SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Transdermal GFR System

Device Trade Name: MediBeacon® Transdermal GFR System (TGFR)

Device Procode: SDK

Applicant's Name and Address: MediBeacon Inc.
425 N New Ballas Road
Suite 100
St. Louis, MO 63141

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P230019

Date of FDA Notice of Approval: January 17, 2025

II. INDICATIONS FOR USE

The MediBeacon® Transdermal GFR System (TGFR) is intended to assess the Glomerular Filtration Rate (GFR) in adult patients with impaired or normal renal function by noninvasively monitoring fluorescent light emission from an exogenous tracer agent over time. This device has been validated in patients with stable renal function.

The MediBeacon® TGFR is not approved for use in patients with GFR <15 ml/min/1.73 m^2, GFR >120 ml/min/1.73m^2, patients on dialysis, or anuric patients. The use of this device in patients with dynamic and rapidly changing renal function has not been validated. This device is not intended to diagnose acute kidney injury (AKI).

The MediBeacon® TGFR Sensor and exogenous tracer agent, Lumitrace® injection, are single use and are only used with the MediBeacon® TGFR.

The MediBeacon® TGFR Sensor is a single use device intended to attach to the patient's skin and excite fluorescence in Lumitrace® injection, the tracer agent, and measure the returning light intensity. The data is sent to the MediBeacon® TGFR Monitor.

Lumitrace® is an injectable exogenous fluorescent tracer indicated for use with the MediBeacon® Transdermal GFR System (TGFR) for Glomerular Filtration Rate assessment.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MediBeacon® Transdermal GFR System labeling.

V. DEVICE DESCRIPTION

The MediBeacon® Transdermal GFR System (TGFR) provides an assessment of GFR at the point of care. Noninvasive transdermal fluorescence detection of the agent clearance rate is converted by the system into GFR indexed by body surface area.

The MediBeacon® Transdermal GFR System is comprised of three distinct parts:

1. Lumitrace® (relmapirazin) injection is the novel and proprietary fluorescent tracer agent, intravenously administered to a patient and then subsequently excreted from the body by the kidneys.

2. The MediBeacon® TGFR Sensor contains the light source and photo detector for noninvasively detecting Lumitrace fluorescence transdermally. This sensor is attached to the upper chest using a biocompatible adhesive. This sensor has a built-in cable that connects to the monitor.

3. The MediBeacon® TGFR Monitor provides power to the sensor, digitizes the data acquired from the sensor, contains the algorithms to convert sensor output to GFR (ml/min/1.73m^2), and reports GFRs to the clinician.

Figure 1: MediBeacon® TGFR System

Table 1: TGFR Components and Functions

System Component	Functions
MediBeacon TGFR Sensor	• Contains light sources (LEDs) of two different wavelengths, two different light detectors, and associated electronics • Contacts subject's skin via medical-grade adhesive (similar to those used for disposable ECG patches) • Generates and delivers light to skin • Measures light emitted by tracer agent as well as autofluorescence of the skin and diffuse reflectance at emission and excitation wavelengths • Receives LED controls from, and transmits sensor data to the monitor as analog signals
MediBeacon TGFR Monitor	• Operates one sensor • Contains software and electronics to control operation of sensor, record measurements, and interact with the operator • Records measured fluorescence data over time • Calculates time constant associated with renal decay (RDTC) over the course of a measurement session

System Component	Functions
	• Displays a digital Average Session GFR value at the completion of the session. • Provides Graphical User Interface (GUI) and workflow instructions for operation
Lumitrace® injection (tracer agent)	• Small volume injectable fluorescent tracer (fluorophore) with characteristics of an ideal renal filtration marker • Eliminated by glomerular filtration in the kidney (not protein bound, does not undergo tubular reabsorption or secretion, is not metabolized, and does not affect kidney function) • Receives excitation light transdermally from the sensor • Emits fluorescent light that is measured by the sensor

The MediBeacon® TGFR provides a non-invasive measure of the change in patient levels of tracer agent over time via the transdermal sensor placed on the patient's skin. The rate of decrease in the emitted fluorescence from Lumitrace® injection is automatically calculated and displayed on the monitor (Figure 1). At the completion of a TGFR session, a validated GFR result is displayed as "Average Session GFR."

A. Active Pharmaceutical Ingredient

The active pharmaceutical ingredient (API) used in the MediBeacon TGFR is the compound relmapirazin. The 3,6-diamino-2,5-bis{N-[(1R)-1-carboxy-2-hydroxyethyl]carbamoyl}pyrazine, is a water-soluble fluorescent tracer agent with a molecular weight of 372.3. In a buffered phosphate solution, the tracer agent is soluble. The chemical structure of relmapirazin is in Figure 2 below. The molecular formula is $C_{12}H_{16}N_6O_8$.

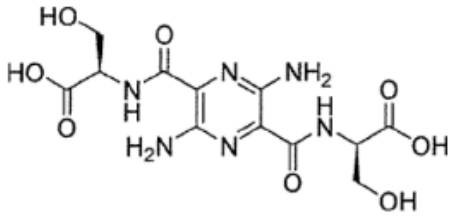

Figure 2: Chemical Structure of Relmapirazin

Lumitrace® is provided as a sterile, pyrogen-free, clear orangish solution in a single concentration. Each milliliter of Lumitrace® injection contains 18.6 mg of relmapirazin with a pH adjusted between 7.0 and 7.6 with hydrochloric acid or sodium hydroxide. All solutions are sterilized by sterile filter and contain no preservatives. Unused portions must be discarded.

Table 2: Lumitrace® Concentration and Osmolality

Concentration (mg/mL)	**Osmolality (mOsm/kg)**
18.6	275-350

Lumitrace® has osmolarities from approximately 0.9 to 1.2 times that of plasma (285 mOsm/kg water) as shown in the above table.

B. Principles of Operation

The transdermal sensor is first attached to a skin surface, upper chest region, and background fluorescence is gathered by the display monitor for approximately twenty minutes. Lumitrace® is then intravenously administered, and the display monitor continues to acquire fluorescence data as a function of time. Data analysis algorithms in the display monitor convert the acquired signal into a normalized GFR value after Lumitrace® injection administration. The GFR is then updated subsequently until the algorithm detects a fluorescence intensity too low for conversion into an accurate GFR. A validated Average Session GFR value is displayed on the monitor.

The transdermal sensor also has components to measure diffusely reflected light, which is used to compensate for local time-varying tissue properties, such as changes in local blood volume. This sensor is intended for a single use on a patient (must be replaced between patients).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternate methodologies and the advantages and disadvantages are outlined in Table 3.

Table 3: Alternate Methodologies

Alternative Diagnostic Method	Description	Advantages/ Benefits	Disadvantages/ Limitations/ Risks
Blood testing for creatinine, and/or blood urea nitrogen	Quantification of endogenous markers such as creatinine, or urea nitrogen in the blood is used to estimate GFR.	Does not require the IV administration of exogenous tracers. Does not require intravenous line placement or prolonged patient immobility.	Relies on estimation equations to determine GFR and can be inaccurate due to variation in laboratory assays and/or physiological factors (e.g., muscle mass, diabetes, age, etc.).
Cystatin C	Blood measurement	Is not muscle mass or race dependent. Does not require the IV administration of exogenous tracers. Does not require intravenous line placement or prolonged patient immobility.	Not a measured GFR value Clinical availability

Alternative Diagnostic Method	Description	Advantages/ Benefits	Disadvantages/ Limitations/ Risks
Urine test for albumin- to-creatinine ratio	A single sample of urine is collected to measure both albumin and creatinine to calculate an albumin-to-creatinine ratio. This is done to provide an accurate indication of how much albumin is being released into the urine, an indication of early kidney disease.	Utilizes a relatively simple technique to assess kidney function.	Timed urine samples provide accurate assessments of kidney function but can delay diagnosis and interventions. Elevated albumin levels can result from factors other than altered kidney function, such as vigorous exercise, blood in the urine, urinary tract infection, dehydration, and some drugs.
Radioactive 125-I iothalamate (Glofil) is an exogenous radioactive agent for real-time measurement of GFR when administered to the patient intravenously	Plasma clearance of this radioactive material measured via timed blood samples through an IV catheter or urine samples is used to measure kidney function.	Provides an accurate measure of kidney function.	Use of this substance should be avoided in patients with potential allergies to iodinated contrast media or iodine and iodide containing products.
Blood testing for clearance of iohexol (Omnipaque) following injection	Following IV administration, plasma and urine concentrations of this nonionic low-osmolar contrast medium can be used for establishing GFR.	Provides an inexpensive non-radioactive marker that can act as a renal clearance agent that is simple and practical to measure in the clinic. Requires only a single IV injection of the marker (5ml in 2 min) with minimal sampling over subsequent 4-8 hours depending on renal function.	Use of this substance should be avoided in patients with potential allergies to iodinated contrast media or iodine and iodide containing products.

