures: Group 2 (Cohort 4 Extended PK Subgroup only)

- Single dose
- Cohort 4: compromised renal function: Enrolled 10 subjects
- 48 hour follow-up
- Iohexol administration
- Urine collection

Post-dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)

- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)
- Clinical laboratory (safety labs) draw at 720 minutes (±10 minutes) (chemistry, hematology, lipids, and coagulation).
- Vital sign collection at 725 minutes (±5 minutes)
- 12 lead ECG will be conducted at approximately 740 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 960 minutes [16 hours] (±30 minutes)
- Vital sign collection at 965 minutes (±30 minutes)
    - *If the ORFM sensors remained attached out to 960 minutes, they may be removed after vital signs are collected. Sensors removed after 12 hours but prior to 16 hours will not be considered a protocol deviation.*
- An ECG will be collected at 1420 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 1440 minutes [24 hours] (±30 minutes)
- Vital signs collection (including temperature) at 1445 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 1920 minutes [32 hours] (±30 minute)

- Vital signs collection at 1925 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 2400 minutes [40 hours] (±30 minute)
- Vital signs collection at 2405 minutes (±30 minutes)
- An ECG will be collected at 2860 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 2880 minutes [48 hours] (±30 minutes)
- Vital signs (including temperature) collection at 2885 minutes (±30 minutes)
- 5 mL urine samples will be collected each time the subject voids. The total volume of urine excreted will be recorded until 48 hours post-dose.
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

13.3 Post-Dose Procedures: Group 3: Cohort 5

- Single dose
- No iohexol
- No urine collection
- 8 hour follow-up
- Healthy to Stage 2 CKD
- Enrolled 8 subjects

Post MB-102 dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)

- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±5 minutes)
- An ECG will be conducted at 460 minutes (±10 minutes) for all Group 3 subjects with the exception of Cohort 7, multiple dose subjects
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Clinical laboratory (safety labs) draw at 480 minutes (±20 minutes) (chemistry, hematology, lipids and coagulation). The venous catheter may be removed.
- Vital sign collection at 485 minutes (±5 minutes)
- Just after removal of the sensor, additional Mexameter measurements of melanin and erythema will be collected at the location where the sensor was attached.
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

13.4 Post-Dose Procedures: Group 3: SOG

- Single dose
- No iohexol
- No urine collection
- 12 hour follow-up
- Normal to stage 2 CKD
- Up to 27 subjects (3 sets of 9; 18 subjects have been enrolled)

Post MB-102 dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)

- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- An ECG will be conducted at 460 minutes (±10 minutes) for all Group 3 subjects with the exception of Cohort 7, multiple dose subjects
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)
- Clinical laboratory (safety labs) draw at 720 minutes (±10 minutes) (chemistry, hematology, lipids, and coagulation). The venous catheter may be removed.
- Vital sign collection (includes temperature) at 725 minutes (±10minutes)
- 12 lead ECG will be conducted at approximately 740 minutes (±10 minutes)
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

13.5 Post-Dose Procedures: Group 3: SeVG, Cohort 6 and 7, 7A: Single Dose Subgroup

- Single Dose
- 12 hour follow-up
- Normal and compromised subjects
- SeVG-1 and SeVG-2: up to 50 subjects
- Cohort 6: 8 subjects
- Cohort 7, 7A (single dose): up to 24 subjects
- A subset of SeVG and Cohort 7 will receive a fixed dose of 7 mL or 130 mg

Post MB-102 dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)

- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)
- Clinical laboratory (safety labs) draw at 720 minutes (±10 minutes) (chemistry, hematology, lipids, and coagulation). The venous catheter may be removed
- Vital sign collection (includes temperature) at 725 minutes (±10 minutes)
- 12 lead ECG will be conducted at approximately 740 minutes (±10 minutes)
- Just after removal of the sensor, additional Mexameter measurements of melanin and erythema will be collected at the location where the sensor was attached.
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period
- Symptom directed physical assessment / exam performed within 2 hours of the completion of the dosing day

13.6 Post-Dose Procedures: Group 3: Cohort 7, 7A and 7B: Multiple Dose Subgroup

- Multiple Dose
- 24 hour – 36 hour follow-up
- Normal to stage 2 CKD
- Up to 24 subjects
- Fixed dose administration (7 mL or 130 mg)

13.6.1 Post First MB-102 Dose Procedures (Cohort 7 and 7A)

Post first MB-102 dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- Vital sign collection at 11 minutes (±1 minute)
- Vital sign collection at 16 minutes (±1 minute)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- For subjects in Cohort 7 and 7A as of protocol Version 12: a PK draw (6 mL) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)

- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- PK draw (6 mL blood) in K2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±10 minutes)

The ORFM device will notify the clinical team when the monitoring session is complete for the study subject. When the device notes that monitoring is complete, the sensor and device should remain hooked up to the subject and will continue to collect background fluorescence data for the duration of the 2nd dose post-dose monitoring period. No Mexameter measurement will be taken at this time.
At approximately 690 minutes, the subject should be prepared for the 2nd dose administration and 2nd round of ORFM monitoring. The following procedures should be followed:

13.6.2 MB-102 Second Dose Administration (Cohort 7 and 7A)

- The location for the new sensor will be cleaned, hair clipped (as needed) (the original sensor will remain in place)
- Mexameter readings of melanin and erythema will be measured at the second intended site of sensor placement.
- Prior to dosing, the 2nd device sensor, along with the adhesive clip should be attached to the subject and ORFM data acquisition initiated
- Photographs of the sensor placement may be collected. Photographs will not include any identifying features or the subject's face.
- PK draw (6 mL blood) in K_2 EDTA tube 720 minutes (±10 minutes) post dose 1 (pre-dose baseline 2)
- Clinical laboratory safety blood collection at 720 minutes (±10 minutes) post dose 1
- Vital signs should be collected at 725 minutes (±10 minutes) post dose 1

- An ECG performed at 730 minutes (±10 minutes) post dose 1

Once these procedures are complete, the catheter to be used for MB-102 dosing should be flushed with saline or a heparin solution and a small volume of blood withdrawn to ensure the catheter is patent, and then the catheter should be flushed again. MB-102 (30 second injection) may be administered again followed by a saline flush (30 seconds). Following the 2nd dose administration of MB-102, the following procedures will be followed:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- Vital sign collection at 11 minutes (±1 minute)
- Vital sign collection at 16 minutes (±1 minute)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- For subjects in Cohort 7A: a PK draw (6 mL) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)

- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes) post dose 2
- Vital sign collection at 485 minutes (±10 minutes) post dose 2
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes) post dose 2; the venous catheter(s) may be removed
- Vital sign collection including temperature at 605 minutes (±10 minutes) post dose 2
- 12 lead ECG will be conducted at approximately 610 minutes (±10 minutes) post dose 2
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period
- Symptom directed physical assessment / exam performed within 2 hours of the completion of the dosing day

The ORFM device will notify the clinical team when the monitoring session is complete for the study subject. When the device notes that monitoring is complete, the sensors and device should remain hooked up to the subject until after the 10 hour (600 minutes) PK collection is completed. At that time, the sensors can be removed from the subject.

- Just after removal of the sensors, additional Mexameter measurements of melanin and erythema will be collected at the location where the sensors were attached.

13.6.3 Post First MB-102 Dose Procedures (Cohort 7B)

Post first MB-102 dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- Vital sign collection at 11 minutes (±1 minute)
- Vital sign collection at 16 minutes (±1 minute)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)

- Vital sign collection at 65 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- PK draw (6 mL blood) in K2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)
- Vital sign collection at 725 minutes (±10 minutes)
- An ECG will be performed at 730 minutes (±10 minutes)
- Sensors and clip may be removed
- Mexameter measurements collected

The ORFM device will notify the clinical team when the monitoring session is complete for the study subject. When the device notes that monitoring is complete, the sensor and device should remain hooked up to the subject and will continue to collect background fluorescence data for the duration of the 12 hour follow-up. At this point, the sensors will be removed; Mexameter measurements collected; the subject assessed for AEs and allowed to rest for approximately 10-11 hours.

13.6.4 MB-102 Second Dose Administration (Cohort 7B)

- The location for the new sensor will be cleaned, hair clipped (as needed) (the original sensor will remain in place)
- Mexameter readings of melanin and erythema will be measured at the second intended site of sensor placement.
- Prior to dosing, the 2nd device sensor, along with the adhesive clip should be attached to the subject and ORFM data acquisition initiated for approximately 20-30 minutes
- Photographs of the sensor placement may be collected. Photographs will not include any identifying features or the subject's face.
- PK draw (6 mL blood) in K_2 EDTA tube 1440 minutes [24 hours] (±10 minutes) post dose 1 (pre-dose baseline 2)
- Clinical laboratory safety blood collection at 1440 minutes (±10 minutes) post dose 1
- Vital signs should be collected at 1445 minutes (±10 minutes) post dose 1
- An ECG performed at 1450 minutes (±10 minutes) post dose 1

Once these procedures are complete, MB-102 (30 second injection) may be administered via direct IV injection followed by a saline flush (30 seconds). For Cohorts 7A and 7B, the second dose will be administered in the same arm but a different vein than the initial injection. Following the 2nd dose administration of MB-102, the following procedures will be followed:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- Vital sign collection at 11 minutes (±1 minute)
- Vital sign collection at 16 minutes (±1 minute)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)

- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes) post dose 2
- Vital sign collection at 485 minutes (±10 minutes) post dose 2
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes) post dose 2; the venous catheter(s) may be removed
- Vital sign collection including temperature at 605 minutes (±10 minutes) post dose 2
- 12 lead ECG will be conducted at approximately 610 minutes (±10 minutes) post dose 2
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

The ORFM device will notify the clinical team when the monitoring session is complete for the study subject. When the device notes that monitoring is complete, the sensors and device should remain hooked up to the subject until after the 10 hour (600 minutes) PK collection is

completed. At that time, the sensors can be removed from the subject. Just after removal of the sensors, additional Mexameter measurements of melanin and erythema will be collected at the location where the sensors were attached.

