Clinical Study Protocol

PROTOCOL NUMBER:	DM199-2019-001
PROTOCOL TITLE:	A Multi-Center Open-label Investigation to Assess the Safety and Efficacy of Multiple Doses of DM199 in Patients with Chronic Kidney Disease (Stage II or III)
STUDY PHASE:	II
STUDY DRUG:	DM199
IND:	137815
SPONSOR:	DiaMedica Therapeutics Inc. 2 Carlson Parkway Suite 260 Minneapolis, MN 55447 USA
PROTOCOL VERSION & DATE:	Version 2.0
TRIAL REGISTRATION NUMBER *(ClinicalTrials.gov Identifier)*:	NCT04123613

Chief Medical Officer

Harry Alcorn Jr. Pharm.D.
DiaMedica Therapeutics, Inc
2 Carlson Parkway
Suite 260
Minneapolis, MN 55447 USA
C: 612.618.1002; O: 762.312.6064
Fax: 763.710.4456
halcorn@diamedica.com

26-June-2020

Signature Date

The confidential information in this document is the property of DiaMedica Therapeutics Inc. It is understood that this information will not be disclosed to any third party, in any form, without prior written authorization.

PROTOCOL AGREEMENT FORM

A Multi-Center Open-label Investigation to Assess the Safety and Efficacy of Multiple Doses of DM199 in Patients with Chronic Kidney Disease (Stage II or III)

Version 2.0

26June2020

I confirm that I have read the above referenced protocol and understand its contents. The information it contains is consistent with the current risk-benefit evaluation of the study drug.

I agree to conduct and supervise the study according to this protocol and to comply with its requirements, subject to scientific, ethical, and safety considerations. I will obtain the required regulatory and Institutional Review Board/Ethics Committee (IRB/EC) approvals prior to initiating the study and will abide by any additional requirements imposed by the IRB/EC. I will provide copies of this clinical study protocol and all pertinent information to the study personnel under my supervision and will discuss this material with them and ensure they are fully informed regarding the study drug and the conduct of the study. I agree to conduct the study in compliance with ICH E6 Guidance for Good Clinical Practice (GCP), applicable privacy laws, Declaration of Helsinki, US Code of Federal Regulations, Title 21, Parts 50, 54, 56, and 312, and according to applicable local requirements.

I will not make changes to the protocol and will contact DiaMedica Therapeutics Inc. with any question or feedback for consideration on protocol changes. All changes related to the protocol will require DiaMedica Therapeutics Inc. and Institutional Review Board/Ethics Committee (IRB/EC) approval except to eliminate an immediate risk to Participants. I agree to administer study drug only to Participants under my personal supervision or the supervision of a Sub-Investigator. I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I understand that I must keep confidential the information contained in study documents that I will be provided with over the course of the study. I understand that, should the decision be made by the Sponsor to prematurely terminate or suspend the study at any time for any reason, such a decision will be communicated to me in writing. Should I decide to withdraw from participating in the study, I will immediately communicate such decision in writing to DiaMedica Therapeutics Inc. and will maintain all study related records for required time period.

_____	_____
Clinical Site No.	Clinical Site Name
_____	_____
Site Principal Investigator (Print Name)	Site Principal Investigator (Signature) Date

TABLE OF CONTENTS

PROTOCOL AGREEMENT FORM **2**
TABLE OF CONTENTS **3**
LIST OF ABBREVIATIONS **7**
PROTOCOL SYNOPSIS **11**
1 INTRODUCTION **17**
1.1 Background 17
1.2 Summary of Nonclinical Studies 18
1.3 Summary of Clinical Studies 18
1.4 Rationale 19
2 STUDY DESIGN **20**
2.1 Objective 20
2.2 Endpoints 21
2.2.1 Primary Endpoints *21*
2.2.2 Secondary Endpoints *21*
2.2.3 Exploratory Endpoints *21*
2.3 Number of Participants 22
2.4 Study Duration 22
3 STUDY POPULATION **22**
3.1 Inclusion Criteria 22
3.2 Exclusion Criteria 23
4 STUDY DRUG ADMINISTRATION **25**
4.1 Study Drug (DM199) 25
4.2 Selection of Doses in the Study 25
4.3 Conditions of Study Drug Storage 26
4.4 Study Drug Administration 26
4.5 Prohibited Therapies 26
4.6 Control of Drug Supply 26
5 STUDY PROCEDURES **28**
5.1 INFORMED Consent 31
5.2 Eligibility Screening 31
5.3 Contraception 32

5.4 Urine Pregnancy Test 32
5.5 Method of Assigning Participants to Study Drug Groups 32
5.6 Previous and Concomitant Medication 33
5.7 Physical Examination 33
5.8 Body Weight and Height 33
5.9 Vital Signs 34
5.10 Blood Pressure 34
5.11 Electrocardiogram 34
5.12 CKD-EPI Creatinine Equation 35
5.13 Laboratory Assessments 35
5.13.1 Clinical Laboratory 35
5.14 Study Drug Administration 37
5.15 Adverse Event Monitoring 37
5.16 Participant Withdrawal 37
6 SAFETY OVERSIGHT 38
6.1 Definitions 38
6.1.1 Adverse Event (AE) 38
6.1.2 Suspected Adverse Reaction (SAR) 38
6.1.3 Serious Adverse Event (SAE)/Serious Suspected Adverse Reaction (SSAR) 39
6.1.4 Unexpected Adverse Event/Unexpected Suspected Adverse Reaction 39
6.1.5 Serious Unexpected Suspected Adverse Reaction (SUSAR) 39
6.2 Evaluation of Adverse Events 39
6.2.1 Assessment of Severity 39
6.2.2 Local (Injection Site) Adverse Event Intensity 40
6.2.3 Assessment of Causality 41
6.3 Reporting of Adverse Events 42
6.3.1 Clinical Laboratory Abnormalities and Other Abnormal Assessments 42
6.3.2 Expedited Reporting of SAEs 42
6.3.3 Serious Adverse Event Reports to the IRB/EC 43
6.3.4 Sponsor Expedited Safety Reporting Requirements 43
6.3.5 Adverse Event Follow-up 43
6.3.6 Post-study Adverse Events 43
6.3.7 Pregnancy Reporting 44
7 DATA COLLECTION AND MANAGEMENT 44

7.1 Data Management 44
7.2 Participant Identification 44
7.3 Case Report Forms 45
7.4 Source Documentation 45
7.4.1 Source Documentation Reporting Requirements 45
8 STATISTICAL CONSIDERATIONS 45
8.1 Statistical Design and Sample Size 45
8.1.1 General Design 45
8.1.2 Sample Size Determination 46
8.1.3 Analysis Populations 46
8.1.4 Interim Analyses 46
8.2 Study Endpoints 46
8.2.1 Primary Endpoints 46
8.2.2 Secondary Endpoints 47
8.2.3 Exploratory Endpoints 47
8.3 Statistical Methods 47
8.3.1 Baseline Summaries 48
8.3.2 Safety 48
8.3.3 Pharmacokinetic (PK) Parameters 50
8.3.4 Urine Concentrations of KLK1 Measurements 50
8.3.5 Pharmacodynamic Parameters 50
9 RISK/BENEFIT ANALYSIS 50
9.1 Potential Risks 50
9.2 Alternative Study Drugs 51
9.3 Potential Benefits 51
9.4 Risk Minimization 51
10 RESPONSIBILITIES 51
10.1 Sponsor Responsibilities 51
10.2 Investigator Responsibilities 52
11 STUDY MONITORING AND AUDITING 53
11.1 Monitoring and Source Document Verification 53
11.2 On-Site Audits/Inspections 53
12 STUDY ADMINISTRATION 54
12.1 Regulatory and Ethical Considerations 54