Alternative Diagnostic Method	Description	Advantages/ Benefits	Disadvantages/ Limitations/ Risks
Blood testing for radioisotope activity following administration of radioactive chromium-51 ethylenediamine tetraacetic acid (Cr-EDTA)	Following IV administration, plasma concentrations or renal clearance of this radioisotope can be used for establishing GFR.	Provides high accuracy measurement of GFR, even for patients with GFR≤ 15 ml/min	Requires administration of a radiolabeled substance and repeated blood samples.
Renal imaging following administration of radioactive Tc-99m diethylene triamine pentaacetate (99mTc-DTPA)	Following IV administration, renal imaging can be used to assess relative function (GFR), blood flow, and possible obstruction to the kidneys.	Renal clearance of Tc-DTPA correlates well with inulin clearance.	Requires administration of radiolabeled substance along with access to imaging facilities and trained radioimaging personnel. This technique can be time consuming and cost prohibitive.

Each alternative has its own advantages and disadvantages. Patients should thoroughly discuss the alternatives with their physician to choose the method that best suits individual expectations and lifestyles.

VII. MARKETING HISTORY

The MediBeacon® Transdermal GFR system (TGFR) has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Table 4: Potential Adverse Effects associated with the MediBeacon® TGFR

Clinical Trials Experience Adverse Event Type	Events (N) Pilot 2 114 Subjects	Events (N) Pivotal Study 249 Subjects	Subjects n (%) 363 Subjects
Injection site extravasation	6	3	9 (2%)
Headache	1	4	5(1%)
Ecchymosis	0	3	3 (1%)

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

The following nonclinical testing was conducted on the MediBeacon® TGFR:

A. Laboratory Studies
1. Device Biocompatibility
2. Device Bench Testing
3. Tracer Agent Nonclinical Testing
4. Tracer Agent Analytical Testing
5. Sterilization Validation

B. Animal Testing

C. Additional Studies
1. Stability and Shelf-Life Testing
2. Clinical Laboratory Interference Testing

A. Laboratory Studies

Pre-clinical testing was conducted to demonstrate the MediBeacon® TGFR performs as intended and meets its product requirements. The verification and validation tests included compliance with international standards and/or guidance documents where available. The MediBeacon® TGFR has various levels of specifications and technological considerations.

Therefore, a combination of full system testing, subsystem and component level testing was performed to demonstrate that the device meets its requirements and is safe for use.

Table 5: Device Biocompatibility

Test	Purpose	Acceptance Criteria	Results
Biocompatibility, Cytotoxicity, ISO 10993-5	Biocompatibility of TGFR Sensor	Non-cytotoxic Complies with ANSI/AAMI ISO 10993- 5. Biological evaluation of medical devices-Part 5: Tests for In vitro cytotoxicity.	Pass

Biocompatibility, Skin Irritation, ISO 10993-10	Biocompatibility of TGFR Sensor	Non-irritant Complies with ANSI/AAMI ISO 10993- 10. Biological evaluation of medical devices-Part 10: Tests for Irritation and skin sensitization.	Pass

Test	Purpose	Acceptance Criteria	Results
Biocompatibility, Maximization Sensitization, ISO 10993-10	Biocompatibility of TGFR Sensor	Non-sensitizer Complies with ANSI/AAMI ISO 10993-10. Biological evaluation of medical devices: Part 10: Tests for Irritation and skin sensitization.	Pass

Table 6: Device Bench Testing

Test	Purpose	Acceptance Criteria	Results
Risk management	Risk management associated with the Entire system	Complies with ISO 14971: 2019 Medical devices - Application of risk management to medical devices	Process Implemented
System Verification	System and components - TGFR Monitor - TGFR Sensor - Software	Verification of inputs/output design requirements	Pass
Reprocessing (cleaning and disinfection procedure) per FDA guidance document: Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling issued on March 2015	Reprocessing of TGFR Monitor; note that the sensor is single use.	The reprocessing procedures are validated according to the guidance document.	Pass
Optical Safety	Safety of Optical Components	Complies with IEC 62471:2006 Photobiological Safety of Lamps and Lamp Systems	Pass
Thermal Safety	Thermal Safety	Complies with ANSI/AAMI ES60601-1:2005/AMD1:2012 Medical electrical equipment	Pass

Test	Purpose	Acceptance Criteria	Results
		Part 1- Part 1: General Requirements for Basic Safety and Essential Performance (IEC 60601-1:2005, MOD) (Consolidated Text) (Includes ANSI/AAMI ES60601-1:2005/(R)2012 And A1:2012, C1:2009/(R)2012 And A2:2010/(R)2012)	
Reliability/Functionality/ Medical electrical equipment safety Testing	Electrical safety of Entire system	Complies with ANSI/AAMI ES60601-1:2005/AMD1:2012 Medical electrical equipment - Part 1- Part 1: General Requirements for Basic Safety and Essential Performance (IEC 60601-1:2005, MOD) (Consolidated Text) (Includes ANSI/AAMI ES60601-1:2005/(R)2012 And A1:2012, C1:2009/(R)2012 And A2:2010/(R)2012)	Pass
Electromagnetic compatibility (EMC) Testing	EMC testing of Entire system	Complies with IEC 60601-1-2 Edition 4.0 2014-02 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests	Pass
Functional Testing	System and components	Flow cell testing (MediBeacon test fixture) demonstrates performance	Pass
Software verification and validation, per IEC 62304: 2015: FDA Guidance document: Content of Premarket Submissions for Software Contained in Medical Devices, issued in May 2005	Testing TGFR System software	Verification tests, unit testing, system level testing and defect tracking and dispositioning met all specifications.	Pass

Test	Purpose	Acceptance Criteria	Results
Cybersecurity per FDA Guidance document: Content of Premarket Submissions for Management of Cybersecurity Medical Devices issued on October 2018	Testing TGFR software	Vulnerabilities and threats were evaluated, security assessment completed and identified mitigations were verified.	Pass
Packaging	TGFR Monitor and TGFR Sensor (Device is not sterile)	ASTM D4169 Distribution cycle 13, Assurance Level 1	Pass
Usability Testing/ Human Factors	Testing usability of entire system	Formative studies completed. Summative usability testing will be completed with clinicians. Testing will be performed according to human factors engineering standards: AAMI/ANSI HE75:2009/(R) 2018 Human factors engineering – Design of medical devices ANSI/AAMI/IEC 62366-1: 2015 Medical Devices-Part 1: Application of usability engineering to medical devices	Pass

Nonclinical Testing (tracer agent):

A total of 25 nonclinical studies (Table 6) have been completed on Lumitrace® (relmapirazin) injection. These include both *in vitro* and *in vivo* studies. The nonclinical study data available support that the chemistry of the tracer agent, and the manufacturing of the tracer agent, does not present risk to human subjects. The nonclinical assessment of Lumitrace® is based on the FDA's Guidance for Industry: *Developing Medical Imaging Drug and Biological Products. Part 1: Conducting Safety Assessments*.

Lumitrace® injection has been shown to have the following characteristics:

- Produces fluorescence *in vivo* when excited by blue light, which can be reliably detected by transdermal measurement when Lumitrace® 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 the therapeutic dose range and in dose escalating toxicity models.
- Has been shown to perform as a GFR tracer agent in preclinical animal models.

Lumitrace® injection has been assessed in single dose and 14-day repeat dose toxicity studies using the IV (rats and dogs) and oral (rats) routes of administration, a battery of genotoxicity studies, and other studies, including phototoxicity and local toxicity.