13.7 Post-Dose Procedures: Group 3: Cohort 8 and 8A

- Single dose
- Renal compromised subjects
- 48 hour follow-up
- Up to 16 subjects
- Fixed dose administration (7 mL or 130 mg)

Post-dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)
- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)

- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)
- Clinical laboratory (safety labs) draw at 720 minutes (±10 minutes) (chemistry, hematology, lipids, and coagulation).
- Vital sign collection at 725 minutes (±10 minutes)
- 12 lead ECG will be conducted at approximately 740 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 960 minutes [16 hours] (±30 minutes)
- Vital sign collection at 965 minutes (±30 minutes)
- An ECG will be collected at 1420 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 1440 minutes [24 hours] (±30 minutes)
- Vital signs collection (including temperature) at 1445 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 1920 minutes [32 hours] (±30 minute)

- Vital signs collection at 1925 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 2400 minutes [40 hours] (±30 minute)
- Vital signs collection at 2405 minutes (±30 minutes)
- An ECG will be collected at 2860 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 2880 minutes [48 hours] (±30 minutes). The venous catheter may be removed.
- Vital signs (including temperature) collection at 2885 minutes (±30 minutes)
- Just after removal of the sensor, additional Mexameter measurements of melanin and erythema will be collected at the location where the sensor was attached.
- Symptom directed physical assessment / exam performed within 2 hours of the completion of the dosing day
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

13.8 Post-Dose Procedures: Group 3: Cohort 8B

- Single dose
- Renal compromised subjects
- 24 hour follow-up
- Up to 8 subjects
- Fixed dose administration (7 mL or 130 mg)

Post-dose study procedures will be performed at the following timepoints:

- PK draw (6 mL blood) in K_2 EDTA tube at 5 minutes (±1 minute)
- Vital sign collection at 6 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 10 minutes (±2 minute)
- Vital sign collection at 11 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 15 minutes (±2 minute)
- Vital sign collection at 16 minutes (±1 minute)
- PK draw (6 mL blood) in K_2 EDTA tube at 30 minutes (±5 minutes)

- Vital sign collection at 35 minutes (±5 minutes)
- An ECG will be conducted at 55 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 60 minutes (±5 minutes)
- Vital sign collection at 65 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 90 minutes (±5 minutes)
- Vital sign collection at 95 minutes (±5 minutes)
- An ECG will be conducted at 115 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 120 minutes (±5 minutes)
- Vital sign collection at 125 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 180 minutes (±5 minutes)
- Vital sign collection at 185 minutes (±5 minutes)
- An ECG will be conducted at 235 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 240 minutes (±5 minutes)
- Vital sign collection at 245 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 300 minutes (±5 minutes)
- Vital sign collection at 305 minutes (±5 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 360 minutes (±10 minutes)
- Vital sign collection at 365 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 480 minutes (±10 minutes)
- Vital sign collection at 485 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 600 minutes (±10 minutes)
- Vital sign collection at 605 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 720 minutes (±10 minutes)

- Clinical laboratory (safety labs) draw at 720 minutes (±10 minutes) (chemistry, hematology, lipids, and coagulation).
- Vital sign collection at 725 minutes (±10 minutes)
- 12 lead ECG will be conducted at approximately 740 minutes (±10 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 960 minutes [16 hours] (±30 minutes)
- Vital sign collection at 965 minutes (±30 minutes)
- An ECG will be collected at 1420 minutes (±30 minutes)
- PK draw (6 mL blood) in K_2 EDTA tube at 1440 minutes [24 hours] (±30 minutes)
- Vital signs collection (including temperature) at 1445 minutes (±30 minutes)
- Just after removal of the sensor, additional Mexameter measurements of melanin and erythema will be collected at the location where the sensor was attached.
- Symptom directed physical assessment / exam performed within 2 hours of the completion of the dosing day
- Adverse events will be collected based on subject and medical team observations throughout the post-dose assessment period

14 References

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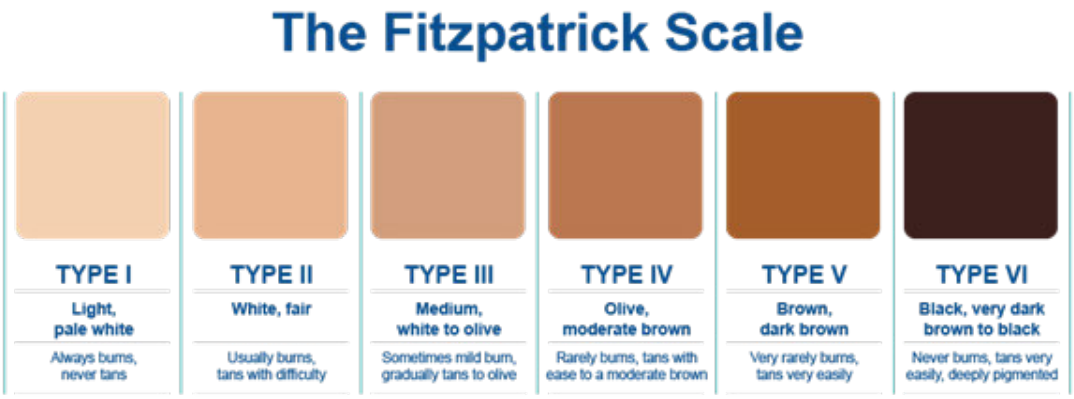
Appendix A Fitzpatrick Scale



Source: Fitzpatrick, 1975

Appendix B: Package Insert for Omnipaque™ 300

GE Healthcare

OMNIPAQUE™ (iohexol) Injection

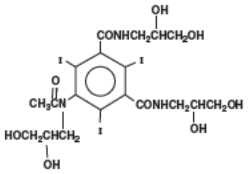
140 | 180 | 240 | 300 | 350

140 | 350 | NOT FOR INTRATHECAL USE

Section I — Intrathecal **R_X ONLY**
Section II — Intravascular
Section III — Oral/Body Cavity Use

DESCRIPTION

Iohexol,N,N′ - Bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodo-isophthalamide, is a nonionic, water-soluble radiographic contrast medium with a molecular weight of 821.14 (iodine content 46.36%). In aqueous solution each triiodinated molecule remains undissociated. The chemical structure is:



OMNIPAQUE is provided as a sterile, pyrogen-free, colorless to pale-yellow solution, in the following iodine concentrations: 140, 180, 240, 300, and 350 mgI/mL. OMNIPAQUE 140 contains 302 mg of iohexol equivalent to 140 mg of organic iodine per mL; OMNIPAQUE 180 contains 388 mg of iohexol equivalent to 180 mg of organic iodine per mL; OMNIPAQUE 240 contains 518 mg of iohexol equivalent to 240 mg of organic iodine per mL; OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. All solutions are sterilized by autoclaving and contain no preservatives. Unused portions must be discarded. Iohexol solution is sensitive to light and therefore should be protected from exposure.

The available concentrations have the following physical properties:

Concentration (mgI/mL)	Osmolality* (mOsm/kg water)	Osmolarity (mOsm/L)	Absolute Viscosity (cp)		Specific Gravity
			20°C	37°C	37°C
140	322	273	2.3	1.5	1.164
180	408	331	3.1	2.0	1.209
240	520	391	5.8	3.4	1.280
300	672	465	11.8	6.3	1.349
350	844	541	20.4	10.4	1.406

* By vapor-pressure osmometry.

OMNIPAQUE 140, OMNIPAQUE 180, OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 have osmolalities from approximately 1.1 to 3.0 times that of plasma (285 mOsm/kg water) or cerebrospinal fluid (301 mOsm/kg water) as shown in the above table and are hypertonic under conditions of use.

SECTION I
CLINICAL PHARMACOLOGY—Intrathecal

Iohexol is absorbed from cerebrospinal fluid (CSF) into the bloodstream and is eliminated by renal excretion. No significant metabolism, deiodination, or biotransformation occurs.

In five adult patients receiving 16 to 18 milliliters of iohexol (180 mgI/mL) by lumbar intrathecal injection, approximately 88 (73.1-98.2) percent of the injected dose was excreted in the urine within the first 24 hours after administration. The renal and body clearances were 99 (47-137) milliliters per minute and 109 (52-138) milliliters per minute. The mean maximal plasma concentration was 119 (72-177) micrograms of iohexol per milliliter and occurred after 3.8 (2-6) hours. The volume of distribution was 557 (350-849) milliliters per kilogram. In one patient with a large spinal cord tumor, excretion was delayed (67 percent of the dose appeared in the urine within the first 24 hours) with no difference in the total overall recovery in the urine after 48 hours. The delay in excretion appeared to be related to a decrease in the rate of transfer of iohexol from the cerebrospinal fluid to the blood (plasma maximal concentration was approximately 30 micrograms/mL).

The initial concentration and volume of the medium, in conjunction with appropriate patient manipulation and the volume of CSF into which the medium is placed, will determine the extent of the diagnostic contrast that can be achieved.

Following intrathecal injection in conventional radiography, OMNIPAQUE 180, OMNIPAQUE 240, and OMNIPAQUE 300 will continue to provide good diagnostic contrast for at least 30 minutes. Slow diffusion of iohexol takes place throughout the CSF with subsequent absorption into the bloodstream. Once in the systemic circulation, iohexol displays little tendency to bind to serum or plasma proteins. At approximately 1 hour following injection, contrast of diagnostic quality will no longer be available for conventional myelography. If computerized tomographic (CT) myelography is to follow, consideration should be given to a delay of several hours to allow the degree of contrast to decrease.

After administration into the lumbar subarachnoid space, computerized tomography shows the presence of contrast medium in the thoracic region in about 1 hour, in the cervical region in about 2 hours, and in the basal cisterns in 3 to 4 hours.

In patients with renal impairment, depending on the degree of impairment, prolonged plasma iohexol levels may be anticipated due to decreased renal elimination.

INDICATIONS AND USAGE—Intrathecal

OMNIPAQUE 180, OMNIPAQUE 240, and OMNIPAQUE 300 are indicated for intrathecal administration in adults including myelography (lumbar, thoracic, cervical, total columnar) and in contrast enhancement for computerized tomography (myelography, cisternography, ventriculography).

OMNIPAQUE 180 is indicated for intrathecal administration in children including myelography (lumbar, thoracic, cervical, total columnar) and in contrast enhancement for computerized tomography (myelography, cisternography).

CONTRAINDICATIONS—Intrathecal

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely.

Intrathecal administration of corticosteroids with OMNIPAQUE is contraindicated.

Because of the possibility of overdosage, immediate repeat myelography in the event of technical failure is contraindicated (see DOSAGE AND ADMINISTRATION).