12.2 Protocol and Amendment Approvals 54
12.3 Protocol Deviation Management 54
12.4 Compliance Oversite and Study Site Termination 55
12.5 Participant Confidentiality 55
12.6 Ongoing Information for IRB/EC and Regulatory Authorities 56
12.7 Record Retention 56
12.8 Financial Disclosure 57
12.9 Liability and Insurance 57
12.10 Study Termination 57
12.11 Final Report 58
12.12 Publication 58
13 REFERENCES 58

Tables

Table 1 Schedule of Assessments 28
Table 2 Clinical Laboratory Parameters 36
Table 3 Toxicity Grading 40
Table 4 Grading of Local (Injection Site) Adverse Event Intensity 41

LIST OF ABBREVIATIONS

Abbreviation	Definition
A1c	Hemoglobin to which glucose is bound
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
AIS	Acute ischemic stroke
ALT	Alanine aminotransferase
Anti-HCV	Anti-hepatitis C virus
APOL1	Apoliprotein L1
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the concentration-time curve extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time 0 until the last quantifiable concentration
$AUC_{0\text{-}24}$	Area under the concentration-time curve from time 0 until 24 hours post-dose
BK	Bradykinin
BK1R	Bradykinin 1 receptor
BK2R	Bradykinin 2 receptor
BLQ	Below the limit of quantitation
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CIs	Confidence intervals
CKD	Chronic kidney disease
CL/F	Total body clearance
cm	Centimeter
C_{max}	Maximum observed urine drug concentration
CO2	Carbon Dioxide
CRP	C-reactive protein
CS	Clinically significant

Abbreviation	Definition
CV%	Coefficient of variation
dL	Deciliter
DMP	Data management plan
DM	Diabetes mellitus
DN	Diabetic nephropathy
E2	Prostaglandins
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ER	Emergency room
FDA	Food and Drug Administration
g	Grams
GCP	Good Clinical Practice
geo CV%	Geometric coefficient of variation
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
hr	Hour
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
KKS	Kallikrein-kinin system

Abbreviation	Definition
KLK1	Kallikrein protein
KIM 1	Kidney Injury Molecule 1
LMWK	Low molecular weight kininogen
m	Meter
mcg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mITT	Modified Intention-to-treat
mmHG	Millimeter of Mercury
mL	Milliliters
MMP-9	Matrix metalloproteinase-9
MRT	Mean Residence Time
MTD	Maximum tolerated dose
N	Number of non-missing observations
n	Number of Participants to be enrolled
NCS	Not clinically significant
NGAL	Neutrophil gelatinase-associated lipocalin
NOAEL	No-observed-adverse-effect level
OH	Orthostatic hypertension
OTC	Over-the-counter
PD	Pharmacodynamic
PHI	Protected health information
PI	Principal Investigator
PK	Pharmacokinetic
pKLK1	Porcine derived KLK-1
PR interval	Time from onset of P wave to start of QRS complex.
PT	Preferred term
QRS interval	Main spike in EKG line
QT	Start of Q wave to end of the T wave on electrocardiogram

Abbreviation	Definition
QTcF	QT interval corrected for heart rate according to Fridericia's formula
rhKLK-1	Recombinant human tissue kallikrein-1
RR Interval	Peak from one QRS complex to peak of next as shown in ECG
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SC	Subcutaneous
Scr	Serum Creatinine
SD	Standard deviation
sec	Second
SOC	System organ class
SOP	Standard Operating Procedure
SSAR	Serious Suspected Adverse Event
SUSAR	Serious Unexpected Suspected Adverse Reaction
T1D	Type I Diabetes Mellitus
T2D	Type II Diabetes Mellitus
TEAE	Treatment emergent adverse event
t_{max}	Time to reach maximum urine concentration
TNFR1	Tumor necrosis factor receptor
$t_{1/2}$	Terminal elimination phase half-life
UACR	Urine albumin creatinine ratio
µg	Microgram
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
V_z/F	Volume of distribution

PROTOCOL SYNOPSIS

PROTOCOL NUMBER	DM199-2019-001
PROTOCOL TITLE	A Multi-Center Open-label Investigation to Assess the Safety and Efficacy of Multiple Doses of DM199 in Patients with Chronic Kidney Disease (Stage II or III)
STUDY PHASE	II
STUDY DRUG	DM199
SPONSOR	DiaMedica Therapeutics Inc. 2 Carlson Parkway Suite 260 Minneapolis, MN 55447 USA
STUDY DRUG INDICATION	DM199 is a pharmaceutical formulation comprised of recombinant human tissue kallikrein-1 (rhKLK-1) that is being developed as an injectable protein drug for the treatment of chronic kidney disease (CKD).
STUDY RATIONALE	DiaMedica Therapeutics Inc. is conducting a Phase II study to support the development of DM199 as a treatment of CKD in the following three Participant cohorts: 1) African Americans with CKD (Stage II or III), hypertension and non-diabetic 2) IgA nephropathy diagnosis and CKD (Stage II or III) 3) Diabetes Mellitus (DM) Type II with CKD (Stage II or III) and hypertension This study is designed to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of DM199.
STUDY DESIGN	This is an open-label, Phase II, multi-center study evaluating DM199 in approximately 30 (thirty) Participants per cohort. Participants will be enrolled in a parallel assignment to one of the following doses for each cohort: Dose 1: DM199 2.0 µg/kg SC 2x week for 95 days Dose 2: DM199 5.0 µg/kg SC 2x week for 95 days **Cohort I** African Americans with CKD (Stage II or III), hypertension, and non-diabetic **Cohort II** Participants with an IgA nephropathy diagnosis and CKD (Stage II or III)

	Cohort III Participants with DM (Type II), hypertension and CKD (Stage II or III) There will be approximately 30 evaluable Participants per cohort that complete the majority of assessments through day 39. Screening may be performed up to 21 days prior to enrollment in the study. Day 4 (dose 2) Participants may be required to return to the site if an AE (symptomatic orthostatic hypotension (OH)) occurred on Day 1 where the second dose will be administered and evaluated for symptomatic OH (this decision will be made by the PI). Should a second AE occur (symptomatic OH) the Participant will have Dose 3 administered at home with nursing staff where OH will be evaluated. Should a third AE occur (symptomatic OH), the PI will review the clinical findings and determine if additional nursing oversight is required or if the Participant should be withdrawn from the study. Participants will receive a SC dose 2 x week and will return to the site monthly along with outpatient visits 2 x week throughout the study to asses safety and tolerability throughout the study. Blood and urine samples for the DM199 PK profile will be collected pre dose, 4 hours post study administration, weekly though week 4, then monthly until the end of the dosing and 4 time points after dosing is complete.
OBJECTIVE	The primary objectives of this study are to evaluate the safety, efficacy, tolerability, PD, and PK profile of DM199 in Participants with CKD in cohort I African Americans, hypertensive, and non-diabetic, cohort II IgA nephropathy or cohort III Diabetic (Type II) and hypertensive. Additionally, all African Americans in cohorts I and III will be tested for APOL1 gene and sickle cell trait. Participants will be administered DM199 with one of two doses 2x week: DM199 2.0 µg/kg SC 2x week for 95 days DM199 5.0 µg/kg SC 2x week for 95 days
PRIMARY ENDPOINTS	1. Safety as assessed by incidence, severity, and causality of adverse events (AEs) 2. Kidney function will be assessed by: • eGFR using CKD EPI • Urine albumin creatine ratio (UACR) • Blood pressure (vitals) 3. Tolerability as assessed by incidence and severity of AEs 4. PK profile of DM199, assessed in plasma 5. DM199 in urine concentrations of KLK1 in pre- and post-study drug administration. (The assay to be used cannot differentiate between DM199 and KLK1 in human urine.)