Table 7: Tracer Agent Nonclinical Studies

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

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
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	No toxicologic effects on cardiac rhythm or ECG morphology
Pharmacology	In vitro Interaction Studies of MB- 102 with Human MATE1, MATE2-K, OAT1, OAT3, and OCT2 Uptake Transporters, [Study ID MBPMA003]	24-Aug-2022	N/A	N/A	Relmapirazin is not a substrate of MATE1, MATE2-K, OAT1, and OCT2 transporters under the investigated conditions relamapirazin is classified as a substrate of the OAT3 (SLC) transporter under the investigated conditions

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
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	[a]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	[a]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	18Aug09	10mM and lower	NA	Negative

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
	[Study No. 8202290]				
Toxicology	Intravenous and Perivenous Local Tolerance Study with MB- 102 in New Zealand White Rabbits [Study Number 8330229]	21Jan16	18.6 mg/mL	3 IV (1 mL) 3 PV (.25 mL)	Relmapirazin was well tolerated in male rabbits IV or PV 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 relmapirazin related bone marrow toxicity
Toxicology	Neutral Red Uptake Phototoxicity Assay of MB-102 in BALB/c3T3 Mouse Fibroblasts [StudyNumber 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 cytotoxicity or phototoxicity potential for MB-102 was noted.

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
Toxicology	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 no

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					morphological changes that were considered 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.

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
Toxicology – Developmental and Reproductive Toxicology	Intravenous (bolus) Injection Dose Range-Finding Embryo-Fetal Developmental and Toxicokinetic Study with MB- 102 in Pregnant Rabbits [Study No. 8401985]	21Jun19	0, 4.5, 45.0, 113.0 mg/kg/day, GD7 - 19	6 per dose group	Relmapirazin related dose-responsive clinical observations were noted in animals receiving 45.0 and 113.0 mg/kg/day and included yellow discolored eyes, ears, urine and skin but were considered non- adverse. No test article related effects were noted on animal health or fetal health.
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 relmapirazin was not associated with any test article related effects on mortality, food consumption, body weight, cesarean section parameters, macroscopic observations,

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					or developmental toxicity. Based on these data, the NOAEL for maternal and fetal toxicity was 113 mg/kg/day (GD 7 Cmax and AUC_{0-6} values of 1780 µM and 2050 h*µM, respectively; GD 19 Cmax and AUC_{0-6} values of 1860 µM and 1930 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 relmapirazin was not associated with any test article-related effects on mortality, mean food consumption

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
					or body weight values, cesarean section parameters, macroscopic observations, or developmental toxicity, including the teratogenic potential. Based on these data, the NOAEL or maternal and fetal toxicity was 225 mg/kg/day (GD 6 Cmax and AUC_{0-6} values of 1460 µM and 1350 h*µM, respectively; GD 17 Cmax and AUC_{0-6} values of 1590 µM and 1640 h*µM, respectively).

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
Pharmacokinetics	Pharmacokinetic Interaction of MB-102 and Iohexol administered as Crossover Intravenous Injections in Non-naïve Male Beagle Dogs [Study Number SW15-2375]	8Jan16	[b]Iohexol: 647 mg/kg MB-102: 3.2 mg/kg Combined: 647 iohexol and 3.2 MB-102 mg/kg	3 per group	Co-administration of relmapirazin and iohexol did not alter the pharmaco-kinetic (PK) parameters measured for either agent
Pharmacokinetics	*InVitro* 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	Relmapirazin 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	Relmapirazin minimally distributes to blood cells with a mean blood to plasma ratio of 0.590 ± 0.003.

Study Type	Study Title and Number	Date of Final Report	Doses or Concentrations	Number per Group	Results
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 relmapirazin is injected in vivo, the agent distributes quickly throughout the test subject, then rapidly clears from the body and does preferentially localize in any tissue or organ with the exception of the bladder which is consistent with a know GFR agent.
Pharmacokinetics	ADME-TOX Drug Transporter Study, [Study No.100044128]	05Nov18	NA	NA	No significant activity in any of the drug transporter assays

Abbreviations: ADME, absorption, distribution, metabolism, excretion; AUC, area under curve; Cmax, maximum (peak) concentration; CNS, central nervous system; CYP-450, cytochromes P450; ECG, electrocardiogram; F, female; GD, gestational days; hERG, human Ether-a-go-go-related gene; IC_{50}, inhibitory concentration 50, M, male; MATE1, multidrug and toxin extrusion protein 1; MATE2-K, multidrug and toxin extrusion protein 2; MB-102, internal code name for relmapirazin (same as MP-3180); MP-3180, internal code name for relmapirazin (same as MB-102); NOAEL, no observed adverse effect level; NOEL,

no observable effect level, OAT1, organic anion transporter 1; OAT2 organic anion transporter 2; OCT2, organic cation transporter 2; SLC solute carrier; TK, toxicokinetic; Tox, toxicology; UVR ultraviolet radiation.

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

Table 8: Analytical Tracer Agent Testing

Test	Testing Summary/Objective	Acceptance Criteria	Result
Identification	Test the drug substance for identity to ensure conformity to specification	Identification confirmed via two different tests	Pass
Appearance, color and clarity	Conforms to specifications	Clear, reddish orange solution	Pass
Assay (potency)	Total relmapirazin content is quantified to ensure contains the labeled dosage	90-110% of labeled claim	Pass
Impurities and degradants	The type and amount of degradants and impurities are quantified to ensure they remain within acceptable levels	ICH Q3B	Pass
pH	Compatible	Meets specification	Pass
Osmolality	Compatible	Meets specification	Pass
Particles (visible and subvisible)	Complies with USP requirements for patient safety	USP <790> USP<788>	Pass
Sterility and Endotoxin	Complies with USP requirements for patient safety	USP <71> USP <85>	Pass

Sterility: Lumitrace® injection, the tracer agent, is aseptically filled using sterilizing filters and is compliant with USP<71> for sterility and USP <85> for endotoxins.

B. Animal Studies

In vivo studies with Relmapirazin were performed in the Sprague-Dawley rat model. On the basis of the fluorescence properties, plasma protein binding, recovery in the urine, and the renal

tubular secretion Relmapirazin was determined to be an acceptable agent to determine GFR. Additionally, probenecid inhibition studies were performed demonstrating that clearance is the same with and without probenecid.

C. Additional Studies

1. Stability and Shelf-Life Studies

Finished product shelf life was established utilizing American Society for Testing and Materials (ASTM) D3330 test methods for the adhesive on the device and per the International Council for Harmonisation (ICH) guidelines for drug products. The data supports the following expiration dates.

- The MediBeacon® TGFR sensor has a two-year shelf life and the TGFR monitor has a five-year service life.
- Lumitrace® injection has a 12-month expiry date when stored at 2-8° C.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of assessment of glomerular filtration rate (GFR) with the MediBeacon® Transdermal GFR System (TGFR) in the US under IDE # G130129. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Study Design

Patients were treated between June 14, 2022, and February 15, 2023. The database for this P230019 PMA reflected data collected through May 22, 2023, and included 505 patients. There were 8 investigational sites (5 US sites and 3 sites in China).

The MediBeacon® TGFR pivotal study was a multi-center, open-label study comparing transdermal glomerular filtration rate (tGFR) to plasma-derived indexed GFR (nGFR) with Lumitrace® (relmapirazin) injection as the fluorophore. Participants spanned the GFR range of values from normal to stage 4 chronic kidney disease (CKD) and spanned the entire range of human skin colors as defined by the Fitzpatrick Skin Scale (FSS). The safety and pharmacokinetics of Lumitrace® and the safety of the MediBeacon® TGFR were also evaluated.

During the study, MediBeacon® convened an internal team to evaluate the performance of the TGFR and to ensure site compliance with all study procedures relating to device usage. This monitoring also allowed MediBeacon to evaluate subject exclusions in accordance

with the Statistical Analysis Plan (SAP) and determine if enrollment should continue based on evaluability of study subjects.

Levels of Lumitrace® in the patient's blood plasma (plasma derived indexed GFR, nGFR) were measured in the control group. A prior pilot study compared relmapirazin pharmacokinetics and excretion to the standard iohexol and established relmapirazin as a renal tracer agent.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the TGFR pivotal study was limited to patients who met the following inclusion criteria:

   - Eligible female non-pregnant participants 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.
   - For women of child-bearing potential, the participant should have a negative serum pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly; i.e. abstinence, oral contraceptive either combined or progesterone alone; injectable progesterone; implants of levonorgestrel; estrogenic vaginal ring; percutaneous contraceptive patches; intrauterine device (IUD) or system or male partner sterilization.
   - Men will not donate sperm during the study and for 1 month following the last dose of study drug.
   - Participants who are capable of directly providing informed, consent and who can comply with the requirements and restrictions required by the protocol.
   - Adequate venous access sufficient to allow blood sampling per protocol requirements.