WARNINGS—General

SEVERE ADVERSE EVENTS—INADVERTENT INTRATHECAL ADMINISTRATION

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that OMNIPAQUE 140 and 350 are not administered intrathecally. (All other concentrations of OMNIPAQUE are approved for intrathecal administration.)

If grossly bloody CSF is encountered, the possible benefits of a myelographic procedure should be considered in terms of the risk to the patient.

Caution is advised in patients with a history of epilepsy, severe cardiovascular disease, chronic alcoholism, or multiple sclerosis.

Elderly patients may present a greater risk following myelography. The need for the procedure in these patients should be evaluated carefully. Special attention must be paid to dose and concentration of the medium, hydration, and technique used.

Patients who are receiving anticonvulsants should be maintained on this therapy. Should a seizure occur, intravenous diazepam or phenobarbital sodium is recommended. In patients with a history of seizure activity who are not on anticonvulsant therapy, premedication with barbiturates should be considered.

Prophylactic anticonvulsant treatment with barbiturates should be considered in patients with evidence of inadvertent intracranial entry of a large or concentrated bolus of the contrast medium since there may be an increased risk of seizure in such cases.

Drugs which lower the seizure threshold, especially phenothiazine derivatives, including those used for their antihistamine properties, are not recommended for use with OMNIPAQUE. Others include MAO inhibitors, tricyclic antidepressants, CNS stimulants, and psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. While the contributory role of these medications has not been established, the use of such drugs should be based on physician evaluation of potential benefits and potential risks. Physicians have discontinued these agents at least 48 hours before and for at least 24 hours postprocedure.

Care is required in patient management to prevent inadvertent intracranial entry of a large dose or concentrated bolus of the medium. Also, effort should be directed to avoid rapid dispersion of the medium causing inadvertent rise to intracranial levels (eg, by active patient movement). Direct intracisternal or ventricular administration for standard radiography (not CT) is not recommended.

In most reported cases of major motor seizures with nonionic myelographic media, one or more of the following factors were present. Therefore avoid:

- Deviations from recommended procedure or in myelographic management.
- Use in patients with a history of epilepsy.
- Overdosage.
- Intracranial entry of a bolus or premature diffusion of a high concentration of the medium.
- Medication with neuroleptic drugs or phenothiazine antinauseants.
- Failure to maintain elevation of the head during the procedure, on the stretcher, or in bed.
- Excessive and particularly active patient movement or straining.

PRECAUTIONS—General

Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred. (See ADVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease). Dehydration in these patients seems to be enhanced by the osmotic diuretic action of contrast agents. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid, cardiovascular or central nervous system reactions, should always be considered (see ADVERSE REACTIONS). Therefore, it is of utmost importance that a course of action be carefully planned in advance for the immediate treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

In patients with severe renal insufficiency or failure, compensatory biliary excretion of the drug is anticipated to occur, with a slow clearance into the bile. Patients with hepatorenal insufficiency should not be examined unless the possibility of benefit clearly outweighs the additional risk.

Administration of contrast media should be performed by qualified personnel familiar with the procedure and appropriate patient management (see PATIENT MANAGEMENT). Sterile technique must be used with any spinal puncture.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Information for Patients (or if applicable, children)

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant (see CLINICAL PHARMACOLOGY).

2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease or known thyroid disorder (see WARNINGS).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including non-prescription drugs, before you are administered this drug.

Drug Interactions

Drugs which lower seizure threshold, especially phenothiazine derivatives including those used for their antihistaminic or antinauseant properties, are not recommended for use with OMNIPAQUE. Others include monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48 hours before myelography, should not be used for the control of nausea or vomiting during or after myelography, and should not be resumed for at least 24 hours postprocedure. In nonelective procedures in patients on these drugs, consider prophylactic use of anticonvulsants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS—Intrathecal

The most frequently reported adverse reactions with OMNIPAQUE are headache, mild to moderate pain including backache, neckache and stiffness, nausea, and vomiting. These reactions usually occur 1 to 10 hours after injection, and almost all occur within 24 hours. They are usually mild to moderate in degree, lasting for a few hours, and usually disappearing within 24 hours. Rarely, headaches may be severe or persist for days. Headache is often accompanied by nausea and vomiting and tends to be more frequent and persistent in patients not optimally hydrated.

Transient alterations in vital signs may occur and their significance must be assessed on an individual basis. Those reactions reported in clinical studies with OMNIPAQUE are listed below in decreasing order of occurrence, based on clinical studies of 1531 patients.

Headaches: The most frequently occurring adverse reaction following myelography has been headache, with an incidence of approximately 18%. Headache may be caused by either a direct effect of the contrast medium or by CSF leakage at the dural puncture site. However, in managing the patient, it is considered more important to minimize intracranial entry of contrast medium by postural management than attempting to control possible CSF leakage (see PATIENT MANAGEMENT).

Pain: Mild to moderate pain including backache, neckache and stiffness, and neuralgia occurred following injection with an incidence of about 8%.

Nausea and Vomiting: Nausea was reported with an incidence of about 6%, and vomiting about 3% (see PATIENT MANAGEMENT). Maintaining normal hydration is very important. The use of phenothiazine antinauseants is not recommended. (See WARNINGS—General.) Reassurance to the patient that the nausea will clear usually is all that is required.

Dizziness: Transient dizziness was reported in about 2% of the patients.

Other Reactions: Other reactions occurring with an individual incidence of less than 0.1% included: feeling of heaviness, hypotension, hypertonia, sensation of heat, sweating, vertigo, loss of appetite, drowsiness, hypertension, photophobia, tinnitus, neuralgia, paresthesia, difficulty in micturition, and neurological changes. All were transient and mild with no clinical sequelae.

Pediatrics

In controlled clinical trials involving 152 patients for pediatric myelography by lumbar puncture, adverse events following the use of OMNIPAQUE 180 were generally less frequent than with adults.

Headache: 9%
Vomiting: 6%
Backache: 1.3%

Other Reactions: Other reactions occurring with an individual incidence of less than 0.7% included: fever, hives, stomachache, visual hallucination, and neurological changes. All were transient and mild with no clinical sequelae.

General Adverse Reactions to Contrast Media

Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above, particularly the following reactions which have been reported in the literature for other nonionic, water-soluble myelographic media, and rarely with iohexol. These have included, but are not limited to, convulsion, aseptic and bacterial meningitis, and CNS and other neurological disturbances.

An aseptic meningitis syndrome has been reported rarely (less than 0.01%). It was usually preceded by pronounced headaches, nausea and vomiting. Onset usually occurred about 12 to 18 hours postprocedure. Prominent features were meningismus, fever, sometimes with oculomotor signs and mental confusion. Lumbar puncture revealed a high white cell count, high protein content often with a low glucose level and with absence of organisms. The condition usually started to clear spontaneously about 10 hours after onset, with complete recovery over 2 to 3 days.

Allergy or Idiosyncrasy: Chills, fever, profuse diaphoresis, pruritus, urticaria, nasal congestion, dyspnea, and a case of Guillain-Barre syndrome.

CNS Irritation: Mild and transitory perceptual aberrations such as hallucinations, depersonalization, amnesia, hostility, amblyopia, diplopia, photophobia, psychosis, insomnia, anxiety, depression, hyperesthesia, visual or auditory or speech disturbances, confusion and disorientation. In addition, malaise, weakness, convulsion, EEG changes, meningismus, hyperreflexia or areflexia, hypertonia or flaccidity, hemiplegia, paralysis, quadriplegia, restlessness, tremor, echoacousia, echolalia, asterixis, cerebral hemorrhage, and dysphasia have occurred.

Profound mental disturbances have also rarely been reported. They have usually consisted of various forms and degrees of aphasia, mental confusion, or disorientation. The onset is usually at 8 to 10 hours and lasts for about 24 hours, without aftereffects. However, occasionally they have been manifest as apprehension, agitation, or progressive withdrawal in several instances to the point of somnolence, stupor, and coma. In a few cases these have been accompanied by transitory hearing loss or other auditory symptoms and visual disturbances (believed subjective or delusional), including unilateral or bilateral loss of vision which may last for hours. In one case, persistent cortical loss of vision has been reported in association with convulsions. Ventricular block has been reported; amnesia of varying degrees may be present for the reaction event.

Rarely, persistent though transitory weakness in the leg or ocular muscles has been reported.

Peripheral neuropathies have been rare and transitory. They include sensory and/or motor or nerve root disturbances, myelitis, persistent leg muscle pain or weakness, 6th nerve palsy, or cauda equina syndrome. Muscle cramps, fasciculation or myoclonia, spinal convulsion, or spasticity is unusual and has responded promptly to a small intravenous dose of diazepam.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95 percent of adverse reactions accompanying the use of water-soluble contrast agents are mild to moderate in degree. However, severe, life-threatening, anaphylactoid and fatal reactions, mostly of cardiovascular origin and central nervous system origin, have occurred.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

OVERDOSAGE

Clinical consequences of overdosage with OMNIPAQUE have not been reported. However, based on experience with other nonionic myelographic media, physicians should be alert to a potential increase in frequency and severity of CNS-mediated reactions. Even use of a recommended dose can produce effects tantamount to overdosage, if incorrect management of the patient during or immediately following the procedure permits inadvertent early intracranial entry of a large portion of the medium.

The intracisternal LD_{50} value of OMNIPAQUE (in grams of iodine per kilogram body weight) is greater than 2.0 in mice.

DOSAGE AND ADMINISTRATION — Intrathecal

The volume and concentration of OMNIPAQUE 180, OMNIPAQUE 240, or OMNIPAQUE 300 to be administered will depend on the degree and extent of contrast required in the area(s) under examination and on the equipment and technique employed.

OMNIPAQUE 180 at a concentration of 180 mgI/mL, OMNIPAQUE 240 at a concentration of 240 mgI/mL, or OMNIPAQUE 300 at a concentration of 300 mgI/mL is recommended for the examination of the lumbar, thoracic, and cervical regions in adults by lumbar or direct cervical injection and is slightly hypertonic to CSF.

OMNIPAQUE 180 at a concentration of 180 mgI/mL is recommended for the examination of the lumbar, thoracic, and cervical regions in children by lumbar injection and is slightly hypertonic to CSF.