SECONDARY ENDPOINTS	1. Plasma pharmacodynamic biomarkers: • TNF R1 • C-reactive protein (CRP) • Matrix metalloproteainase-9 (MMP-9) • Vascular endothelial growth factor (VEGF) • Cystatin C • Prostaglandin E2 • Prostacyclin 2. Urine pharmacodynamic biomarkers: • Kim 1 • NGAL
EXPLORATORY ENDPOINTS	1. Blood glucose 2. Electrocardiogram (ECG) 3. APOL1 gene cohort I and African Americans in cohort III only (test for both alleles) 4. Sickle cell trait cohort I and African Americans in cohort III only 5. IgA biomarkers cohort II only • Serum IgG • Plasma IgA • Plasma BAFF • Plasma APRIL • Anti Gd IgA
SAMPLE SIZE & SAMPLE SIZE DETERMINATION	No formal sample size calculation was performed. A total of approximately 90 Participants will be enrolled with 30 evaluable Participants per cohort that complete Day 39. A sample size of 30 Participants per cohort is considered adequate to evaluate the study endpoints. **Cohort I** African American with hypertension, non-diabetic, CKD (Stage II or III) **Cohort II** IgA nephropathy CKD (Stage II or III) **Cohort III** DM (Type II) with CKD (Stage II or III) and hypertension Any early withdrawal or loss of follow-up Participants who did not complete Day 39 visit may be replaced, to ensure 30 evaluable Participants per cohort.
INCLUSION CRITERIA	**Cohort I** 1. African American 2. Hypertension as defined by the American Heart Association for Stage I hypertension where systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥ 80 mmHg[1] or on medication for treatment of hypertension.

	Cohort II 3. IgA nephropathy confirmed by medical history with biopsy (Must have had biopsy within last 8 years prior to screening for study) **Cohort III** 4. DM (Type II) with hypertension where systolic BP ≥130 mmHg or diastolic BP ≥ 80 mmHg[1] or on medication for treatment of hypertension. 5. Hemoglobin A1c ≥ 7% at screening **All Cohorts** 6. Participant is willing and able to provide informed consent for study participation 7. Participant male or female ≥ 18 years of age 8. Participant has CKD as defined by using CKD EPI for Stage II 60 to <90 mL/min/1.73 m^2 or Stage III 30 to <60 mL/min/1.73 m^2 (may repeat x2 at screen)[2] 9. UACR >150 mg/g and <5000 mg/g at screening 10. Participant is clinically stable with respect to underlying renal impairment as assessed by the Investigator's medical evaluation *NOTE: This includes medical and surgical history, as well as a complete physical examination including vital signs, ECG, and laboratory test results. Repeat assessments (up to 3) are permitted for any laboratory, ECG, or vital sign parameter required for enrollment.* 11. Participant has a body mass index (BMI) between 18 to 48 kg/m^2 (inclusive)
EXCLUSION CRITERIA	1. Participant has positive drug test for drugs of abuse and/or positive alcohol breath test at screening and Day 1 *NOTE: Participants should be enrolled only after passing the urine drug screen and alcohol breath test. Any positive drug screen for prescription medication is allowed. (Rx Meds i.e. Opioids and Narcotics are acceptable)* 2. Participant has a current diagnosis and/or is taking medication or diet control for diabetes (cohort I and II only) 3. Participant has an A1c > 7% at screening (cohort I and II only) 4. Participant received corticosteroid therapy within last 3 months 5. Participant is unable or unwilling to comply with protocol requirements, including assessments, tests, and follow-up visits

	6. Participant has a history of significant allergic diathesis such as urticaria, angioedema, or anaphylaxis 7. Participant has been previously diagnosed with kidney disease other than for hypertension, IgA or DM (Type II) 8. Participant has hypotension as defined by systolic blood pressure ≤ 90 mmHg and diastolic blood pressure ≤ 60 mmHg at screen 9. ACEi or GLP-1 medication prescribed for and taken by Participant (must not be taking for 5 half-lives prior to study drug administration and for 10 days post study drug administration) 10. Participant has a current malignancy or active malignancy ≤ 2 years prior to enrollment except basal cell or squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy and ≥ 6 months have elapsed since the procedure 11. Participant has an active infection at the time of enrollment, and/or a history of clinically significant acute bacterial, viral, or fungal systemic infections that required systemic treatment with a completed therapy in the last 7 days prior to enrollment 12. Participant has known medical history of alpha 1-antitrypsin deficiency (α1-antitrypsin deficiency) 13. Participant is pregnant or nursing or is planning a pregnancy during the study period 14. Participant is male or female of childbearing potential, is participating in sexual activity that could lead to pregnancy and is unable or unwilling to practice medically effective contraception during the study *NOTE: Participants should agree to use two reliable methods of contraception (e.g., double-barrier condom plus diaphragm, condom or diaphragm plus a stable dose of hormonal contraception) throughout the study period.* 15. Participant has received any investigational drug or device within 14 days (or 5 half-lives, whichever is longer) prior to study drug administration starting on Day 1 *NOTE: Participants should agree not to participate in any other study while participating in this trial.* 16. Participant has renal artery stenosis as determined at screen with medical history 17. Participant received a kidney transplant

	18. Participant does not have adequate venous access for blood sampling 19. Participant has any other medical condition which, in the opinion of the Investigator, will make participation medically unsafe or interfere with the study results 20. Participant has any other clinically significant abnormalities in laboratory test results at screening that would, in the opinion of the Investigator, increase the Participant's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data *Note: Tests that are acceptable to be outside of normal limits due to CKD: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin within 2 × upper limit of normal (ULN)* 21. Participant has any significant arrhythmia or conduction abnormality, which in the opinion of the Investigators and Medical Monitor may interfere with the safety of the Participant *Note: Up to three repeat ECGs are allowed for eligibility determination*

1 INTRODUCTION

1.1 BACKGROUND

DM199 is a recombinant form of the endogenous human tissue kallikrein protein (KLK1) and is being developed as an subcutaneous injectable protein drug to treat CKD and ischemic diseases like acute ischemic stroke (AIS). KLK1 isolated from porcine pancreas has been approved for use in Japan, China and Korea to treat numerous vascular diseases including chronic kidney disease, hypertension and retinopathy. DiaMedica believes that millions of patients have been treated with porcine KLK1 marketed by companies including Bayer (Kallidinogenase), Sanwa Kagaku Kenkyusho Co., Ltd (Carnaculin®) and ChangZhou Qianhong Bio-Pharma Co., Ltd (Kallidinogenase). DiaMedica has completed enzymatic studies comparing DM199 to porcine KLK1 that demonstrated similar KLK1 enzymatic activity profiles. The kallikrein-kinin system (KKS) triggers a cascade of events, including the regulated release of active bradykinin in endothelial cells. This system increases nitric oxide and prostacyclin to improve capillary blood flow and reduce fibrosis and inflammation To date DM199 has been administered safely to over 200 healthy, diabetics and stroke research subjects in Europe, Australia, and the United States.

CKD is characterized by a gradual loss of kidney function resulting from decreased filtration efficiency. The primary treatment for CKD is the strict control of blood pressure with angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEi) therapy. However, these treatments are not kidney specific and can result in poorly tolerated side effects (e.g., hypotension, hyperkalemia, and cough). DM199 is intended to be used as an adjunct to these treatment regimens. The treatment for IgA and DM Type II are disease specific and do not improve kidney function.