   Patients were not permitted to enroll in the TGFR Pivotal study if they met any of the following exclusion criteria:

   - Participants positive via polymerase chain reaction (PCR) testing for COVID-19 (Vaccinated participants without symptoms of COVID-19 are not required to undergo PCR testing but may be tested at the discretion of the study site).
   - 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.
   - Non-steroidal anti-inflammatory (NSAID) use within 3 days of Lumitrace® injection dosing.
   - Participant has participated in a clinical trial and has received an investigational product within the following time ranges: prior to the first

dosing day in the current study: either 30 days or 5 half-lives of the investigational product (whichever duration is longer).
- 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, Lumitrace® injection or other related products (intolerance to a drug is not considered a drug allergy).
- Any characteristics which, in the opinion of the investigator, makes the participant a poor candidate for participation in the clinical trial.
- Significant scaring, tattoos or alterations in pigmentation on the sternum. or other sensor location testing areas that would alter sensor readings versus other areas of the skin.
- Any 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 participant's ability to complete study requirements or may put the participant at increased risk or compromise the interpretability of study results.
- Currently receiving dialysis.
- Currently anuric.
- Positive serum pregnancy test.
- Participants with an eGFR > 120 mL/min/1.73m^2.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 7 ± 3 days of dosing.

Clinical assessments during follow-up included:

- Physical Assessment (at a minimum: Assessment of head, ears, eyes, nose, throat, (HEENT) respiratory, cardiovascular, abdominal systems).
- Vital signs including blood pressure, respiration rate, heart rate and temperature.
- Concomitant medications administered through follow-up.
- Adverse events.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 9: Study Schedule of Events

Period	Pre-Screen (optional)	Screening	Dosing Day	Dosing Day	Dosing Day	Dosing Day	Follow-up Visit
		21 days to day - 2 prior to Dosing	*Pre-dose*	*Dosing (time 0)*	*During 12 – 24 hours post IP injectio*	*Completion of 12 hours or up to 24 hours post IP*	*7 days±3 days*

Period	Pre-Screen (optional)	Screening	Dosing Day	Dosing Day	Dosing Day	Dosing Day	Follow-up Visit
					n	*injection*	
Informed Consent[a]	X	X					
Inclusion / Exclusion		X	X				
Demographics		X					
Medical History		X	X				
Pregnancy Test for WOCBP[b]		X	X				
PE or Limited PA[c]		X	X				X
Vital Signs[d]		X	X		X	X	X
Height and Weight[e]		X	X				
Clinical Labs[f]		X	X			X	X
Mexameter® measurements			X				
Transdermal Data Collection[g]			X	X	X	X	
Drink water[h]			X	X			
Administration of MB-102[i]				X			
PK blood collection[j]			X		X	X	
ECG[k]		X	X			X	
Concomitant Therapies[l]		X	X		X	X	X
Adverse Events[m]			X	X	X	X	X
Document Fitzpatrick Skin Color Type[n]	X	X					

Abbreviations: ECG, electrocardiogram; GFR, glomerular filtration rate; HEENT, head, eyes, ears, nose, and throat; IP, investigational product; IV, intravenous; PA, physical assessment; PE, physical examination; PK, pharmacokinetics; tGFR, transdermal GFR; WOCBP, woman of childbearing potential.

a. Pre-screening consent could be used to evaluate skin color only. Full informed consent was required prior to any study-related procedures was conducted.
b. Negative pregnancy serum human chorionic gonadotropin test at screening for WOCBP was required for eligibility. On dosing day, a urine pregnancy test was conducted for WOCBP who agreed to use an acceptable method of birth control
c. A full PE was required at the screening visit. A full PE or limited PA could be conducted prior to dosing. (Limited PA included assessments of HEENT, respiratory, cardiovascular, and abdominal systems). A full or limited exam could be conducted at the follow-up visit.
d. Vital signs included blood pressure, respiration rate, heart rate, and temperature. Note: temperature was collected at screening, pre-dose, and at the follow-up visit (and not during multiple timepoints on dosing day). Whenever possible, subjects were resting for approximately 5 minutes prior to all measurements. Vital signs were collected at screening, pre-dose and at the following post-dose timepoints: 90, 250, 500, and 710 minutes (±5 minutes). For subjects followed

for 24 hours, an additional measurement was taken at 1450 minutes.

e. Height and weight were measured at screening; weight was also measured on the day of dosing.
f. Clinical laboratory assessments were analyzed by a central laboratory and consisted of standard chemistry, hematology, and urinalysis parameters per Table 3 of the protocol. Coagulation panel was conducted at Screening only.
g. MediBeacon Transdermal GFR Measurement System data collection was done prior to dose administration. At least 20 minutes prior to dosing, sensors were placed on the subject and the MediBeacon® Transdermal GFR Measurement System started. Data collection was continued through 12 to 24 hours of PK sampling. Once tGFR was measured, sensors might have been removed while PK sampling continues.
h. The subject was given 240 mL of ambient water to drink the night prior (if brought in the night before dosing), the morning of dosing, and just prior to MB-102 dose administration.
i. MB-102 was administered as a dose of 130 mg (7 mL) via IV injection over a 30 to 60 second injection period. This was followed by a saline flush over 30 to 60 seconds. Time of administration was recorded.
j. Stratum 1: PK sampling was collected pre-dose and at 5, 15, 30, 60, 90 (±2 minutes), 120, 180, 240, 300, 360, 480, 600 (±5 minutes) and 720 minutes post-dose
(12-hour collection period). Stratum 2: PK sampling was collected pre-dose and at 5, 15, 30, 60, 90 (±2 minutes), 120, 180, 240, 300, 360, 480, 600, 720, 960, 1200, and 1440 (±5 minutes) minutes post-dose (24-hour collection period). Blood draws were via a venous catheter and were processed in accordance with instructions available in the Study Procedure Manual.
k. A 12-lead ECG was performed at Screening, prior to dosing, and at 700 minutes post dosing (±5 minutes). Subjects were resting quietly for 10 to 15 minutes prior to the ECG collection.
l. Concomitant medications administered within 3 days prior to baseline through the final follow-up visit were recorded.
m. Adverse events were collected from the time of sensor placement (for baseline measurement) through the follow-up visit.
n. Fitzpatrick Skin Scale was assessed by evaluating the skin on the upper chest (where sensors were placed).

3. Clinical Endpoints

With regards to safety, the Lumitrace® injection safety was evaluated through treatment emergent adverse events (TEAEs), where treatment emergence is defined with respect to the dosing of Lumitrace® injection. Safety of the MediBeacon® TGFR was evaluated through treatment-emergent adverse events, where treatment emergence is defined with respect to the start time of Transdermal GFR Measurement System use (placement of the sensor on the skin). Additional safety variables include physical examinations, clinical laboratory assessments, ECGs, and concomitant medication use. All safety analyses were done for subjects receiving a single dose of Lumitrace® injection.

With regards to effectiveness, the primary endpoint was the proportion P30 of average session transdermal-derived GFR (TGFR) results within 30% of plasma-derived indexed GFR normalized to body surface area (nGFR), with a 95% confidence interval (CI) used to assess the pre-specified performance goal of 85%. Success for the study was defined by the lower limit of the 95% CI for P30 being greater than 85%.

A. Accountability of PMA Cohort

At the time of database lock, 505 subjects were screened and enrolled in the United States and China, of whom 249 (49.3%) subjects were dosed and 243 (48.1%) subjects completed

the study. Reasons for not completing the study included screen failures (62.2%), cohort full (41.4%) and lost to follow-up (1.6%).