A total dose of 3060 mg iodine or a concentration of 300 mgI/mL should not be exceeded in adults and a total dose of 2700 mg iodine or a concentration of 180 mgI/mL should not be exceeded in children in a single myelographic examination. This is based on clinical trial evaluation to date. As in all diagnostic procedures, the minimum volume and dose to produce adequate visualization should be used. Most procedures do not require either maximum dose or concentration.

Anesthesia is not necessary. Premedication sedatives or tranquilizers are usually not needed (see PRECAUTIONS). Patients should be well hydrated prior to and following contrast administration. Seizure-prone patients should be maintained on anticonvulsant medication.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, concurrent drugs should not be physically admixed with contrast agents.

Rate of Injection: To avoid excessive mixing with CSF and consequent dilution of contrast, injection should be made slowly over 1 to 2 minutes.

Depending on the estimated volume of contrast medium which may be required for the procedure a small amount of CSF may be removed to minimize distention of the subarachnoid spaces.

The lumbar or cervical puncture needle may be removed immediately following injection since it is not necessary to remove OMNIPAQUE after injection into the subarachnoid space.

Adults: The usual recommended total doses for use in lumbar, thoracic, cervical, and total columnar myelography in adults are 1.2 gI to 3.06 gI as follows:

Procedure	Formulations	Concentration (mgI/mL)	Volume (mL)	Dose (gI)
Lumbar Myelography (via lumbar injection)	OMNIPAQUE 180	180	10-17	1.8-3.06
	OMNIPAQUE 240	240	7-12.5	1.7-3.0
Thoracic Myelography (via lumbar or cervical injection)	OMNIPAQUE 240	240	6-12.5	1.7-3.0
	OMNIPAQUE 300	300	6-10	1.8-3.0
Cervical Myelography (via lumbar injection)	OMNIPAQUE 240	240	6-12.5	1.4-3.0
	OMNIPAQUE 300	300	6-10	1.8-3.0
Cervical Myelography (via C1-2 injection)	OMNIPAQUE 180	180	7-10	1.3-1.8
	OMNIPAQUE 240	240	6-12.5	1.4-3.0
	OMNIPAQUE 300	300	4-10	1.2-3.0
Total Columnar Myelography (via lumbar injection)	OMNIPAQUE 240	240	6-12.5	1.4-3.0
	OMNIPAQUE 300	300	6-10	1.8-3.0

Pediatrics: The usual recommended total doses for lumbar, thoracic, cervical, and/or total columnar myelography by lumbar puncture in children are 0.36 gI to 2.7 gI (see table below). Actual volumes administered depend largely on patient age and the following guidelines are recommended.

Age	Conc. (mgI/mL)	Volume (mL)	Dose (gI)
0 to < 3 mos.	180	2-4	0.36-0.72
3 to < 36 mos.	180	4-8	0.72-1.44
3 to < 7 yrs.	180	5-10	0.9-1.8
7 to < 13 yrs.	180	5-12	0.9-2.16
13 to 18 yrs.	180	6-15	1.08-2.7

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile syringes. Spinal puncture must always be performed under sterile conditions.

Parenteral products should be inspected visually for particulate matter or discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body. An interval of at least 48 hours should be allowed before repeat examination; however, whenever possible, 5 to 7 days is recommended.

PATIENT MANAGEMENT—Intrathecal

Suggestions for Usual Patient Management

Good patient management should be exercised at all times to minimize the potential for procedurally related complications.

Preprocedure

- Discontinuance of neuroleptic drugs (including phenothiazines, eg, chlorpromazine, prochlorperazine, and promethazine) at least 48 hours beforehand should be considered.
- Maintain normal diet up to 2 hours before procedure.
- Ensure hydration-fluids up to procedure.

During Procedure

- Use minimum dose and concentration required for satisfactory contrast (see DOSAGE AND ADMINISTRATION).
- In all positioning techniques keep the patient's head elevated above highest level of spine.
- Do not lower head of table more than 15° in moving contrast medium cranially.
- In patients with excessive lordosis, consider lateral position for injection and movement of the medium cephalad.
- Inject slowly (over 1 to 2 minutes) to avoid excessive mixing.
- To maintain as a bolus, move medium to distal area very slowly. Use fluoroscopic monitoring.
- Avoid intracranial entry of a bolus.
- Avoid early and high cephalad dispersion of the medium.
- Avoid abrupt or active patient movement to minimize excessive mixing of medium with CSF. Instruct patient to remain passive. Move patient slowly and only as necessary.

Postprocedure

- Raise head of stretcher to at least 30° before moving patient onto it.
- Movement onto and off the stretcher should be done slowly with the patient completely passive, maintaining head-up position.
- Before moving patient onto bed, raise head of bed 30° to 45°.
- Advise patient to remain still in bed, in a sitting or semisitting position, especially in the first few hours.
- Maintain close observation for at least 12 hours after myelogram.
- Obtain visitors' cooperation in keeping the patient quiet and in head-up position, especially in first few hours.
- Encourage oral fluids. Diet as tolerated.
- If nausea or vomiting occurs, do not use phenothiazine antinauseants. Persistent nausea and vomiting will result in dehydration. Therefore, prompt consideration of replacement by intravenous fluids is recommended.

Alternative Postprocedure Method

- Recent evidence with nonionic, water-soluble contrast media suggests that maintaining the patient postmyelography in an upright position (via wheelchair or ambulation) may help minimize adverse effects. The upright position may help to delay upward dispersion of the medium and to maximize the spinal arachnoid absorption.

SECTION II
CLINICAL PHARMACOLOGY—Intravascular

Following intravascular injection, iohexol is distributed in the extracellular fluid compartment and is excreted unchanged by glomerular filtration. It will opacify those vessels in the path of flow of the contrast medium permitting radiographic visualization of the internal structures until significant hemodilution occurs.

Approximately 90% or more of the injected dose is excreted within the first 24 hours, with the peak urine concentrations occurring in the first hour after administration. Plasma and urine iohexol levels indicate that the iohexol body clearance is due primarily to renal clearance. An increase in the dose from 500 mgI/kg to 1500 mgI/kg does not significantly alter the clearance of the drug. The following pharmacokinetic values were observed following the intravenous administration of iohexol (between 500 mgI/kg to 1500 mgI/kg) to 16 adult human subjects: renal clearance—120 (86-162) mL/min; total body clearance—131 (98-165) mL/min; and volume of distribution—165 (108-219) mL/kg.

Renal accumulation is sufficiently rapid that the period of maximal opacification of the renal passages may begin as early as 1 minute after intravenous injection. Urograms become apparent in about 1 to 3 minutes with optimal contrast occurring between 5 to 15 minutes. In nephropathic conditions, particularly when excretory capacity has been altered, the rate of excretion may vary unpredictably, and opacification may be delayed after injection. Severe renal impairment may result in a lack of diagnostic opacification of the collecting system and, depending on the degree of renal impairment, prolonged plasma iohexol levels may be anticipated. In these patients, as well as in infants with immature kidneys, the route of excretion through the gallbladder and into the small intestine may increase.

Iohexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.

OMNIPAQUE probably crosses the placental barrier in humans by simple diffusion. It is not known to what extent iohexol is excreted in human milk.

Animal studies indicate that iohexol does not cross an intact blood-brain barrier to any significant extent following intravascular administration.

OMNIPAQUE enhances computed tomographic imaging through augmentation of radiographic efficiency. The degree of density enhancement is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid intravenous injection. Blood levels fall rapidly within 5 to 10 minutes and the vascular compartment half-life is approximately 20 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about ten minutes; thereafter, the fall becomes exponential.

The pharmacokinetics of iohexol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest immediately after bolus administration (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive two-to-three second scans performed within 30 to 90 seconds after injection (ie, dynamic computed tomographic imaging). Utilization of a continuous scanning technique (ie, dynamic CT scanning) may improve enhancement and diagnostic assessment of tumor and other lesions such as abscess, occasionally revealing unsuspected or more extensive disease. For example, a cyst may be distinguished from a vascularized solid lesion when precontrast and enhanced scans are compared; the nonperfused mass shows unchanged x-ray absorption (CT number). A vascularized lesion is characterized by an increase in CT number in the few minutes after a bolus of intravascular contrast agent; it may be malignant, benign, or normal tissue, but would probably not be a cyst, hematoma, or other nonvascular lesion.

Because unenhanced scanning may provide adequate diagnostic information in the individual patient, the decision to employ contrast enhancement, which may be associated with risk and increased radiation exposure, should be based upon a careful evaluation of clinical, other radiological, and unenhanced CT findings.

CT SCANNING OF THE HEAD

In contrast enhanced computed tomographic head imaging, OMNIPAQUE does not accumulate in normal brain tissue due to the presence of the normal blood-brain barrier. The increase in x-ray absorption in normal brain is due to the presence of contrast agent within the blood pool. A break in the blood-brain barrier such as occurs in malignant tumors of the brain allows for the accumulation of contrast medium within the interstitial tissue of the tumor. Adjacent normal brain tissue does not contain the contrast medium.

Maximum contrast enhancement in tissue frequently occurs after peak blood iodine levels are reached. A delay in maximum contrast enhancement can occur. Diagnostic contrast enhanced images of the brain have been obtained up to 1 hour after intravenous bolus administration. This delay suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine containing medium within the lesion and outside the blood pool, although the mechanism by which this occurs is not clear. The radiographic enhancement of nontumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool.

In patients where the blood-brain barrier is known or suspected to be disrupted, the use of any radiographic contrast medium must be assessed on an individual risk to benefit basis. However, compared to ionic media, nonionic media are less toxic to the central nervous system.

CT SCANNING OF THE BODY

In contrast enhanced computed tomographic body imaging (nonneural tissue), OMNIPAQUE diffuses rapidly from the vascular into the extravascular space. Increase in x-ray absorption is related to blood flow, concentration of the contrast medium, and extraction of the contrast medium by interstitial tissue of tumors since no barrier exists. Contrast enhancement is thus due to the relative differences in extravascular diffusion between normal and abnormal tissue, quite different from that in the brain.

INDICATIONS AND USAGE, GENERAL—Intravascular

OMNIPAQUE 350 is indicated in adults for angiocardiography (ventriculography, selective coronary arteriography), aortography including studies of the aortic root, aortic arch, ascending aorta, abdominal aorta and its branches, contrast enhancement for computed tomographic head and body imaging, intravenous digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels, peripheral arteriography, and excretory urography.