The primary biological function of tissue KLK1 is the cleavage of low molecular weight kininogen (LMWK) to produce kinins, like bradykinin (BK), that bind to and activate the bradykinin 1 (BK1R) and 2 receptor (BK2R). Evidence also suggests KLK1 may directly exert physiological effects on the BK receptors. Published reports indicate BK2R agonism and/or exogenous KLK1 treatment can reduce plasma levels of C-reactive protein (a well-known marker of inflammation).

Downstream mechanisms of BK receptor binding of kinins include blood glucose uptake, glycogen synthesis, blood pressure regulation, angiogenesis, anti-oxidative stress, and vasodilation.[3] Similarly, kallidinogenase (porcine derived KLK1 [pKLK1]) is an approved drug used to treat clinical populations diagnosed with diabetic nephropathy (DN; a form of CKD) in China. Numerous clinical trials published in China have shown positive effects of pKLK1, including decreases in urinary albuminuria excretion, cystatin C as well as significant improvements in markers of renal health including blood urea nitrogen (BUN), serum creatinine, creatinine clearance, and improved renal hemodynamics.

For more information see the Investigator's Brochure (IB).

1.2 SUMMARY OF NONCLINICAL STUDIES

DM199 has shown beneficial activity in multiple nonclinical models of disease including rat models of T2D, mouse models of T1D, and amyloid toxin-induced neurodegeneration *in vitro*. DM199 also prevents neuronal death in culture models for hypoxia and ischemia.

Good Laboratory Practice (GLP) toxicology studies demonstrated that DM199 is safe and well tolerated at doses 20-fold higher than expected human therapeutic doses following 28-days of SC repeated administration in Sprague Dawley rats and cynomolgus monkeys. Based on the results of the 28-day studies, the no-observed-adverse-effect level (NOAEL) was 3600 µg/kg/day and 1440 µg/kg/day in rats and cynomolgus monkeys, respectively. The doses of 2ug/kg and 5ug/kg in humans for this Phase II protocol are well below this dose. Additional information regarding the nonclinical evaluation of DM199 can be found in the IB.

1.3 SUMMARY OF CLINICAL STUDIES

DM199 has been tested for safety, tolerability, and PK in four separate clinical trials. First, in the Netherlands, DM199 was administered by SC injection in a Phase 1/2 placebo-controlled clinical trial including 50 healthy volunteers and 48 T2D subjects. The maximum tolerated dose (MTD) was determined to be 30 µg/kg. At that dose and higher doses (50 µg/kg), a majority of study Participants experienced modest decreases in systolic and diastolic blood pressure and postural orthostatic hypotension. It was also noted in some subjects at 25.0 µg/kg, only moderate to mild AEs were noted in a portion of the subjects. Chronic 28-day dosing of 3.0 and 15.0 µg/kg given every 72 hours to subjects with T2D was generally safe and well-tolerated for the duration of the study.

1) In the Phase 1/2 study following single SC doses of DM199 in healthy subjects, systemic exposure for DM199 was shown to be dose proportional. Total body clearance (CL/F) was low at approximately 7 mL/hr/kg, and volume of distribution (V_z/F) was notably larger than human plasma volume. Mean terminal elimination phase half-life ($t_{1/2}$) estimates ranged from 50 to 64 hours. Following repeat SC dosing of DM199 once every three days (at 3.0 and 15.0 µg/kg), modest accumulation was observed and increases in exposure were dose proportional. Median time to reach maximum plasma concentration (t_{max}) was 12 hours for both dose levels. Mean CL/F was low and the observed V_z/F was again larger than human plasma volume. The corresponding mean apparent $t_{1/2}$ estimates were similar to Day 1 values at approximately 50 hours.
2) DM199 was also tested in a two-part Phase 1b bridging study, a single center clinical trial in Australia with 36 healthy volunteers. The first part investigated the safety, tolerability, and PK in four different doses (0.25, 0.50, 0.75 and 1.0 µg/kg) of intravenous (IV) administration. The second part compared the safety, tolerability, and PK profile of a single IV (0.75 µg/kg) dose and a single SC (3.0 µg/kg) dose. Again, the drug was safe and well tolerated in both parts of the study. The PK profile following a 30-minute IV infusion showed peak plasma concentrations around 30-minutes post-dose and declined

exponentially after the infusion was finished. The peak concentration following SC dosing was more gradual and the elimination or absorption was longer.

3) DM199 was tested in a Phase Ib study in the United States. *A Multi-Center Open-label Investigation to Assess the Pharmacokinetics, Safety and Tolerability of DM199 in Patients with Diabetes Mellitus and Chronic Kidney Disease*. The single dose study assigned Participants to one of the following doses 3.0 µg/kg, 5.0 µg/kg or 8.0 µg/kg with no safety or tolerability issues, and no SAEs observed.
4) DM199 was tested in a randomized, multi-center phase 2 study in Australia. Participants with acute ischemic stroke were randomized 1:1 to receive placebo or DM199 administered by a single intravenous dose followed by eight subsequent doses. Results demonstrated that DM199 was safe and well tolerated. The Pharmacodynamic data correlated with the DM199 Mechanism of Action activity and differentiated DM199 from placebo.

1.4 RATIONALE

To support the development of DM199 as a treatment for CKD, DiaMedica Therapeutics Inc. intends to conduct a Phase II study.

DM199 is hypothesized to improve kidney function by restoring and stimulating the kallikrein-kinin system (KKS), restoring KLK1 level to normal range which maintains a sufficient level of BK in the kidney and associated vasculature. BK has well known activity as a vasodilator and is a primary pathway for the beneficial effect of ACEi in CKD. ACEi are also known to increase renal blood flow after acute administration to humans. Since DM199 is expected to stimulate the same pathway, we anticipate that DM199 will also acutely increase renal blood flow.

This study is designed to investigate the efficacy and safety, PD and PK of DM199 in Participants with CKD (Stage II or III) in cohort I: African Americans, hypertensive, and non-diabetic, cohort II: IgA nephropathy or cohort III: diabetic and hypertension.

The tissue kallikrein (KLK1) system is important for maintaining kidney homeostasis, and KLK1 levels are hypothesized to be reduced in at least some patients with kidney disease and hypertension.[4-8] Observational studies have noted lower KLK1 levels in hypertensive patients when compared to normotensive controls, and epidemiological studies have demonstrated an inverse relationship between KLK1 levels and blood pressure.[9-11] Alterations in KLK1 levels have been associated with specific genetic polymorphisms in both Chinese and African American populations with hypertension.[12-13] This suggests that variability within the KLK1 gene may account for at least some types of hypertension among groups, supporting the rationale for clinical trials of KLK1 replenishment therapy.

The kallikrein system and measurable KLK1 has been demonstrated to be altered in hypertensive subjects. Observational studies have noted lower KLK1 levels in hypertensive patients when compared to controls and epidemiological studies have demonstrated an inverse relationship

between KLK1 levels and blood pressure.[9-11] These alterations have been associated with specific genetic polymorphisms in both Chinese and African American populations with hypertension.[12-13] Specifically the African Americans appear to have lower KLK1 levels and renal blood flow. This suggests that genetic variability may account for differing rates of hypertension among groups and would allow for targeted therapy.

The APOL1 gene has been well documented to be associated with hypertension in African American patients with hypertension, which may correlate with altered KLK1 levels. This protocol will recruit African American hypertensive patients as they are at high risk for progression of chronic kidney disease. By assessing enrolled subjects for APOL1 polymorphisms, and measuring KLK1 levels, we will be able to assess the correlation between the two. This will permit the planning of future studies for DM199.