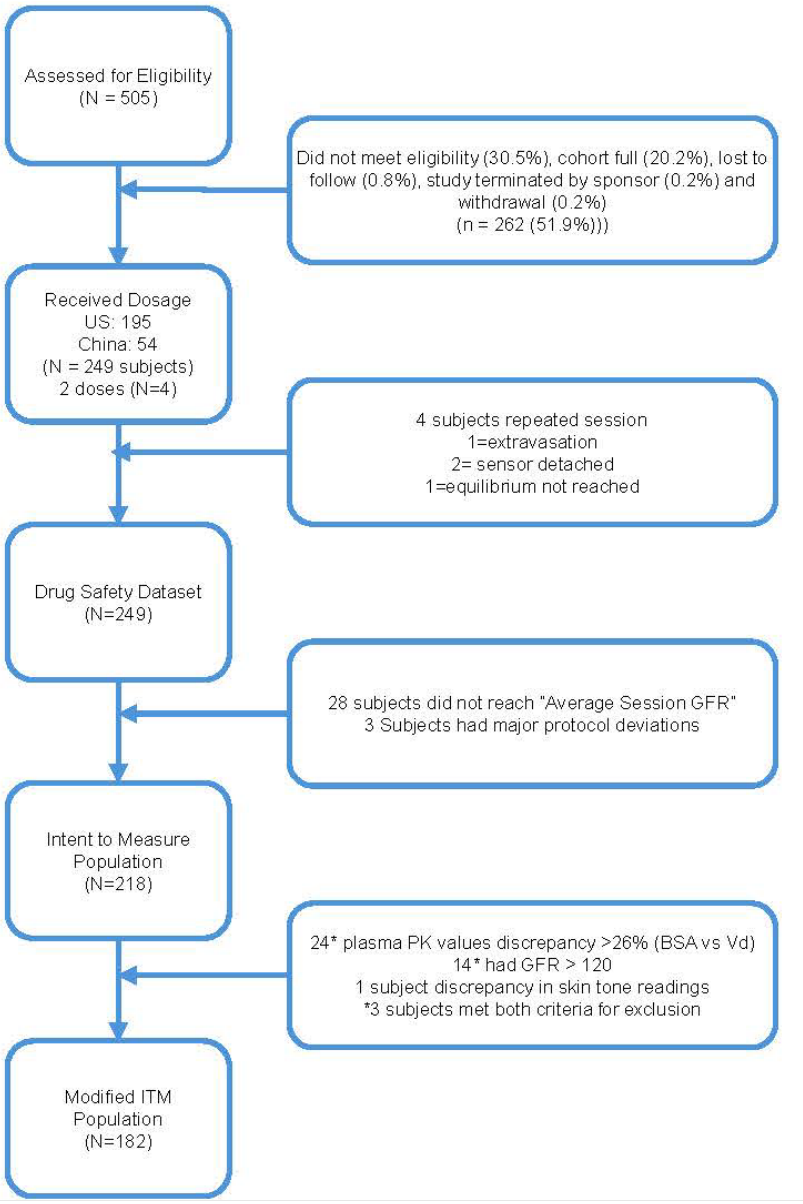

Figure 3: Subject Accountability

B. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a prospective study performed in the US.

Subject demographics and baseline characteristics are provided in Table 10. As targeted, the modified intent to measure (mITM) population of subjects with impaired

and normal renal function equally in the study; 49% with an eGFR ≥ 70 mL/min/1.73m^2 and 50% with an eGFR < 70 mL/min/1.73m^2. Likewise, in the United States, the modified intent to measure population was studied across the spectrum of the Fitzpatrick Skin Scale (FSS) with 55% of subjects with a FSS of I-III and 45% of subjects with a FSS of IV-VI. Note that in the total study population 27% of subjects in the mITM population were from China.

Of 249 subjects included in the Safety Population, 201 (80.7%) subjects had at least one current medical history record. The most common (≥20% of subjects) medical histories were cardiovascular (57.8%), genitourinary (51.0%), endocrine metabolic (41.4%), gastrointestinal (27.7%), musculoskeletal (23.7%), neurologic (22.9%), head, eyes, ears, nose, and throat (HEENT) (22.1%), and other (20.1%) conditions.

Table 10: Baseline Demographics

Characteristic Statistic	**Stratum 1 (N=130) n (%)**	**Stratum 2 (N=119) n (%)**	**Total (N=249) n (%)**
Age at Screening (years)			
n	130	119	249
Mean (SD)	46.9 (14.19)	61.5 (13.45)	53.9 (15.63)
Median	46.5	64.0	57.0
Min, Max	19, 79	21, 87	19, 87
Sex, n (%)			
Male	68 (52.3)	74 (62.2)	142 (57.0)
Female	62 (47.7)	45 (37.8)	107 (43.0)
Race, n (%)			
White	58 (44.6)	49 (41.2)	107 (43.0)
Black or African American	33 (25.4)	43 (36.1)	76 (30.5)
Asian	37 (28.5)	27 (22.7)	64 (25.7)
American Indian or Alaska Native	2 (1.5)	0	2 (0.8)
Ethnicity, n (%)			
Hispanic or Latino	36 (27.7)	14 (11.8)	50 (20.1)
Not Hispanic or Latino	94 (72.3)	103 (86.6)	197 (79.1)
Unknown or Not Reported	0	2 (1.7)	2 (0.8)
Height (cm)			
n	129	119	248
Mean (SD)	168.151 (9.5878)	168.239 (9.2247)	168.194 (9.3964)

Median	167.600	168.900	167.640
Min, Max	144.00, 198.00	144.80, 185.50	144.00, 198.00
eGFR Result Group			
≥ 90	80 (61.5)	0	80 (32.1)
60 - 89	38 (29.2)	30 (25.2)	68 (27.3)
45 - 59	0	39 (32.8)	39 (15.7)
30 - 44	0	24 (20.2)	24 (9.6)
15 - 29	0	18 (15.1)	18 (7.2)
Weight at Dosing (kg)			
n	129	119	248
Mean (SD)	80.806 (17.6937)	85.528 (21.2543)	83.071 (19.5867)
Median	78.300	83.688	80.593
Min, Max	43.64, 147.60	48.60, 135.90	43.64, 147.60
Body Mass Index at Dosing (kg/m^2) [a]			
n	129	119	248
Mean (SD)	28.420 (5.1634)	30.071 (6.4389)	29.213 (5.8571)
Median	28.192	29.237	28.638
Min, Max	18.18, 46.65	17.46, 45.71	17.46, 46.65
Mexameter-Based Skin Color Type			
Type I	16 (12.3)	27 (22.7)	43 (17.3)
Type II	25 (19.2)	21 (17.6)	46 (18.5)
Type III	34 (26.2)	22 (18.5)	56 (22.5)
Type IV	29 (22.3)	16 (13.4)	45 (18.1)
Type V	9 (6.9)	17 (14.3)	26 (10.4)
Type VI	17 (13.1)	15 (12.6)	32 (12.9)
Missing	0	1 (0.8)	1 (0.4)
Mexameter-Based Skin Color Group			
Type I-III	75 (57.7)	70 (58.8)	145 (58.2)
Type IV-VI	55 (42.3)	48 (40.3)	103 (41.4)
Missing	0	1 (0.8)	1 (0.4)

C. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Intent to Measure cohort of 249 patients/procedures, etc. available for the 7 day follow-up. The key safety

outcomes for this study are presented below in Table 11. Adverse effects are also reported in Table 11.

There were no device related adverse events reported in the clinical trial.

Adverse effects that occurred in the PMA clinical study:

A total of 26 subjects had at least one adverse event reported 26/249 (10.4%), and of these adverse events, 0 (0.0%) were considered serious adverse events.

Table 11: Lumitrace® Injection Adverse Events by Type

Adverse Event Type	Events (N) Pilot 2 114 Subjects	Events (N) Pivotal Study 249 Subjects	Subjects n (%) 363 Subjects
Injection site extravasation	6	3	9 (2%)
Headache	1	4	5(1%)
Ecchymosis	0	3	3 (1%)
Cardiac Murmur	0	2	2 (1%)
Hypertension	0	2	2 (1%)
Oropharyngeal pain	1	0	1 (<1%)
Rash	1	0	1 (<1%)
Hot Flush	1	0	1 (<1%)
Fatigue	0	1	1 (<1%)
Edema	0	1	1 (<1%)
Diarrhea	0	1	1 (<1%)
Dyspepsia	0	1	1(<1%)
Nausea	0	1	1 (<1%)
Blood Glucose Increased	0	1	1 (<1%)
Weight Decreased	0	1	1 (<1%)
Pruritus	0	1	1 (<1%)
Hematoma	0	1	1 (<1%)
Hyperglycemia	0	1	1 (<1%)
Hypoglycemia	0	1	1 (<1%)
Cough	0	1	1 (<1%)
Nasal congestion	0	1	1 (<1%)
Urinary tract infection	0	1	1 (<1%)
Contusion	0	1	1 (<1%)
Glycosuria	0	1	1 (<1%)

2. Effectiveness Results

The analysis of effectiveness was based on the 249 evaluable patients at the end of the TGFR session. Key effectiveness outcomes are presented in Tables 11 to 15.