OMNIPAQUE 350 is indicated in children for angiocardiography (ventriculography, pulmonary arteriography, and venography; studies of the collateral arteries and aortography, including the aortic root, aortic arch, ascending and descending aorta).

OMNIPAQUE 300 is indicated in adults for aortography including studies of the aortic arch, abdominal aorta and its branches, contrast enhancement for computed tomographic head and body imaging, cerebral arteriography, peripheral venography (phlebography), and excretory urography.

OMNIPAQUE 300 is indicated in children for angiocardiography (ventriculography), excretory urography, and contrast enhancement for computed tomographic head imaging.

OMNIPAQUE 240 is indicated in adults for contrast enhancement for computed tomographic head imaging and peripheral venography (phlebography).

OMNIPAQUE 140 is indicated in adults for intra-arterial digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels.

OMNIPAQUE 240 is indicated in children for contrast enhancement for computed tomographic head imaging.

CONTRAINDICATIONS

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General

Nonionic iodinated contrast media inhibit blood coagulation, *in vitro*, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General

Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease), infants and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with preexisting renal disease) following excretory

urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant (see CLINICAL PHARMACOLOGY—Intravascular).
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including nonprescription drugs, before you are administered this drug.

Drug/Laboratory Test Interaction

If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS: Intravascular—General

Adverse reactions following the use of OMNIPAQUE 140, OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 are usually of mild to moderate severity. However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo (including dizziness and lightheadedness) (0.5%), pain (3%), vision abnormalities (including blurred vision and photomas) (2%), headache (2%), and taste perversion (1%). Others including anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication.

Pediatrics

In controlled clinical trials involving 391 patients for pediatric angiocardiography, urography, and contrast enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).

Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).

Respiratory System: Congestion (0.3%) and apnea (0.3%).

Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).

Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media

Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above.

The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria, and rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing and lacrimation and, rarely, anaphylactic reactions. Rare fatalities have occurred, due to this or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; *or to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema, especially facial cramps, neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears two days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95 percent of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy are twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

OVERDOSAGE

Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include: cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION — General

As with all radiopaque contrast agents, the lowest dose of OMNIPAQUE necessary to obtain adequate visualization should be used. A lower dose may reduce the possibility of an adverse reaction. Most procedures do not require use of either the maximum volume or the highest concentration of OMNIPAQUE. The combination of volume and concentration of OMNIPAQUE to be used should be carefully individualized accounting for factors such as age, body weight, size of the vessel and the rate of blood flow within the vessel. Other factors such as anticipated pathology, degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed should be considered.

Sterile technique must be used in all vascular injections involving contrast media.

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile equipment. Sterile techniques must be used with any invasive procedure.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

It may be desirable that solutions of radiopaque diagnostic agents be used at body temperature when injected.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions of OMNIPAQUE should be used only if clear and within the normal colorless to pale yellow range. If particulate matter or discoloration is present, do not use.

INDIVIDUAL INDICATIONS AND USAGE

ANGIOCARDIOGRAPHY

Pharmacology—Hemodynamic Changes

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for angiocardiography (ventriculography, aortic root injections, and selective coronary arteriography).

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in children for angiocardiography (ventriculography, pulmonary arteriography, and venography, and studies of the collateral arteries).

OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in children for angiocardiography (ventriculography).

After both ventricular and coronary injection, decreases in systolic pressure were less pronounced and returned to baseline values earlier with OMNIPAQUE 350 than with diatrizoate meglumine and diatrizoate sodium injection.

OMNIPAQUE 350 produced less Q-T interval prolongation than seen with diatrizoate meglumine and diatrizoate sodium injection.

In children, after injection of all sites, but particularly following ventricular and pulmonary artery injections, decreases in both systolic and diastolic intravascular pressure were significantly less pronounced with OMNIPAQUE 350 than with diatrizoate meglumine and diatrizoate sodium injection. In children, OMNIPAQUE 350 produced significantly less shortening of the R-R interval than seen with diatrizoate meglumine and diatrizoate sodium injection.

If repeat injections are made in rapid succession, all these changes are likely to be more pronounced. (See DOSAGE AND ADMINISTRATION.)

Precautions

During administration of large doses of OMNIPAQUE 350, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the preexisting condition. Hypotension should be corrected promptly since it may induce serious arrhythmias.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of the hemodynamic changes which may occur after injection into the right heart outflow tract. (See PRECAUTIONS—General.)

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Adverse Reactions

Cardiovascular system reactions in angiocardiography included angina (8%), hypotension (2.5%), bradycardia (1.0%), and tachycardia (1.0%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The individual dose or volume is determined by the size of the structure to be visualized, the anticipated degree of hemodilution, and valvular competence. Weight is a minor consideration in adults, but must be considered in infants and young children. The volume of each individual injection is a more important consideration than the total dosage used. When large individual volumes are administered, as in ventriculography and aortography, it has been suggested that several minutes be permitted to elapse between each injection to allow for subsidence of possible hemodynamic disturbances.

The recommended single injection volume of OMNIPAQUE 350 for angiocardiographic procedures in adults and the recommended single injection volumes of OMNIPAQUE 350 and OMNIPAQUE 300 for angiographic procedures in children are as follows:

Ventriculography

Adults: The usual adult volume for a single injection is 40 mL with a range of 30 mL to 60 mL. This may be repeated as necessary. When combined with selective coronary arteriography, the total administered volume should not exceed 250 mL (87.5 gI).

Pediatrics: The usual single injection dose of OMNIPAQUE 350 is 1.25 mL/kg of body weight with a range of 1.0 mL/kg to 1.5 mL/kg. For OMNIPAQUE 300 the usual single injection dose is 1.75 mL/kg with a range of 1.5 mL/kg to 2.0 mL/kg. When multiple injections are given, the total administered dose should not exceed 5 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350 or up to a total volume of 291 mL of OMNIPAQUE 300.

Selective Coronary Arteriography

The usual adult volume for right or left coronary arteriography is 5 mL (range 3 mL to 14 mL) per injection.

Aortic Root and Arch Study When Used Alone

The usual adult single injection volume is 50 mL, with a range of 20 mL to 75 mL.

Pulmonary Angiography

Pediatrics: The usual single injection dose is 1.0 mL/kg of OMNIPAQUE 350.

Combined Angiocardiographic Procedures

Multiple Procedures

Adults: The visualization of multiple vascular systems and target organs is possible during a single radiographic examination of the patient.

Large doses of OMNIPAQUE 350 were well tolerated in angiographic procedures requiring multiple injections.

The maximum total volume for multiple procedures should not exceed 250 mL of 350 mgI/mL (87.5 gI).

Pediatrics: Visualization of multiple vascular systems and target organs is possible during a single radiographic examination of the patient.

The maximum total dose for multiple injection procedures should not exceed 5.0 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350 or 6.0 mL/kg up to a total volume of 291 mL of OMNIPAQUE 300.

AORTOGRAPHY AND SELECTIVE VISCERAL ARTERIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL and OMNIPAQUE 350 at a concentration of 350 mgI/mL are indicated in adults for use in aortography and selective visceral arteriography including studies of the aortic arch, ascending aorta, and abdominal aorta and its branches (celiac, mesenteric, renal, hepatic and splenic arteries).

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in children for use in aortography including studies of the aortic root, aortic arch, ascending and descending aorta.

Precautions

Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows. (See PRECAUTIONS—General.)

Adverse Reactions

See ADVERSE REACTIONS: Intravascular—General, and ADVERSE REACTIONS—ANGIOCARDIOGRAPHY.

Dosage and Administration

Adults: The usual adult volume as a single injection is 50 mL to 80 mL for the aorta, 30 mL to 60 mL for major branches including celiac and mesenteric arteries, and 5 mL to 15 mL for renal arteries. Repeated injections may be performed if indicated, but the total volume should not exceed 291 mL of OMNIPAQUE 300 or 250 mL of OMNIPAQUE 350 (87.5 gI).

Pediatrics: The usual single injection dose is 1.0 mL/kg of OMNIPAQUE 350 and should not exceed 5.0 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350.

CEREBRAL ARTERIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in adults for use in cerebral arteriography.

The degree of pain and flushing as the result of the use of OMNIPAQUE 300 in cerebral arteriography is less than that seen with comparable injections of many contrast media.

In cerebral arteriography, patients should be appropriately prepared consistent with existing or suspected disease states.

Precautions

Cerebral arteriography should be undertaken with extreme care with special caution in elderly patients, patients in poor clinical condition, advanced arteriosclerosis, severe arterial hypertension, recent cerebral embolism or thrombosis, and cardiac decompensation.

Since the contrast medium is given by rapid injection, the patient should be monitored for possible untoward reactions. (See PRECAUTIONS—General.)

Adverse Reactions

Cerebral arteriography with water-soluble contrast media has been associated with temporary neurologic complications including seizures, drowsiness, transient paresis, and mild disturbances in vision such as photomas of 1-second or less duration.

Central nervous system reactions in cerebral arteriography included photomas (15%), headache (5.5%), and pain (4.5%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

OMNIPAQUE 300 is recommended for cerebral arteriography at the following volumes: common carotid artery (6 mL to 12 mL), internal carotid artery (8 mL to 10 mL), external carotid artery (6 mL to 9 mL), and vertebral artery (6 mL to 10 mL).

CONTRAST ENHANCED COMPUTED TOMOGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL, OMNIPAQUE 300 at a concentration of 300 mgI/mL, and OMNIPAQUE 350 at a concentration of 350 mgI/mL are indicated in adults for use in intravenous contrast enhanced computed tomographic head and body imaging by rapid injection or infusion technique.

OMNIPAQUE 240 at a concentration of 240 mgI/mL and OMNIPAQUE 300 at a concentration of 300 mgI/mL are indicated in children for use in intravenous contrast enhanced computed tomographic head imaging by rapid bolus injection.

CT SCANNING OF THE HEAD

OMNIPAQUE may be used to redefine diagnostic precision in areas of the brain which may not otherwise have been satisfactorily visualized.