IgA nephropathy is caused by formation of inappropriate IgA-based immune complexes that trigger inflammation and glomerular damage. KLK1 replenishment therapy may have a combined mechanism of action for treating IgA nephropathy. The well-understood triggering of the kallikrein-kinin system by KLK1 is hypothesized to maintain proper blood flow and reduce local inflammatory responses in the kidney (see above). At the same time, KLK1 is also known to play a critical role in modulating autoimmunity.[14] In fact preclinical studies have shown that DM199 treatment increased the level of T-regulatory cells in a mouse model of autoimmune diabetes.[15] These two complementary mechanisms represent a compelling rationale for testing the effect of DM199 treatment in patients with IgA nephropathy.

2 STUDY DESIGN

This is a Phase II, multi-center, open label study to be conducted in the United States (US). This study is designed to evaluate the safety and efficacy of multiple doses of DM199. Participants will admit on Day 1 for study drug dosing and then have follow-up visits through Day 104.

Cohort I: African American Participants with CKD (Stage II or III) hypertension and non-diabetic

Cohort II: Participants with IgA nephropathy diagnosis and CKD (Stage II or III)

Cohort III: Participants with DM (Type II), hypertension and CKD (Stage II or III)

For all cohorts, enrolled Participants will receive an initial dose of DM199 on Day 1 proceeded by 104 days of follow-up. Any early withdrawal or lost to follow-up Participants who did not complete day 39 visit may be replaced for a minimum of 30 evaluable subjects. Replaced subjects will assume the same study drug dose assignment of the Participant they are replacing.

2.1 OBJECTIVE

The primary objectives of this study are to evaluate the safety, efficacy, tolerability, PD, and PK profile of DM199 in Participants with CKD in cohort I African Americans, hypertensive, and non-diabetic, cohort II IgA nephropathy or cohort III Diabetic (Type II) and hypertensive.

Additionally, all African Americans in cohorts I and III will be tested for the APOL1 gene and sickle cell trait.

2.2 ENDPOINTS

2.2.1 Primary Endpoints

1. Safety as assessed by incidence, severity and causality of AEs
2. Kidney function assessed by:
    a. eGFR using CKD EPI
    b. Urine albumin creatinine ratio
    c. Blood pressure (vitals)
3. Tolerability as assessed by incidence and severity of AEs
4. PK profile of DM199, assessed in plasma
5. DM199 in urine concentrations of KLK1 in pre- and post-study drug administration. (The assay to be used cannot differentiate between DM199 and KLK1 in human urine.)

2.2.2 Secondary Endpoints

1. Plasma PD biomarkers:
    a. TNF R1
    b. C-reactive protein (CRP)
    c. Matrix metalloproteainase-9 (MMP-9)
    d. Vascular endothelial growth factor (VEGF)
    e. Cystatin C
    f. Prostaglandin E2
    g. Prostacyclin
2. Urine PD biomarkers:
    a. Kidney injury molecule-1 (Kim 1)
    b. Neutrophil gelatinase-associated lipocalin (NGAL)

2.2.3 Exploratory Endpoints

1. Blood glucose
2. ECG
3. APOL1 gene cohort I and African Americans in cohort III only (test for both alleles)
4. Sickle cell trait cohort I and African Americans in cohort III only
5. IgA biomarkers
    a. Serum IgG
    b. Plasma IgA

c. Plasma BAFF
d. Plasma APRIL
e. Anti Gd IgA

2.3 NUMBER OF PARTICIPANTS

Approximately 90 evaluable Participants will be enrolled in cohorts I, II and III (cohort I: n=30, cohort II: n=30 and cohort III: n=30). Any early withdrawal or lost to follow-up Participants who did not complete day 39 visit will be replaced. Replaced Participants will assume the same study drug dosing assignment of the Participant they are replacing. Participants may be enrolled at approximately ten sites in the United States.

2.4 STUDY DURATION

The duration of each individual's participation in the study will consist of a screening period of 1-21 days (rescreening is allowed), in-patient day for study drug administration, and 104 days of follow-up totalling 125 days from the time of consent to completion of all study activities. It is anticipated it will take up to 2 months to obtain Institutional Review Board/Ethics Committee (IRB/EC) approval and execute Clinical Trial Agreements. It is estimated that approximately ten months will be needed to recruit the total number of study Participants from all sites.

3 STUDY POPULATION

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or Participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

3.1 INCLUSION CRITERIA

In order to qualify for enrollment in this study, each Participant must meet the following inclusion criteria:

Cohort I

1. African American
2. Hypertension as defined by the American Heart Association for Stage I hypertension where systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥ 80 mmHg or on medication for treatment of hypertension

Cohort II

3. IgA nephropathy confirmed by medical history with biopsy
(Must have had biopsy within last 8 years prior to screening for study)

Cohort III

4. DM (Type II) with hypertension where systolic BP ≥130 mmHg or diastolic BP ≥ 80 mmHg or on medication for treatment of hypertension
5. Hemoglobin A1c ≥ 7% at screening

All Cohorts

6. Participant is willing and able to provide informed consent for study participation
7. Participant male or female is ≥ 18 years of age
8. Participant has CKD as defined by using CKD EPI for Stage II 60 to <90 mL/min/1.73 m^2 or Stage III 30 to < 60 mL/min/1.73 m^2 (may repeat x2 at screen)
9. UACR >150 mg/g and <5000 mg/g at screening
10. Participant is clinically stable with respect to underlying renal impairment as assessed by the Investigator's medical evaluation

NOTE: This includes medical and surgical history, as well as a complete physical examination including vital signs, ECG, and laboratory test results. Repeat assessments (up to 3) are permitted for any laboratory, ECG, or vital sign parameter required for enrollment.

11. Participant has a body mass index (BMI) between 18 to 48 kg/m^2 (inclusive)

3.2 EXCLUSION CRITERIA

Participants meeting any of the following exclusion criteria are not eligible for study enrollment:

1. Participant has positive drug test for drugs of abuse and/or positive alcohol breath test at screening and Day 1

NOTE: Participants should be enrolled only after passing the urine drug screen and alcohol breath test. Any positive drug screen for prescription medication is allowed. (Rx Meds i.e. Opioids and Narcotics are acceptable)

2. Participant has a current diagnosis and or is taking medication or diet control for diabetes (cohort I and II only)
3. Participant has an A1c >7% at screening (cohort I and II only)
4. Received corticosteroid therapy within last 3 months
5. Participant is unable or unwilling to comply with protocol requirements, including assessments, tests, and follow-up visits
6. Participant has a history of significant allergic diathesis such as urticaria, angioedema, or anaphylaxis
7. Participant has been previously diagnosed with kidney disease other than for hypertension, IgA or DM (Type II)
8. Participant has hypotension as defined by systolic blood pressure ≤ 90 mmHg and diastolic blood pressure ≤ 60 mmHg at screen

9. ACEi or GLP-1 medication prescribed for and taken by Participant (must not be taking for 5 half-lives prior to study drug administration and for 10 days post study drug administration)
10. Participant has a current malignancy or active malignancy ≤ 2 years prior to enrollment except basal cell or squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy and ≥ 6 months have elapsed since the procedure
11. Participant has an active infection at the time of enrollment, and/or a history of clinically significant acute bacterial, viral, or fungal systemic infections that required systemic treatment completed therapy in the last 7 days prior to enrollment
12. Participant has known medical history of alpha 1-antitrypsin deficiency (α1-antitrypsin deficiency)
13. Participant is pregnant or nursing or is planning a pregnancy during the study period
14. Participant is male or female of childbearing potential, is participating in sexual activity that could lead to pregnancy and is unable or unwilling to practice medically effective contraception during the study

NOTE: Participants should agree to use two reliable methods of contraception (e.g., double-barrier condom plus diaphragm, condom or diaphragm plus a stable dose of hormonal contraception) throughout the study period.