The primary objective of this study was a P30 estimate with a lower 95% confidence interval that was greater than 85%.

P30 estimates represent the percentage of average session GFR values that were within 30% of the measured GFR values.

The device met its primary objective in the clinical trial where it was shown that 94.0% of the average session GFR values obtained using this device were within 30% of the measured GFR values with a 95% confidence interval of 89.4 – 95%. Table 12 below represents the P30 comparison with measured GFR.

Table 12: Average session GFR results comparison with measured GFR results.

P30 Estimate	95% CI lower limit	95% CI upper limit
94%	89.4%	96.9%

The rate of decrease of Lumitrace® fluorescence measured on the skin has been shown in clinical studies to be highly correlated with nGFR as determined via Lumitrace® plasma clearance.

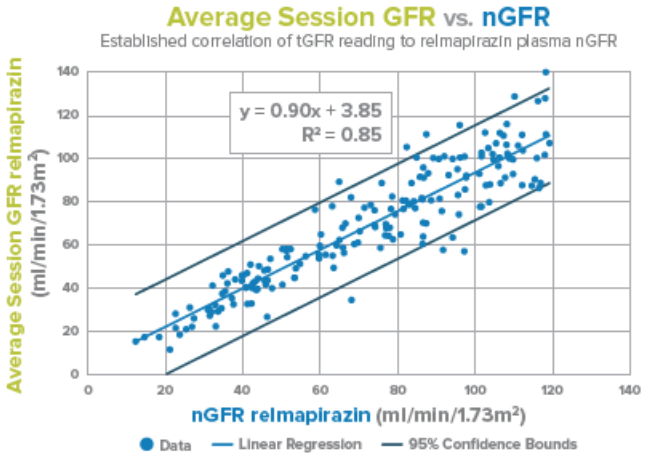

Figure 4. Establishment of the correlation between Average Session GFR and nGFR.

Through post hoc analysis, average session GFR values obtained in the pivotal trial using this device were also compared with estimated GFR (eGFR) values (creatinine based 2009 CKD-EPI equation[1]). The results of this comparison are summarized in Table 13. While 94.0% of the average session GFR values obtained using this device were within 30% of the measured GFR values; 92.9% of the eGFR values were also within 30% of the measured GFR values. Additionally, the 95% confidence intervals for the average session GFR overlap with the 95% confidence intervals for the eGFR (Table 13). This suggests that the accuracy of the average session GFR results obtained using this device is very similar to the accuracy of the eGFR results obtained using creatinine based 2009 CKD- EPI equation[1].

Table 13: Average Session GFR results comparison with estimated GFR (eGFR) results:

	Average Session GFR	eGFR*
P30 Estimate	94.0%	92.9%
95% Confidence Interval	89.4-96.9%	88.1-96.1%

*The eGFR results were obtained via a post hoc analysis, (which was not a predetermined outcome measure of the study).

3. Subgroup Analyses

Patients were grouped into Stratum 1 (eGFR ≥70 mL/min/1.73m2) and Stratum 2 (eGFR < 70 mL/min/1.73m2) based on the screening estimated GFR results (Table 14)

Table 14: Subgroup Analyses based on eGFR Screening

Patient Population	P30 Estimate	95% CI lower limit	95% CI upper limit
Stratum 1 (eGFR ≥70 mL/min/1.73m2) N=90	95.6%	89.0%	98.8%
Stratum 2 (eGFR < 70 mL/min/1.73m2) N=92	92.4%	84.9%	96.9%

The pivotal trial P30 target value was that the lower 95% confidence interval should be greater than 85%. Table 14 shows that the lower limit of the 95 % confidence interval for

P30 estimate was above the target value for stratum 1 and just below the target value for stratum 2. This suggests that the device performance is consistent and acceptable in both eGFR strata.

Note that in the total study population 27% of subjects in the modified intent to measure (mITM) population were from China.

Results in Table 15 show data classified according to the eGFR strata (Stratum 1 and 2) subgroups globally and for each region (USA and China).

Since the P30 estimate for all the subgroups is greater than 90%, this suggests consistency of the performance measure, suggesting that the device performance is consistent and acceptable across all subgroups.

Table 15: Primary Endpoint Evaluation by eGFR based stratum (mITM)

Variable Statistic	**Stratum 1 (eGFR ≥70 mL/min/1.73m2)**	**Stratum 2 (eGFR < 70 mL/min/1.73m2)**	**Total**
Global:	**N=90**	**N=92**	**N=182**
Variable Statistic	**Stratum 1 (eGFR ≥70 mL/min/1.73m2)**	**Stratum 2 (eGFR < 70 mL/min/1.73m2)**	**Total**
P30 estimate	95.6%	92.4%	94%
95% CI lower limit	89%	84.9%	89.4%
95% CI upper limit	98.8%	96.9%	96.9%
USA:	**N=65**	**N=68**	**N=133**
P30 Estimate	93.8%	91.2%	92.5%
95% CI lower limit	85%	81.8%	86.6%
95% CI upper limit	98.3%	96.7%	96.3%
China:	**N=25**	**N=24**	**N=49**
P30 estimate	100%	95.8%	98%
95% CI lower limit	86.3%	78.9%	89.1%
95% CI upper limit	100%	99.9%	99.9%

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; mITM, Modified Intent-to- Measure; USA, United States of America.

The modified intent to measure (mITM) population was studied across the spectrum of the Fitzpatrick Skin Scale (FSS) with 42.3% of subjects with a FSS of I-II, 37.9% of subjects

with FSS of III-IV and 19.8% of subjects with a FSS of IV-VI. The study was not specifically powered for skin color subgroup analysis.

Table 16: Subgroup Analyses of Fitzpatrick Skin Scale (FSS)

Patient Population	P30 Estimate	95% CI lower limit	95% CI upper limit
FSS Type I-II N=77	96.1% (74/77)	89.0 %	99.2%
FSS Type III-IV N=69	92.8% (64/69)	83.9%	97.6%
FSS Type V-VI N=36	91.7% (33/36)	77.5%	98.3%

Table 16 shows the P30 estimate stratified by Fitzpatrick skin scale (FSS) type. The P30 estimates did not exhibit a statistically significant trend across FSS (exact p value from 2-sided Cochran-Armitage trend test is 0.1397).

Table 17: Proportion of average session GFR results within 30% of nGFR stratified by FSS.

Fitzpatrick Skin Scale (FSS)	P30 Estimate n/N (%)
Type I	37/38 (97.4)
Type II	37/39 (94.9)
Type III	41/43 (95.3)
Type IV	23/26 (88.5)
Type V	18/18 (100.0)
Type VI	15/18 (83.3)
Overall	171/182 (94.0)

The accuracy of TGFR measurements did not decrease significantly across the FSS groups in Table 17 (Cochran-Armitage trend test exact p value was 0.4136). The darker skin patients fall short of the trial performance goal of 85% since the lower 95 % confidence intervals of the FSS III-VI patients are less than 85%. Also, the P30 estimate of the Type VI patients is 83.3% compared to (88.3-100%) in the lighter skin color categories. However, the point estimates per FSS level are uncertain and the 95% confidence intervals per FSS level are wide because the pivotal trial was not powered to detect statistically significant differences in average session GFR accuracy among skin color groups.

4. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The supplemental clinical information includes:

- Pharmacokinetics of MP-3180 in Healthy Volunteers (Pilot 1A), NCT02098174.
- Pharmacokinetics of MP-3180 and Use of Noninvasive Fluorescence Detection Device in Healthy Volunteers (ORFM-1B), NCT02098187.
- Pharmacokinetics of MB-102 and 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, NCT02772276.