Tumors

OMNIPAQUE may be useful to investigate the presence and extent of certain malignancies such as: gliomas including malignant gliomas, glioblastomas, astrocytomas, oligodendrogliomas and gangliomas, ependymomas, medulloblastomas, meningiomas, neuromas, pinealomas, pituitary adenomas, carniopharyngiomas, germinomas, and metastatic lesions. The usefulness of contrast enhancement for the investigation of the retrobulbar space and in cases of low grade or infiltrative glioma has not been demonstrated. In calcified lesions, there is less likelihood of enhancement. Following therapy, tumors may show decreased or no enhancement. The opacification of the inferior vermis following contrast media administration has resulted in false-positive diagnosis in a number of otherwise normal studies.

Nonneoplastic Conditions

OMNIPAQUE may be beneficial in the image enhancement of nonneoplastic lesions. Cerebral infarctions of recent onset may be better visualized with contrast enhancement, while some infarctions are obscured if contrast medium is used. The use of iodinated contrast media results in enhancement in about 60 percent of cerebral infarctions studied from one to four weeks from the onset of symptoms.

Sites of active infection may also be enhanced following contrast medium administration.

Arteriovenous malformations and aneurysms will show contrast enhancement. For these vascular lesions the enhancement is probably dependent on the iodine content of the circulating blood pool. Hematomas and intraparenchymal bleeders seldom demonstrate contrast enhancement. However, in cases of intraparenchymal clot, for which there is no obvious clinical explanation, contrast media administration may be helpful in ruling out the possibility of associated arteriovenous malformation.

CT SCANNING OF THE BODY

OMNIPAQUE may be useful for enhancement of computed tomographic images for detection and evaluation of lesions in the liver, pancreas, kidneys, aorta, mediastinum, pelvis, abdominal cavity, and retroperitoneal space.

Enhancement of computed tomography with OMNIPAQUE may be of benefit in establishing diagnoses of certain lesions in these sites with greater assurance than is possible with CT alone. In other cases, the contrast agent may allow visualization of lesions not seen with CT alone (ie, tumor extension) or may help to define suspicious lesions seen with unenhanced CT (ie, pancreatic cyst).

For information regarding the use of dilute oral plus intravenous OMNIPAQUE in CT of the abdomen, see INDIVIDUAL INDICATIONS AND USAGE—Oral Use.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Immediately following intravascular injection of contrast medium, a transient sensation of mild warmth is not unusual. Warmth is less frequent with OMNIPAQUE than with ionic media. (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The concentration and volume required will depend on the equipment and imaging technique used.

OMNIPAQUE (iohexol) Injection

The dosage recommended for use in adults for contrast enhanced computed tomography is as follows:

Head Imaging by Injection:	70 mL to 150 mL (21 gI to 45 gI) of OMNIPAQUE 300 (300 mgI/mL) 80 mL (28 gI) of OMNIPAQUE 350 (350 mgI/mL)
Head Imaging by Infusion:	120 mL to 250 mL (29 gI to 60 gI) of OMNIPAQUE 240 (240 mgI/mL)
Body Imaging by Injection:	50 mL to 200 mL (15 gI to 60 gI) of OMNIPAQUE 300 (300 mgI/mL) 60 mL to 100 mL (21 gI to 35 gI) of OMNIPAQUE 350 (350 mgI/mL)

The dosage recommended for use in children for contrast enhanced computed tomographic head imaging is 1.0 mL/kg to 2.0 mL/kg for OMNIPAQUE 240 or OMNIPAQUE 300. It should not be necessary to exceed a maximum dose of 28 gI with OMNIPAQUE 240 or 35 gI with OMNIPAQUE 300.

DIGITAL SUBTRACTION ANGIOGRAPHY

Intravenous Administration

OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for use in intravenous digital subtraction angiography (I.V.DSA) of the vessels of the head, neck, and abdominal, renal and peripheral vessels.

Arteriograms of diagnostic quality can be obtained following the intravenous administration of contrast media employing digital subtraction and computer imaging enhancement techniques. The intravenous route of administration using these techniques has the advantage of being less invasive than the corresponding selective catheter placement of medium. The dose is administered into a

peripheral vein, the superior vena cava or right atrium, usually by mechanical injection although sometimes by rapid manual injection. The technique has been used to visualize the ventricles, aorta and most of its larger branches, including the carotids, cerebrals, vertebrals, renal, celiac, mesenterics, and the major peripheral vessels of the limbs. Radiographic visualization of these structures is possible until significant hemodilution occurs.

OMNIPAQUE 350 can be injected intravenously as a rapid bolus to provide arterial visualization using digital subtraction radiography. Preprocedural medications are not considered necessary. OMNIPAQUE 350 has provided diagnostic arterial radiographs in about 95% of patients. In some cases, poor arterial visualization has been attributed to patient movement. OMNIPAQUE 350 is very well tolerated in the vascular system. Patient discomfort (general sensation of heat and/or pain) following injection is less than with various other contrast media.

Precautions

Since the contrast medium is usually administered mechanically under high pressure, rupture of smaller peripheral veins can occur. It has been suggested that this can be avoided by using an intravenous catheter threaded proximally beyond larger tributaries or, in the case of the antecubital vein, into the superior vena cava. Sometimes the femoral vein is used. (See PRECAUTIONS—General.)

Adverse Reactions

Cardiovascular system reactions in digital arteriography included transient PVCs (16%) and PACs (6.5%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The usual injection volume of OMNIPAQUE 350 for the intravenous digital technique is 30 mL to 50 mL of a 350 mgI/mL solution. This is administered as a bolus at 7.5 to 30 mL/second using a pressure injector. The volume and rate of injection will depend primarily on the type of equipment and technique used.

Frequently three or more injections may be required, up to a total volume not to exceed 250 mL (87.5 gI).

Intra-arterial Administration

OMNIPAQUE 140 at a concentration of 140 mgI/mL is indicated for use in intra-arterial digital subtraction angiography of head, neck, abdominal, renal and peripheral vessels. The intra-arterial route of administration has the advantages of allowing a lower total dose of contrast agent since there is less hemodilution than with the intravenous route of administration. Patients with poor cardiac output would be expected to have better contrast enhancement following intra-arterial administration as compared with intravenous administration. A higher concentration of contrast agent may be needed to facilitate catheter placement under fluoroscopic control.

Precautions

High pressure intra-arterial injections may cause the rupture of smaller peripheral arteries. (See PRECAUTIONS—General.)

Adverse Reactions

Central nervous system reactions in intra-arterial digital angiography include transient ischemia attacks (1.6%) and cerebral infarctions (1.6%). These occurred in high risk patients having a cerebral examination and the relationship to the contrast medium was uncertain. (See ADVERSE REACTIONS—General.) Headache occurred in 6.3% of the patients, all of whom were having cerebral examinations.

Dosage and Administration

Mechanical or hand injection can be used to administer one or more bolus intra-arterial injections of OMNIPAQUE 140. The volume and rate of injection will depend on the type of equipment, technique used, and the vascular area to be visualized. The following volumes and rates of injection have been used with OMNIPAQUE 140.

Arteries	Volume/Injection (mL)	Rate of Injection (mL/sec)
Aorta	20-45	8-20
Carotid	5-10	3-6
Femoral	9-20	3-6
Vertebral	4-10	2-8
Renal	6-12	3-6
Other Branches of the Aorta (includes subclavian, axillary, innominate and iliac)	8-25	3-10

PERIPHERAL ANGIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL or OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for use in peripheral arteriography. OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in adults for use in peripheral venography.

Sedative medication may be employed prior to use. Anesthesia is not considered necessary.

Patient discomfort during and immediately following injection is substantially less than that following injection of various other contrast media. Moderate to severe discomfort is very unusual.

Precautions

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all. (See PRECAUTIONS—General.)

Adverse Reactions

A transient sensation of mild warmth is usual, immediately following injection. This has not interfered with the procedure.

In phlebography the incidence of leg pain was 21%. This usually was mild and lasted a short time after injection. (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The volume required will depend on the size, flow rate, and disease state of the injected vessel and on the size and condition of the patient, as well as the imaging technique used.

The dosage recommended for use in peripheral angiography is as follows:

Aortofemoral runoffs:	20 mL to 70 mL of OMNIPAQUE 350 (350 mgI/mL) 30 mL to 90 mL of OMNIPAQUE 300 (300 mgI/mL)
Selective arteriograms: (femoral/iliac)	10 mL to 30 mL of OMNIPAQUE 350 (350 mgI/mL) 10 mL to 60 mL of OMNIPAQUE 300 (300 mgI/mL)
Venography (per leg):	20 mL to 150 mL of OMNIPAQUE 240 (240 mgI/mL) 40 mL to 100 mL of OMNIPAQUE 300 (300 mgI/mL)

EXCRETORY UROGRAPHY

OMNIPAQUE 300 at a concentration of 300 mgI/mL or OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated for use in adults in excretory urography to provide diagnostic contrast of the urinary tract.

OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in children for excretory urography. (See Section III for information on voiding cystourethrography.)

For pharmacokinetics of excretion in adults, see CLINICAL PHARMACOLOGY—Intravascular.

Precautions

Preparatory dehydration is not recommended in the elderly, infants, young children, diabetic or azotemic patients, or in patients with suspected myelomatosis.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Since there is a possibility of temporary suppression of urine formation, it is recommended that a suitable interval elapse before excretory urography is repeated, especially in patients with unilateral or bilateral reduction in renal function. (See PRECAUTIONS—General.)

Adverse Reactions

See ADVERSE REACTIONS: Intravascular—General.

Dosage and Administration

Adults: OMNIPAQUE 300 and OMNIPAQUE 350 at dosages from 200 mgI/kg body weight to 350 mgI/kg body weight have produced diagnostic opacification of the excretory system in patients with normal renal function.

Pediatrics

Excretory Urography

OMNIPAQUE 300 at doses of 0.5 mL/kg to 3.0 mL/kg of body weight has produced diagnostic opacification of the excretory tract. The usual dose for children is 1.0 mL/kg to 1.5 mL/kg. Dosage for infants and children should be administered in proportion to age and body weight. The total administered dose should not exceed 3 mL/kg.

SECTION III
CLINICAL PHARMACOLOGY—Oral/Body Cavity Use

For most body cavities, the injected iohexol is absorbed into the surrounding tissue and eliminated by the kidneys and bowel as previously described in SECTION II, CLINICAL PHARMACOLOGY—Intravascular. Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.

Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5 percent of the oral dose was excreted by the kidneys. This amount may increase in the presence of bowel perforation or bowel obstruction. Iohexol is well tolerated and readily absorbed if leakage into the peritoneal cavity occurs.