15. Participant has received any investigational drug or device within 14 days (or 5 half-lives, whichever is longer) prior to study drug administration starting on Day 1

NOTE: Participants should agree not to participate in any other study while participating in this trial.

16. Participant has renal artery stenosis as determined at screen with medical history
17. Participant received a kidney transplant
18. Participant does not have adequate venous access for blood sampling
19. Participant has any other medical condition which, in the opinion of the Investigator, will make participation medically unsafe or interfere with the study results
20. Participant has any other clinically significant abnormalities in laboratory test results at screening that would, in the opinion of the Investigator, increase the Participant's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data

Note: Tests that are acceptable to be outside of normal limits due to CKD: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin within 2 × upper limit of normal (ULN)

21. Participant has any significant arrhythmia or conduction abnormality, which in the opinion of the Investigators and Medical Monitor may interfere with the safety of the Participant

Note: Up to three repeat ECG's are allowed for eligibility determination

4 STUDY DRUG ADMINISTRATION

4.1 STUDY DRUG (DM199)

Active substance	DM199
Activity	Recombinant form of the endogenous serine protease protein, human tissue kallikrein-1 (rhKLK-1)
Indication	Chronic Kidney Disease and African American with hypertension and non-diabetic, Chronic Kidney Disease and IgA nephropathy or DM (Type II) with Chronic Kidney Disease and hypertension
Strength	500 µg/mL in a 2 mL glass vial, 1 mL fill volume
Dose	Dose 1: 2.0 µg/kg SC
	Dose 2: 5.0 µg/kg SC
Duration	104 days with biweekly SC injections through Day 95
Dosage form	SC injection
Manufacturer	Catalent

4.2 SELECTION OF DOSES IN THE STUDY

The doses selected in the current study were found to be safe and well tolerated in three previous clinical trials evaluating DM199. Specifically, the 3.0 µg/kg, 5.0 µg/kg and 8.0 µg/kg doses were safe and well tolerated in patients with T2D and T1D. Based on the initial PK results from the Phase Ib study administering 3.0 µg/kg or 5.0 µg/kg or 8.0 µg/kg doses with a half-life of approximately 72 hours supports the doses of 2.0 µg/kg and 5.0 µg/kg for this study. Nonclinical toxicology studies with DM199 doses showing significantly higher exposure levels than that in the human showed no toxicological effects following chronic administration. Each single dose will be administered via SC injection in the abdomen with rotation of injection site. In the Phase 1b bridging study, SC injections were found to result in more consistent and longer PK levels than IV administration.

The drug concentration for DM199 has been increased from 350 µg /ml to 500 µg /ml to reduce the volume of drug to be administered subcutaneously, as the weights are seen to be greater in CKD population.

4.3 CONDITIONS OF STUDY DRUG STORAGE

Pharmacy: The DM199 drug product is supplied in vials containing 1 mL of 500 µg/mL DM199 in phosphate buffered saline and is to be stored at -80°C. Study drug (DM199) must be stored in a temperature controlled, secure area to prevent unauthorized access or use (FDA 21 CFR, Part 312, Subpart D).

Clinic Site / Nursing: Participant specific prefilled syringes received from the pharmacy will be stored at 2-8°C. The Investigator is responsible for preventing use of the study drug for non-investigational purposes.

4.4 STUDY DRUG ADMINISTRATION

The appropriate dose of DM199 will be calculated using the screening body weight (kg) and then drawn up in a syringe per the instructions in the study Pharmacy Manual. If the Participant's weight changes by more than 10kg from the previous month then the appropriate dose must be recalculated and used for future doses. DM199 drug preparation for administration will be done using sterile aseptic technique. Prior to administration, the solution in the vial will be carefully inspected visually for particulate matter and discoloration. Following good pharmacy practice, the solution is clear (colorless) and if visible opaque particles, discoloration (other than colorless) or other foreign particulates are observed, the product will not be used.

SC injection should be on the lower abdomen excluding the area two inches around the navel. If the condition of the skin prevents lower abdominal injection (e.g. successive SC injections for a condition unrelated to the study), alternative injection sites include the sides of the arms or the lateral side of the thighs. Multiple injections may be required to deliver the total required dose and all of these injections should be administered subcutaneously in the lower abdomen successively with rotation of injection site. Different sites of the lower abdomen may be chosen to administer multiple injections to avoid previous injection site location.

4.5 PROHIBITED THERAPIES

ACEi or GLP-1 medication for 5 half-lives prior to study drug administration and for 10 days post study drug administration.

4.6 CONTROL OF DRUG SUPPLY

The Sponsor will control the availability of the study drug by shipping drug supplies only to qualified study Investigators who have or are pending Institutional Review Board/Ethics Committee (IRB/EC) approval to begin the clinical study. Drug supplies are not transferrable between Investigators unless prior written approval is obtained from the Sponsor.

Pharmacy: All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by DiaMedica Therapeutics Inc., the pharmacy must not destroy any unused, used, or partially used DM199 vials. The pharmacy must maintain an accurate

record of the drug supply, shipment, and drug, dispensed with initials and enrollment number with date and time. Accountability will be reviewed by the monitor during site visits and at the completion of the trial. The pharmacy will provide a copy of the accountability log to the monitor as requested and will return or destroy any unused drug supplies as instructed by the Sponsor.

Clinic Site / Nursing: All drug supplies are to be used only for this protocol and not for any other purpose. Accountability log will be reviewed by the monitor during site visits and at the completion of the trial. The site / nursing will provide a copy of the accountability log to the monitor as requested and will return or destroy any unused prefilled DM199 syringes as instructed by the Sponsor.

5 STUDY PROCEDURES

Table 1: Schedule of Assessments

Assessment / Study Day	Screening (-21 to Day 1)	Day 1 Pre- Dose	Day 1 Dose	Day 1, 2 Hour	Day 1, 4 Hour	Day 4	Week 2 (Day 8/11)	Week 3 (Day 15/18)	Week 5 (Day 29/32)	Week 6 (Day 36/39)	Week 7 (Day 43/46)	Week 9 (Day 57/60)	Week 10 (Day 64/67)	Week 11 (Day 71/74)	Week 13 (Day 85/88)	Weeks 4, 8 ,12, 14 (In Clinic)[1]	Week 15, 16[10]	Early Withdrawal[2]	Window (Day 1 Only)
Informed consent	X																		
Medical history/ demographics	X																		
Inclusion/exclusion criteria	X	X																	
Drug of abuse (urine)	X	X																	
Alcohol breath screen	X	X																	
HIV, HBsAg, anti-HCV[3]	X																		
Urine pregnancy test[4]	X	X														X		X	
Sequential assignment[5]		X																	
Previous and concomitant medication	X	X			X	X	2x	2x	2x	2x	2x	2x	2x	2x	2x	X		X	
Physical examination	X	X			X											X		X	1 Hour
Weight, height, and BMI calculation[6]	X	X														X		X	
Orthostatic BP[7]	X	X			X	X*	X*												1 Hour
Vital signs[8]	X	X		X	X	X	2x	2x	2x	2x	2x	2x	2x	2x	2x	X*		X	30 Min