Table 18: Pilot Study Summary

Characteristic	Pilot 1A	Pilot 1B	Pilot 2, Group 1	Pilot 2, Group 2	Pilot 2, Group 3
Number of Sites	One	One	Two	Two	Two
Number of subjects analyzed	16	16	60	60	114
Renal function of subjects	Normal	Normal	31 subjects with CKD of normal to stage 2 29 patients with CKD stage 3-4	20 subjects with CKD of normal to stage 2 40 subjects with CKD stage 3-5	77 subjects with CKD of normal to stage 2 enrolled 37 subjects with CKD stage 3-5 enrolled

Characteristic	Pilot 1A	Pilot 1B	Pilot 2, Group 1	Pilot 2, Group 2	Pilot 2, Group 3
Design	Single dose of MB-102 (1 µmol/ kg) plus single dose of iohexol (Omnipaque-300, 5 mL of a 300 mg iodine (I)/mL solution)	Single ascending dose of MB-102 (0.5 µmol/kg, 1.0 µmol/kg, 2.0 µmol/kg, and 4.0 µmol/kg) and iohexol (Omnipaque-300,	Single dose of MB-102 (4 µmol/kg) in combination with standard dose of iohexol (Omnipaque-300, 5 mL of a 300 mg iodine). Second generation prototype (QuantumLeap)	Single dose of MB-102 at 4 µmol/kg in combination with standard dose of iohexol (Omnipaque-300, 5 mL of a 300 mg iodine). An extended PK cohort of subjects with impaired renal function (where PK collections	Single dose of MB-102 (4 µmol/kg); or Single dose 130 mg (7 mL); or Two doses of MB- 102 130 mg (7 mL) administered for subjects with normal kidney function to CKD stage
Design	Single dose of MB-102 (1 µmol/ kg) plus single dose of iohexol (Omnipaque-300, 5 mL of a 300 mg iodine (I)/mL solution)	5 mL of a 300 mg iodine (I)/mL solution) Deployed the first transdermal fluorescence device.	transdermal fluorescence device employed.	will extend to 48 hours) will be included. Radiance prototype transdermal fluorescence device employed, primarily software revisions to the QuantumLeap device	2. Brilliance prototype transdermal fluorescence device employed.

Characteristic	Pilot 1A	Pilot 1B	Pilot 2, Group 1	Pilot 2, Group 2	Pilot 2, Group 3
Duration of stay	Subjects confined to study clinic for ~12h	Subjects confined to study clinic for ~12h	Subjects confined to study clinic for ~12h Follow-up within 7± 3 days	Subjects confined to study clinic for ~12h or up to 48 hours (small cohort) Follow-up within 7± 3 days	Subjects confined to study clinic for up to 24 hours if normal renal function and for up to 48 hours if impaired renal function. Follow-up within 7+/-3 days
Measurements	Plasma concentrations of Lumitrace® and iohexol, urinary excretion of Lumitrace®	• Multiple locations of patient sensor site (forehead, upper arm, trunk, sternum)	Plasma concentrations of Lumitrace® and iohexol, urinary excretion of Lumitrace®, transdermal fluorescence measurements of Lumitrace®	Plasma concentrations of Lumitrace® and iohexol, urinary excretion of Lumitrace®, transdermal fluorescence measurements of Lumitrace®	Plasma concentrations of Lumitrace®, transdermal fluorescence measurements of Lumitrace®

Characteristic	Pilot 1A	Pilot 1B	Pilot 2, Group 1	Pilot 2, Group 2	Pilot 2, Group 3
		• Fluorescence measurement of Lumitrace® Plasma concentrations of Lumitrace® and iohexol, urinary excretion of Lumitrace®			
Assessments	• Safety and tolerability of TGFR • PK of Lumitrace® compared to PK of iohexol	• Optical detection of Lumitrace® fluorescence • Correlation/ comparison of the plasma clearances of LUMITRACE® • Placement of light transmission assembly on the body	• Safety and tolerability of TGFR • PK of Lumitrace® Optical detection of Lumitrace® fluorescence • Correlation/ com parison of the plasma clearances of Lumitrace® and iohexol as measurements of GFR with those from optical detection of Lumitrace®	• Safety and tolerability of TGFR • PK of Lumitrace® • Optical detection of Lumitrace® fluorescence • Correlation/com parison of the plasma clearances of Lumitrace® and iohexol as measurements of GFR with those from optical detection of Lumitrace®	• Safety and tolerability of TGFR • PK of Lumitrace® • Optical detection of Lumitrace® fluorescence • Correlation/com parison of the plasma clearances of Lumitrace® as measurements of GFR with those from optical detection of Lumitrace®

Characteristic	Pilot 1A	Pilot 1B	Pilot 2, Group 1	Pilot 2, Group 2	Pilot 2, Group 3
			• Assessment of the urinary excretion of Lumitrace® based on 12 and 24hr urine collections • Selection of device settings for subsequent studies • Effect of skin color on optical detection • Dose optimization: dose optimization was initially evaluated at the 4 µmol/kg dose level; however, criteria were not met for lowering this level. All subjects in Group 1 received 4 µmol/kg.	• Assessment of the urinary excretion of Lumitrace® based on 12 and 24hr urine collections • Selection of device settings for subsequent studies • Effect of skin color on optical detection	• Selection of device settings/design for subsequent studies • Effect of skin color on optical detection
Plasma half-life (approximate)	2 hours	2 hours	2 hours – Normal cohort 4 hours – Stage 3 8 hours – Stage 4	2 hours – Normal cohort 4 hours – Stage 3 8 hours – Stage 4	2 hours – Normal cohort 4 hours–Stage 3 8 hours – Stage 4

Characteristic	Pilot 1A	Pilot 1B	Pilot 2, Group 1	Pilot 2, Group 2	Pilot 2, Group 3
Adverse Events	3 adverse events in 2 subjects; no serious adverse events in the study or follow-up period	All subjects reported injection site reactions (application site erythema) other AEs included headaches and discomfort. All events were mild in severity	A total of 40 adverse events were reported in 28 treated subjects in Groups 1, 2 and 3 for an AE rate of 12.0% in the treated population. A total of 31 events 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		
Conclusions	Approximately 100% of the dose was recovered in urine within 12 hours without metabolites. Measured GFR (mGFR) from Lumitrace® and Iohexol were comparable and had an R^2 correlation of >98% Lumitrace® transdermal fluorescence time dependence highly correlated with Lumitrace® plasma time dependence. Continuous monitoring window expected to range from 6 to 12 hours		MediBeacon has developed a robust and accurate assay for the measurement of Lumitrace® clearance in plasma. The PK of Lumitrace® was described using 2-compartment model regardless of kidney function. Lumitrace® clearance is comparable to that of iohexol. Lumitrace® is a human GFR tracer agent. Plotting of GFR derived from the Lumitrace® plasma concentrations against the GFR derived from the iohexol concentrations showed a linear regression of the data yields and r-squared correlation of 0.99. Based on the fluorescent analysis, results show that the MediBeacon® Transdermal GFR Measurement System (TGFR), formerly known as the Optical Renal Function Monitor [ORFM]) can measure the Lumitrace® transdermal fluorescence reduction rate which is consistent with Lumitrace® plasma concentration depletion rate. This will be further tested in a pivotal study. Lumitrace® was well tolerated in the population studied. No serious adverse events have been reported and all reported AEs were mile or moderate in severity. All device related AEs were also mild or moderate in severity. There were no other clinically		

	depending on kidney health.		significant findings with regard to hematology,		
Characteristic	**Pilot 1A**	**Pilot 1B**	**Pilot 2, Group 1**	**Pilot 2, Group 2**	**Pilot 2, Group 3**
	Well tolerated at escalating doses.		Clinical chemistry, urinalysis, vital signs, ECGs, or physical examinations.		

An analysis of Supplementary Pilot Study 2 data is shown in Figure 5 below. The GFR derived from the Lumintrace® (relmapirazin) plasma pharmacokinetics was plotted against the GFR derived from the iohexol plasma pharmacokinetics. After adjustment by a factor of 1.09 due to laboratory calibration differences, the slope of the regression line is 0.99 suggesting that there was a tight correlation between GFR measured by plasma containing relmapirazin and plasma iohexol pharmacokinetics. This high correlation qualified Lumitrace® to be used as a renal tracer agent in the MediBeacon® TGFR.[2]

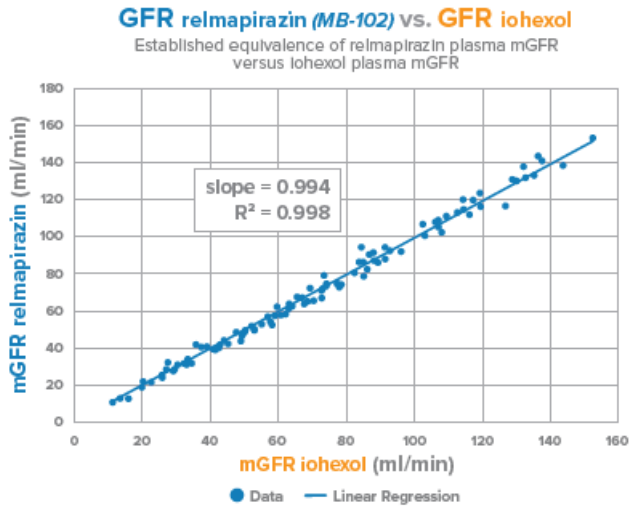

Figure 5. Establishment of Lumitrace® as a renal tracer.