Visualization of the joint spaces, uterus, fallopian tubes, peritoneal herniations, pancreatic and bile ducts, and bladder can be accomplished by direct injection of contrast medium into the region to be studied. The use of appropriate iodine concentrations assures diagnostic density.

Orally administered OMNIPAQUE produces good visualization of the gastrointestinal tract. OMNIPAQUE is particularly useful when barium sulfate is contraindicated as in patients with suspected bowel perforation or those where aspiration of contrast medium is a possibility.

INDICATIONS AND USAGE, GENERAL—Oral/Body Cavity Use

OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 have osmolalities from approximately 1.8 to 3.0 times that of plasma (285 mOsm/kg water) and are hypertonic under conditions of use.

Adults: OMNIPAQUE 350 is indicated in adults for arthrography and oral pass-thru examination of the gastrointestinal tract.

OMNIPAQUE 300 is indicated in adults for arthrography and hysterosalpingography.

OMNIPAQUE 240 is indicated in adults for arthrography, endoscopic retrograde pancreatography and cholangiopancreatography, herniography, and hysterosalpingography.

OMNIPAQUE diluted to concentrations from 6 mgI/mL to 9 mgI/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in adults for contrast enhanced computed tomography of the abdomen.

Children: OMNIPAQUE 300 is indicated in children for examination of the gastrointestinal tract.

OMNIPAQUE 240 is indicated in children for examination of the gastrointestinal tract.

OMNIPAQUE 180 is indicated in children for examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 50 mgI/mL to 100 mgI/mL is indicated in children for voiding cystourethrography.

OMNIPAQUE diluted to concentrations from 9 mgI/mL to 21 mgI/mL administered orally in conjunction with OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in children for use in contrast enhanced computed tomography of the abdomen.

CONTRAINDICATIONS

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General

See SECTION II, WARNINGS—General.

PRECAUTIONS—General

See SECTION II, PRECAUTIONS—General.

Orally administered hypertonic contrast media draw fluid into the intestines which, if severe enough, could result in hypovolemia. Likewise, in infants and young children, the occurrence of diarrhea may result in hypovolemia. Plasma fluid loss may be sufficient to cause a shock-like state which, if untreated, could be dangerous. This is especially pertinent to the elderly, cachectic patients of any age as well as infants and small children.

ADVERSE REACTIONS: Oral/Body Cavity Use—General

Body Cavities

In controlled clinical trials involving 285 adult patients for various body cavity examinations using OMNIPAQUE 240, 300, and 350, the following adverse reactions were reported.

Cardiovascular System
Incidence > 1%: None
Incidence ≤ 1%: Hypertension

Nervous System
Incidence > 1%: Pain (26%)
Incidence ≤ 1%: Headache, somnolence, fever, muscle weakness, burning, unwell feeling, tremors, lightheadedness, syncope

Respiratory System
None

Gastrointestinal System
Incidence > 1%: None
Incidence ≤ 1%: Flatulence, diarrhea, nausea, vomiting, abdominal pressure

Skin and Appendages
Incidence > 1%: Swelling (22%), heat (7%)
Incidence ≤ 1%: Hematoma at injection site

The most frequent reactions, pain and swelling, were almost exclusively reported after arthrography and were generally related to the procedure rather than the contrast medium. Gastrointestinal reactions were almost exclusively reported after oral pass-thru examinations. For additional information on adverse reactions that may be expected with specific procedures, see INDIVIDUAL INDICATIONS AND USAGE. For information on general adverse reactions to contrast media, see SECTION II, ADVERSE REACTIONS: Intravascular—General.

No adverse reactions associated with the use of OMNIPAQUE for VCU procedures were reported in 51 pediatric patients studied.

Oral Use

See INDIVIDUAL INDICATIONS AND USAGE: Oral Use—Adverse Reactions.

OVERDOSAGE

See also SECTION II, OVERDOSAGE.

The recommended dose of OMNIPAQUE 350 at a concentration of 350 mgI/mL for adult oral pass-thru examination of the gastrointestinal tract is 50 mL to 100 mL. In a Phase I study, 150 mL of OMNIPAQUE 350 was administered orally to 11 healthy male subjects. The incidence of diarrhea was 91% (10 of 11) and abdominal cramping was 27% (3 of 11). Despite all of these events being mild and transient the occurrences were more than double that seen at the recommended doses. It is apparent from this finding that larger volumes of hypertonic contrast media, like OMNIPAQUE, increase the osmotic load in the bowel, which may result in greater fluid shifts.

DOSAGE AND ADMINISTRATION—General

See SECTION II, DOSAGE AND ADMINISTRATION—General.

INDIVIDUAL INDICATIONS AND USAGE

Oral Use

Adults: OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in adults for use in oral pass-thru examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 6 mgI/mL to 9 mgI/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in adults for use in contrast enhanced computed tomography of the abdomen. Dilute oral plus intravenous OMNIPAQUE may be useful when unenhanced imaging does not provide sufficient delineation between normal loops of the bowel and adjacent organs or areas of suspected pathology.

Children: OMNIPAQUE 300 at a concentration of 300 mgI/mL administered orally or rectally is indicated in children for use in examination of the gastrointestinal tract.

OMNIPAQUE 240 at a concentration of 240 mgI/mL administered orally or rectally is indicated in children for use in examination of the gastrointestinal tract.

OMNIPAQUE 180 at a concentration of 180 mgI/mL administered orally or rectally is indicated in children for use in examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 9 mgI/mL to 21 mgI/mL administered orally in conjunction with OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in children for use in contrast enhanced computed tomography of the abdomen.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Oral administration of OMNIPAQUE is most often associated with mild, transient diarrhea especially when high concentrations and large volumes are administered. Nausea, vomiting, and moderate diarrhea have also been reported following orally administered OMNIPAQUE, but much less frequently. For CT examinations using dilute oral plus intravenous contrast medium, adverse events are more likely to be associated with the intravenous injection than the hypotonic oral solution. It should be noted that serious or anaphylactoid reactions that may occur with intravascular iodinated media are possible following administration by other routes.

Adults: In controlled clinical trials involving 54 adult patients for oral pass-thru examination of the gastrointestinal tract using OMNIPAQUE 350, the following adverse reactions were reported: diarrhea (42%), nausea (15%), vomiting (11%), abdominal pain (7%), flatulence (2%), and headache (2%).

In controlled clinical studies involving 44 adult patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (2%).

Children: In controlled clinical studies involving 58 pediatric patients for examination of the gastrointestinal tract at concentrations of 180 and 300 mgI/mL, the following adverse reactions were reported: diarrhea (36%), vomiting (9%), nausea (5%), fever (5%), hypotension (2%), abdominal pain (2%), and urticaria (2%). In clinical studies an increased frequency and severity of diarrhea was noted with an increase in the administered concentration and dose of the radiocontrast agent.

In controlled clinical studies involving 69 pediatric patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 240 and OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (1.4%).

Dosage and Administration

Adults: The recommended dosage of undiluted OMNIPAQUE 350 at a concentration of 350 mgI/mL for oral pass-thru examination of the gastrointestinal tract in adults is 50 mL to 100 mL depending on the nature of the examination and the size of the patient.

The recommended oral dosage of OMNIPAQUE diluted to concentrations of 6 mgI/mL to 9 mgI/mL for contrast enhanced computed tomography of the abdomen in adults is 500 mL to 1000 mL. Smaller administered volumes are needed as the concentration of the final solution is increased (see Table below). In conjunction with dilute oral administration, the recommended dosage of OMNIPAQUE 300 administered intravenously is 100 mL to 150 mL. The oral dose is administered about 20 to 40 minutes prior to the intravenous dose and image acquisition.

Children: The dosage of undiluted OMNIPAQUE 300 at a concentration of 300 mgI/mL, OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 180 at a concentration of 180 mgI/mL for oral pass-thru examination of the gastrointestinal tract in children is dependent on the nature of the examination and the size of the patient. Based on clinical experience, it is recommended that OMNIPAQUE 180 be used in children less than 3 months of age. OMNIPAQUE 180, OMNIPAQUE 240 or OMNIPAQUE 300 may be used in children 3 months of age and older. The following dosage guidelines are recommended:

Age	Volume of OMNIPAQUE
Less than 3 months	5 — 30 mL
Three months to 3 years	Up to 60 mL
Four years to 10 years	Up to 80 mL
Greater than 10 years	Up to 100 mL

When given rectally, larger volumes may be used.

The recommended oral dosage of OMNIPAQUE diluted to concentrations of 9 mgI/mL to 21 mgI/mL for contrast enhanced computed tomography of the abdomen in children is 180 mL to 750 mL. Smaller administered volumes are needed as the concentration of the final solution is increased (see Table below). The total oral dose in grams of iodine should generally not exceed 5 gI for children under 3 years of age and 10 gI for children from 3 to 18 years of age. The oral dosage may be given all at once or over a period of 30 to 45 minutes if there is difficulty in consuming the required volume.

In conjunction with dilute oral administration the recommended dosage of OMNIPAQUE 240 and OMNIPAQUE 300 is 2.0 mL/kg when administered intravenously with a range of 1.0 mL/kg to 2.0 mL/kg. Dosage for infants and children should be administered in proportion to age and body weight. The total intravenously administered dose should not exceed 3 mL/kg. The oral dose is administered about 30 to 60 minutes prior to the intravenous dose and image acquisition.

OMNIPAQUE may be diluted with water or beverage as follows:

To Achieve One Liter of Contrast Medium at A Final Concentration (mgI/mL) of	Add Stock Concentration of OMNIPAQUE (mgI/mL)	Volume (mL)	To Water, Carbonated Beverage, Milk, or Juice (mL)
6	240	25	975
	300	20	980
	350	17	983
9	240	38	962
	300	30	970
	350	26	974
12	240	50	950
	300	40	960
	350	35	965
15	240	63	937
	300	50	950
	350	43	957
18	240	75	925
	300	60	940
	350	52	948
21	240	88	912
	300	70	930
	350	60	940

Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

VOIDING CYSTOURETHROGRAPHY (VCU)

OMNIPAQUE diluted to concentrations from 50 mgI/mL to 100 mgI/mL is indicated in children for voiding cystourethrography. VCUs are often performed in conjunction with excretory urography.