Study Day Assessment	Screening (-21 to Day 1)	Day 1 Pre- Dose	Day 1 Dose	Day 1, 2 Hour	Day 1, 4 Hour	Day 4	Week 2 (Day 8/11)	Week 3 (Day 15/18)	Week 5 (Day 29/32)	Week 6 (Day 36/39)	Week 7 (Day 43/46)	Week 9 (Day 57/60)	Week 10 (Day 64/67)	Week 11 (Day 71/74)	Week 13 (Day 85/88)	Weeks 4, 8 ,12, 14 (In Clinic)[1]	Week 15, 16[10]	Early Withdrawal[2]	Window (Day 1 Only)
Blood Pressure						X*	2x	2x	2x	2x	2x	2x	2x	2x	2x	X*		X	
12-lead ECG	X	X														X		X	
Hematology Labs	X	X														X		X	
Urinalysis	X	X														X		X	
Other Labs	X[11]	X														X		X	
Serology	X																		
eGFR/UACR	X	X					X			X			X			X	X[12]	X	
Urine KLK/Plasma DM199		X		X	X		X	X								X	X	X	Blood- 15 Min Urine- 1 Hour
DM199 SC Dose[9]			X			X	2x	2x	2x	2x	2x	2x	2x	2x	2x	X*			
Adverse Event			X	X	X	X	2x	2x	2x	2x	2x	2x	2x	2x	2x	X	X	X	

1. On weeks 4, 8, and 12, one visit must be done inside the clinic. For week 14 the clinic day should be on day 95. On home visits of these weeks, the following assessments are to be performed: vitals, dosing, blood pressure. These assessments are marked with an asterisk (*)
2. For any early Participant withdrawal, every effort should be made to complete an early withdrawal visit. Withdrawal visit must be completed in clinic
3. Participants with positive HepC screening may be enrolled if LFT show normal liver function
4. For women of childbearing potential only. A negative test must be confirmed prior to dose administration and monthy throughout the study
5. A Participant must meet all inclusion criteria and none of the exclusion criteria prior to sequential assignment
6. Weight, height, and BMI calculation required prior to dose administration. Subsequent height measurements not required, however, updated weights and BMI calculation required on each clinic visit for the remainder of the study. Use screening weight for Day 1 and unless <10kg monthly change, no change in dose
7. Orthostatic blood pressure is to be taken at screen, pre-dose, and four hours post-dose. If the Participant has symptomatic orthostatic hypotension on Day 1, they must return to the clinic for Day 4 and be tested again. If they are symptomatic on Day 4, a nurse must perform orthostatic blood pressure at the home visit on Day 8. If symptomatic orthostatic hypotension persists, it is to the discretion of the PI whether the Participant will continue in the study. These days are marked with an asterisk (*)
8. Vitals include heart rate, breathing rate, and oral body temperature
9. Dosing is recommended to be done within 6 hours of original dose time for duration of the study

10. Visits completed at home on Days 99, 100, 102 and 104
11. Only labs drawn at screening: A1c, APOL1 and Sickle cell trait
12. Only collected on Day 104

5.1 INFORMED CONSENT

The informed consent and documents must contain all the information required by FDA 21 CFR, Part 50.25, ICH E6 Guidance for Good Clinical Practice (GCP), and any additional elements required by local regulations. An informed consent template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB/EC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the Informed Consent Form (ICF) is revised during the course of the study, all active Participants must sign the revised (most current) form if required by the IRB/EC.

Prior to screen and enrolling in the study, potential Participants must be fully informed of the nature of the study, details of study procedures, anticipated benefits, and potential risks of study participation as required by applicable law. Before screen and enrolling in the study or performing any study-specific procedures (including screening and baseline tests), provide the Participant with a copy of the most current ICF and verbally review its content, allowing adequate time for questions. All information pertinent to the clinical study shall be provided in writing and in non-technical language that is understandable to the Participant. Once the Participant has read and understands the ICF, he/she will indicate his/her willingness to participate in the study by signing and dating the ICF. The ICF must also be signed and dated by the person obtaining informed consent. A copy of the signed informed consent will be given to the Participant. The original consent documents will be retained in the Investigator Study File. The case history for each individual Participant will include documentation that informed consent was obtained prior to participation in the study (FDA 21 CFR, Part 312.62).

5.2 ELIGIBILITY SCREENING

After informed consent has been obtained, determine if the Participant meets all inclusion criteria and none of the exclusion criteria prior to successful study drug administration (Enrollment).

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize patient safety, scientific integrity of the study, or regulatory acceptability. Therefore, adherence to the criteria as specified in the protocol is essential. All inclusion and exclusion criteria will be assessed during the screening period (Day -21-Day 1) unless otherwise specified within the individual criterion.

Participants will complete screening, testing and assessments in accordance with the requirements specified in **Table 1 Schedule of Assessments**, including medical history/demographics and screens for drug of abuse (urine), alcohol (breath), HIV, and Hepatitis B and C. All eligibility screening must occur between Screening Day -21 and Day 1 prior to study drug administration. Rescreening is allowed if informed consent is reobtained and all required screening assessments are reconfirmed.

5.3 CONTRACEPTION

Participants participating in sexual activity that could lead to a pregnancy must use medically acceptable contraceptive measures to prevent a pregnancy. All women of childbearing potential (defined as sexually mature women who have had menses within the preceding 12 months and have not undergone hysterectomy, bilateral oophorectomy, etc.) must have a negative pregnancy test performed at screening.

Women of childbearing potential must agree not to attempt to become pregnant or undergo in vitro fertilization. If participating in sexual activity that could lead to pregnancy, women must use two reliable methods of contraception simultaneously while receiving protocol-specified medication and during the study follow-up period. Male heterosexual Participants engaging in sexual activity must agree to use two reliable methods of contraception simultaneously while receiving protocol-specified medication and during the study follow-up period if their partner is of childbearing potential.

A combination of two of the following methods must be used:

- Condoms (male or female)
- Diaphragm or cervical cap
- Intrauterine device
- Stable hormonal-based contraception

Women who are not of reproductive potential (who have been postmenopausal for more than 12 consecutive months or have undergone hysterectomy, bilateral oophorectomy) are not required to use contraception.

5.4 URINE PREGNANCY TEST

A urine pregnancy test is required to confirm eligibility at screening and prior to dosing on Day 1 for any woman of child bearing potential (refer to **Section 5.3 Contraception**). To ensure pregnancy has not occurred during the study, a urine pregnancy test will be performed during monthly site visits and at the end of the study on Day 104 or early withdrawal for any woman of childbearing potential.

5.5 METHOD OF ASSIGNING PARTICIPANTS TO STUDY DRUG GROUPS

Upon completion of the screening and signed informed consent, Participants in each cohort will be assigned to a dosing group of DM199 (2.0 or 5.0 µg/kg) and considered enrolled in the trial once initial dosing is complete. The first Participant will receive 2.0 µg/kg and the next Participant will receive 5.0 µg/kg. The pattern will repeat until all dosing groups have a minimum of 30 Participants that reached the Day 39 visit. Replaced Participants will assume the same study drug assignment of the Participant they are replacing. Participants and replacement Participants will be assigned unique ID numbers from DiaMedica.

5.6 PREVIOUS AND CONCOMITANT MEDICATION

Use of all prior medications (within 30 days) will be recorded at screening, updated on Day 1, and each subsequent visit day until the end of study on Day 104 or early withdrawal.

The minimum requirement is: the drug name (generic name), dose, route, indication and the dates of administration (start and stop) are to be recorded for the previous 30 days. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter (OTC) medications. Any changes in prior or concomitant medications will also be recorded in the Participant's eCRF. Changes in CKD-related medication are acceptable and must be recorded.