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology, an FDA advisory committee, for review and recommendation.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The pivotal trial concluded that the MediBeacon® Transdermal GFR Measurement System (TGFR) provides GFR assessment in healthy and renally compromised patients with a certain level of accuracy in the GFR range 15-120 ml/min/1.73m^2. Specifically, 94% (171/182) of the average session GFR values were within 30% of the plasma derived indexed GFR (nGFR) (gold standard) with a 95% confidence interval of 89.4-96.9%. Additionally, the accuracy of the GFR results obtained from the TGFR is similar to the accuracy of GFR results obtained via serum creatinine (2009 CKD- EPI equation based[1]).

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The pivotal trial demonstrated that the MediBeacon® TGFR is safe to use. There were no study device-related treatment emergent adverse events (TEAEs), or Unanticipated Adverse Device Effect (UADE)s. The Lumitrace® intravenous injection was well tolerated, with a low incidence of transient mild or moderate TEAEs like injection site extravasation, ecchymosis, headache, hypertension, or cardiac murmur in very few patients. There were no serious TEAEs and or TEAEs leading to death. Patients exposed to Lumitrace® did not show hypersensitivity. Overall, 26/249 (10.4%) of patients had at least one adverse event reported and of these adverse events 0 (0.0%) were considered serious adverse events.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

Use of the MediBeacon® TGFR provides the clinician with a GFR assessment. In the pivotal trial, a pre-specified endpoint was established to evaluate the primary effectiveness by comparing the performance of the transdermal average session GFR with plasma measured GFR (gold standard for GFR). This pre-specified primary endpoint was P30, the proportion of average session GFR measurements made by the TGFR system that are within 30% of the gold standard. In the pivotal study, the estimate of P30 was 94% (171/182) with 95% CI (89.4-96.9%). The pre-specified performance goal of 85% for P30 was met with statistical significance because the lower limit of the 95% confidence interval (CI) on P30 is greater than 85%.

In a post hoc analysis of the data obtained from the clinical trial, the performance of transdermal average session GFR was compared with the participant estimated GFR (eGFR), which is one of the many other modalities available for GFR assessment (Table 3). The performance of creatinine based eGFR (CKD- EPI 2009 equation[1]) was found comparable with the performance of the transdermal average session GFR in the pivotal study.

The MediBeacon TGFR provides a point-of-care GFR assessment due to the transdermal detection of the novel fluorescent tracer agent. This methodology avoids issues associated with some other methods of GFR assessment or measurement (Table 3). For example, radioactive agents such as Glofil (I125 labeled iothalamate), 99mTc-DTPA, and 51Cr-EDTA involve handling and waste concerns that limit their routine use in the clinic. Cold iohexol requires blood draws over hours and subsequent laboratory processing to yield a GFR result, while the proposed device is much less invasive in measuring the decay of a fluorescence signal through the patient's skin.

There are uncertainties associated with these benefits.

Average session GFR obtained from the subject device was compared with measured GFR normalized to body surface area (nGFR), the acceptance limit of the average session GFR being within 30% of nGFR in the pivotal study. While this acceptance limit was chosen based on a similar acceptance limit for serum creatinine-based method of GFR determination (2009 CKD-EPI equation), there are other methods of GFR measurement that could have been used.

Although the trial was not statistically powered to detect differences in accuracy between skin types, there were no statistically significant differences observed in GFR accuracy between patients of different skin color types. However, there was less representation in certain skin types raising potential uncertainty of generalizability across skin color types (Tables 16 &17).

While the device technology of measuring transdermal florescence to assess a patient's GFR is new, there is some concern about how well the study results will generalize, since eGFR in the current study (93%) is higher than the previously known estimate (84%) based on the CKD-EPI 2009 study (Levey et al., 2009[1]).

While this device does offer some practical advantages, it also requires placement of an intravenous (IV) line for administration of the exogenous tracer agent, produces results in 8-24 hours depending on the kidney function, and necessitates limited patient movement during the baseline measurements. Additionally, comparison of the accuracy of this device with eGFR assessment using cystatin C blood level concentration was not presented.

The risks of the device include errors in GFR assessment and subsequent clinical implications, interference with other necessary clinical chemistry testing, and potential for device misuse.

The MediBeacon® TGFR is a diagnostic device that is intended to be used as a standalone (and not adjunctive) device for GFR assessment. Therefore, errors in GFR assessment could potentially lead to patient harm as would be the case for any other standalone diagnostic device. For example, patient harm could occur with the possibility of misclassifying a patient's chronic kidney disease (CKD) stage. The GFR results obtained from this device will be used to determine a patient's CKD stage. A patient misclassified to an inaccurate CKD stage could receive inappropriate treatments or interventions, which may have serious

deleterious health consequences. As interim snapshot values were not validated in the pivotal trial, the following warning was placed above the graph display of Snapshot GFR versus time from injection "Limitation: Graph Values Not Validated." The limitation statement reduces the potential device misuse in which an unvalidated Snapshot GFR value will be obtained from the TGFR and used in clinical decision making.

The PMA application submitted in support of this device did not include sufficient testing of potential Lumitrace® interference with the most common analytes and technologies used in other diagnostic tests used in the intended patient population. Therefore, the risks of Lumitrace® interference with other clinical diagnostic tests are unknown. Lumitrace® may be present in the blood and urine of patients with impaired kidney function for 72 hours following injection. Thus, there remains a risk that Lumitrace® may impact results from other diagnostic tests. The potential risks of Lumitrace® interference are mitigated by prominent warnings in device labeling and Provider and Patient Fact Sheets, which must be provided to patients and healthcare providers.

There are also some uncertainties in the risks associated with this device. The pivotal trial was a clinical performance study, which did not assess the clinical outcomes of patients who are managed according to TGFR results. However, the demonstrated accuracy of TGFR mitigates patient risks associated with the uncertainty of TGFR effects on patient outcomes when managed according to MediBeacon® TGFR results.

In the clinical data submitted, the overall reported adverse events (AE) were low, and there were no serious AEs reported. However, certain potential AEs were not studied in the pivotal trial. For example, patients using this device are required to limit movement. This could potentially predispose the patients to the effects of prolonged immobility.

1. Patient Perspectives

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

   In conclusion, given the available information above, the data support that for the assessment of GFR in adult patients with stable renal function the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use and appropriate labelling. The analysis of the pivotal clinical study provides valid scientific evidence to support the safety and effectiveness

of MediBeacon® Transdermal GFR System for the determination of GFR at the point-of-care with a certain level of accuracy.

XV. CDRH DECISION

CDRH issued an approval order on January 17, 2025

The final clinical conditions of approval cited in the approval order are described below.

1. MediBeacon® must provide a Fact Sheet (in addition to the Lumitrace® package insert) to all health care providers prior to prescription of the MediBeacon® Transdermal GFR System to patients. The Fact Sheet must inform healthcare providers of the probable benefits and risks of use of the MediBeacon® Transdermal GFR System and that there is a risk that Lumitrace® may interfere with other diagnostic testing on the patient for up to 72 hours after the injection.

2. MediBeacon® must provide a Fact Sheet to be given to all patients prescribed the MediBeacon® Transdermal GFR System. The Fact Sheet must advise patients of the probable benefits and risks of use of the MediBeacon® Transdermal GFR System and that there is a risk that Lumitrace® may interfere with other diagnostic testing for up to 72 hours after the injection.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

1. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006. Erratum in: Ann Intern Med. 2011 Sep 20;155(6):408.

2. Dorshow RB, Debreczeny MP, Goldstein SL, Shieh JJ. Clinical validation of the novel fluorescent glomerular filtration rate tracer agent relmapirazin (MB-102). Kidney Int. 2024 Oct;106(4):679-687. doi: 10.1016/j.kint.2024.06.012. Epub 2024 Jul 2. PMID: 38964736.