Precautions

See PRECAUTIONS—General.

Since the VCU procedure requires instrumentation, special precautions should be observed in those patients known to have an acute urinary tract infection. Filling of the bladder should be done at a steady rate, exercising caution to avoid excessive pressure. Sterile procedures are essential.

Adverse Reactions

See ADVERSE REACTIONS—General.

Dosage and Administration

OMNIPAQUE may be diluted, utilizing aseptic technique, with Sterile Water for Injection to a concentration of 50 mgI/mL to 100 mgI/mL for voiding cystourethrography. The concentration may vary depending upon the patient's size and age and also with the technique and equipment used. Sufficient volume of contrast medium should be administered to adequately fill the bladder. The usual volume ranges from 50 mL to 300 mL of OMNIPAQUE at a concentration of 100 mgI/mL and 50 mL to 600 mL of OMNIPAQUE at a concentration of 50 mgI/mL.

OMNIPAQUE may be diluted with Sterile Water for Injection as indicated in the table below:

To Achieve A Final Concentration	Add To Each 100 mL of OMNIPAQUE Sterile Water for Injection, USP (mL)		
(mgI/mL)	OMNIPAQUE 240	OMNIPAQUE 300	OMNIPAQUE 350
100	140	200	250
90	167	233	289
80	200	275	338
70	243	330	400
60	300	400	483
50	380	500	600

Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

ARTHROGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL or OMNIPAQUE 350 at a concentration of 350 mgI/mL is indicated in radiography of the knee joint in adults, and OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in radiography of the shoulder joint in adults, and OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in radiography of the temporomandibular joint in adults. Arthrography may be helpful in the diagnosis of posttraumatic or degenerative joint diseases, synovial rupture, the visualization of communicating bursae or cysts, and in meniscography.

Precautions

See PRECAUTIONS—General.

Strict aseptic technique is required to prevent infection. Fluoroscopic control should be used to ensure proper needle placement, prevent extracapsular injection, and prevent dilution of contrast medium. Undue pressure should not be exerted during injection.

Adverse Reactions

Injection of OMNIPAQUE into the joint is associated with transient discomfort, ie, pain, swelling. However, delayed, severe or persistent discomfort may occur occasionally. Severe pain may often result from undue use of pressure or the injection of large volumes. Joint swelling after injection is less with OMNIPAQUE than with high osmolar ionic contrast medium. These types of reactions are generally procedurally dependent and of greater frequency when double-contrast technique is employed.

Nervous system: Swelling sensation (42%), pain (29%), heat sensation (13%), and muscle weakness (0.7%).

Skin and appendages: Hematoma at injection site (0.7%).

Dosage and Administration

Arthrography is usually performed under local anesthesia. The amount of OMNIPAQUE injected is dependent on the size of the joint to be examined and the technique employed. Lower volumes of contrast medium are usually injected for knee and shoulder arthrography when double-contrast examinations using 15 mL to 100 mL of air are performed.

The following concentrations and volumes are recommended for normal adult knee, shoulder, and temporomandibular joints but should serve as guidelines since joints may require more or less contrast medium for optimal visualization.

KNEE

OMNIPAQUE 240 5 mL to 15 mL
OMNIPAQUE 300 5 mL to 15 mL
OMNIPAQUE 350 5 mL to 10 mL

SHOULDER

OMNIPAQUE 300 10 mL
OMNIPAQUE 240 3 mL

TEMPOROMANDIBULAR

OMNIPAQUE 300 0.5 mL to 1.0 mL

} Lower volumes recommended for double-contrast examinations; higher volumes recommended for single-contrast examinations.

Passive or active manipulation is used to disperse the medium throughout the joint space.

ENDOSCOPIC RETROGRADE PANCREATOGRAPHY (ERP)/ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)

OMNIPAQUE 240 at a concentration of 240 mgI/mL is indicated in adults for use in ERP/ERCP.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Injection of OMNIPAQUE in ERP/ERCP is associated with transient pain. However, delayed, severe or persistent pain may occur and can persist for 24 hours. The cause of the pain may be due as much to the contrast medium injected, therefore, attention should be paid to the injection pressure and total volume injected to minimize disruptive distention of the ducts examined.

Cardiovascular system: Hypertension (1%).

Nervous system: Pain (17%), somnolence (1%), and burning (1%).

Gastrointestinal system: Vomiting, diarrhea, and pressure, each with an individual incidence of 1%.

Dosage and Administration

The recommended dose of OMNIPAQUE 240 at a concentration of 240 mgI/mL is 10 mL to 50 mL but may vary depending on individual anatomy and/or disease state.

HYSTEROSALPINGOGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL is indicated in radiography of the internal group of adult female reproductive organs: ovaries, fallopian tubes, uterus, and vagina. Hysterosalpingography is utilized as a diagnostic and therapeutic modality in the treatment of infertility and other abnormal gynecological conditions.

Contraindications

The procedure should not be performed during the menstrual period or when menstrual flow is imminent, nor should it be performed when infection is present in any portion of the genital tract, including the external genitalia. The procedure is also contraindicated for pregnant women or for those in whom pregnancy is suspected. Its use is not advised for 6 months after termination of pregnancy or 30 days after conization or curettage.

Precautions

In patients with carcinoma or in those in whom the condition is suspected, caution should be exercised to avoid possible spreading of the lesion by the procedure.

Adverse Reactions

Injection of OMNIPAQUE in hysterosalpingography is associated with immediate but transient pain. The cause of the pain may be due as much to the procedure itself as to the contrast medium injected, therefore attention should be paid to the injection pressure and volume instilled to avoid disruptive distention of the uterus and fallopian tubes. Fluoroscopic monitoring is recommended.

Nervous system: Pain (49%), somnolence and fever each with an individual incidence of 3%.

Gastrointestinal system: Nausea (3%).

Dosage and Administration

The recommended dosage of OMNIPAQUE 240 is 15 mL to 20 mL and of OMNIPAQUE 300 is 15 mL to 20 mL but will vary depending on individual anatomy and/or disease state.

HERNIOGRAPHY

OMNIPAQUE 240 at a concentration of 240 mgI/mL is indicated in adults for use in herniography.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Nervous system: Pain (7%), headache (3%), and unwell feeling (3%).

Gastrointestinal system: Diarrhea (3%) and flatulence (10%).

Dosage and Administration

The recommended dosage of OMNIPAQUE 240 is 50 mL but may vary depending on individual anatomy and/or disease state.

HOW SUPPLIED

OMNIPAQUE 140
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1401-52)

OMNIPAQUE 180
- 10 mL glass vial, 180 mgI/mL, boxes of 10 (NDC 0407-1411-10)
- 20 mL glass vial, 180 mgI/mL, boxes of 10 (NDC 0407-1411-20)

OMNIPAQUE 240
- 10 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-10)
- 20 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-20)
- 50 mL glass vial, 240 mgI/mL, boxes of 10 (NDC 0407-1412-50)
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-30)
- 100 mL glass bottle, 240 mgI/mL, boxes of 10 (NDC 0407-1412-60)
- 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-33)
- 150 mL glass bottle, 240 mgI/mL, boxes of 10 (NDC 0407-1412-49)
- 150 mL fill in 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-34)
- 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-35)

OMNIPAQUE 300
- 10 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-10)
- 30 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-30)
- 30 mL fill in 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-59)
- 50 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-50)
- 50 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-51)
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-61)
- 75 mL fill in 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-62)
- 100 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-60)
- 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-63)
- 125 mL fill in 150 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-53)
- 150 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-90)
- 150 mL fill in 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-65)
- 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-66)

OMNIPAQUE 350
- 50 mL glass vial, 350 mgI/mL, boxes of 10 (NDC 0407-1414-50)
- 50 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-51)
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-89)
- 75 mL fill in 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-90)
- 100 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-60)
- 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-91)
- 125 mL fill in 150 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-76)
- 150 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-03)
- 150 mL fill in 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-93)
- 200 mL fill in 250 mL bottle with hanger, 350 mgI/mL, boxes of 10 (NDC 0407-1414-04)
- 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-94)
- 250 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-80)

FEDERAL GOVERNMENT CODES

OMNIPAQUE 240
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-29)
- 150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-27)
- 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1412-28)

OMNIPAQUE 300
- 10 mL glass vial, 300 mgI/mL, boxes of 10 (NDC 0407-1413-11)
- 50 mL glass bottle, 300 mgI/mL, boxes of 10 (NDC 0407-1413-95)
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-98)
- 75 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-99)
- 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-91)
- 150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-92)
- 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1413-93)

OMNIPAQUE 350
- 50 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-52)
- 100 mL glass bottle, 350 mgI/mL, boxes of 10 (NDC 0407-1414-53)
- 50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-21)
- 75 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-20)
- 100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-22)
- 150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-23)
- 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-1414-24)

Protect vials and glass or polymer bottles of OMNIPAQUE from strong daylight and direct exposure to sunlight. Do not freeze. OMNIPAQUE should be stored at controlled room temperature, 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

OMNIPAQUE injection in all presentations may be stored in a contrast media warmer for up to one month at 37°C (98.6°F).

SPECIAL HANDLING AND STORAGE FOR POLYMER BOTTLES ONLY:

DO NOT USE IF TAMPER-EVIDENT RING IS BROKEN OR MISSING.

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Investigator Signature Page

Protocol Title: A Pilot Safety and Pharmacokinetic Study of MB-102 versus Iohexol and the Use of the Non-invasive Optical Renal Function Monitor (ORFM) device, in Subjects with Normal and Impaired Renal Function and a Range of Skin Color Types

Protocol Number: ORFM Pilot 2

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and other documents that may be considered part of the investigational plan, and I will conduct the study as described in compliance with this protocol, GCP, the ethical principles defined by the World Medical Association Declaration of Helsinki (2008) and relevant ICH guidelines.

Once the protocol has been approved by the IEC, I will not modify this protocol without obtaining prior approval of the MediBeacon Inc. and of the IEC. I will submit the protocol modifications and/or any ICF modifications to MediBeacon Inc. and IEC, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

I will oversee all aspects of study conduct and will only appropriately delegate responsibilities to adequately qualified and trained staff. I will oversee the completion of source data collection such that all data collected for the study may be substantiated against accurate source medical records.

Information developed in this clinical study may be disclosed by MediBeacon Inc. to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date