Any concomitant medication related to their diagnosis or deemed necessary for the well-being of the Participant during the study may be given at the discretion of the Investigator. The Investigator is responsible for ensuring that details regarding concomitant medication use are recorded in the eCRF. For each concomitant medication administered after Day 1 dosing, the following details will be documented and recorded in the Participant's eCRF: drug name (generic name), dose, route, indication, and the dates of administration (start and stop).

ACEi or GLP-1 medication for 5 half-lives prior to study drug administration and for 10 days post-study drug administration is prohibited.

5.7 PHYSICAL EXAMINATION

Physical examinations will be performed at the timepoints presented in **Table 1 Schedule of Assessments**. The exam will include, at a minimum, general appearance and assessment of the following systems: skin, head, ears, eyes, throat, respiratory system, cardiovascular system, gastrointestinal system, neurologic system, blood and lymphatic systems, and the musculoskeletal system. A licensed physician or qualified designee will conduct the examinations.

Symptom-directed physical examinations will be performed as appropriate for Participants experiencing AEs.

Abnormal findings will be classified as clinically significant (CS) or non-clinically significant (NCS) by the Investigator or qualified designee. Any clinically significant abnormal findings should be reported as AEs.

5.8 BODY WEIGHT AND HEIGHT

Body weight, height, and updated weight and BMI calculations will be obtained with Participants in scrubs (change out of street clothes) prior to study drug administration, monthly and on Day 95 or early withdrawal. Body height (centimeters/inches) and weight (kilograms/pounds) will be measured to the nearest tenth, and BMI will be calculated (example: BMI [kg/m^2] = body weight [kg] / height^2 [m^2]). Body weight at screening will be used to determine the DM199 dose on Day 1.

5.9 VITAL SIGNS

Vital sign measurements including heart rate, respiratory rate, and oral body temperature will be performed at the timepoints specified in **Table 1 Schedule of Assessments**. Participants will remain at rest for a minimum of 5 minutes before vital sign measurements are obtained. A confirmatory repeat vital sign measurement may be performed at the discretion of the Investigator.

5.10 BLOOD PRESSURE

Both systolic and diastolic blood pressure measurements will be taken. Orthostatic (sitting and standing) blood pressure will be performed at screening, Day 1 (pre-dose and 4 hours post-dose). If a Participant has an AE for symptomatic orthostatic hypotension on Day 1, on Day 4 a repeat orthostatic blood pressure needs to be obtained 4 hours post SC dose. If symptomatic orthostatic hypotension occurs also on Day 4, then a repeat measurement needs to be repeated at Day 8, 4 hours post SC dose. All other blood pressure assessments will be taken while Participant is seated for at least 5 minutes. See **Table 1: Schedule of Assessments** for details.

Orthostatic blood pressure should be measured in the following order:

- Have the Participant sit down for 5 minutes.
- Measure and record blood pressure and pulse rate.
- Have the Participant stand for 1 minute (stand by Participant for safety).
- Measure and record blood pressure and pulse rate at 1-minute post-sitting measurement.
- Have the patient remain standing for 3 minutes (stand by Participant for safety).
- Measure and record blood pressure and pulse rate at 3 minutes post-sitting measurement.

Note: A symptomatic drop in blood pressure of > 20 mm Hg, or in diastolic blood pressure of >10 mm Hg, or experiencing lightheadedness or dizziness is considered abnormal and should be captured as an adverse event.

5.11 ELECTROCARDIOGRAM

The 12-lead electrocardiograms (ECGs) will be obtained after the Participant has been resting in a supine position for approximately 5 minutes. ECGs must occur at screening, pre-dose, and during monthly site visits or early withdrawal. See **Table 1: Schedule of Assessments** for details.

For all Participants, ECGs will be reviewed, signed, and dated by the Investigator or a qualified designee. The ECGs will be classified as being one of three categories: normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). Any clinically significant worsening changes from baseline ECG will be reported as AEs. The Investigator (or a qualified observer) will interpret the ECG and record the results including the following

parameters: rhythm, heart rate, RR interval, PR interval, QT interval, QRS interval, and QTCF. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

All abnormal rhythms will be reviewed by the Investigator for the presence of rhythms of potential clinical concern. The Investigator should utilize medical judgment in the reporting of AEs and serious adverse events (SAEs) as well as determination of additional cardiac work-up. A printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

5.12 CKD-EPI CREATININE EQUATION

The following equation will be used to calculate the GFR for study inclusion and follow-up:

$GFR=141X \min(Scr/\kappa,1)^{\alpha} X \max(Scr/\kappa, 1)^{-1.209} X 0.993^{Age} X 1.018$ [if female] X 1.159 [if black]

κ=0.7 if female

κ=0.9 if male

α =-0.329 if female

α = -0.411 if male

min=the minimum of Scr/κ or 1

max=the maximum of Scr/κ or 1

Scr=serum creatinine (mg/dL)

5.13 LABORATORY ASSESSMENTS

5.13.1 Clinical Laboratory

All serum and urine samples will be collected and sent to a central laboratory for analysis. See **Table 1: Schedule of Assessments** for more details.

In the event of unexplained or unexpected clinical laboratory test values, the test(s) will be repeated at each subsequent study visit until results return to baseline and/or values are deemed acceptable by the Investigator (or medically qualified designee) and the Sponsor's medical monitor (or his/her designated representative), or an adequate explanation for the abnormality is found. The central laboratory will clearly mark all laboratory test values that are outside the normal range, and the Investigator will indicate which of these are clinically significant. Clinically significant laboratory test results should then be recorded as AEs and the relationship to the study drug will be indicated (refer to **Section 6 Safety Oversight**).

Table 2: Clinical Laboratory Parameters

Hematology	**Hematology**	**Urinalysis**
Alanine aminotransferase	White blood cell count	pH
Alkaline phosphatase	with differential (total and %):	Specific gravity
Aspartate aminotransferase	Neutrophils	Protein
Bilirubin Total and Direct	Lymphocytes	Glucose
Blood urea nitrogen	Monocytes	Ketones
Calcium	Eosinophils	Bilirubin
Chloride	Basophils	Blood
CO_2	Aldosterone	Nitrite
Creatinine	Renin	Urobilinogen
Glucose		Microscopic examination (if
Phosphorous		positive blood, nitrite,
Potassium	**Kidney**	leukocyte esterase, or protein)
Sodium	eGFR	Creatinine
Hematocrit	UACR	Albumin
Hemoglobin		
Red blood cell count		
Quantitative platelet count		

Other Tests	**Serology**	**Drug Screen**
Antibodies (DM199)	Antigen/antibody (HIV screen)	Alcohol test –Breathalyzer
TNF1	HbsAg (Hepatitis B screen)	Urine drug screen:
Hypertensive meds	Anti-HCV (Hepatitis C screen)	Cocaine
C-reactive protein (CRP)		Amphetamines
Cystatin C		Barbiturates
MMP-9		Benzodiazepines
Prostaglandin E2		Opiates
Prostacyclin		Methadone
NGAL		Oxycodone
Kim1		Methamphetamines
VEGF		
Troponin T		
Treg CD4/CD8		
NT pro BNP		
Hemoglobin A1c (screen only)		
APOL-1 (cohort I and African American in cohort III screen only)		
Sickle cell trait (cohort I and African American in cohort III screen only)		
Serum IgG (cohort II only)		
Plasma IgA (cohort II only)		
Plasma BAFF (cohort II only)		
Plasma APRIL (cohort II only)		
Anti Gd-IgA (cohort II only)		

5.14 STUDY DRUG ADMINISTRATION

In both cohorts a SC dose of DM199 (2.0 or 5.0 µg/kg) will be administered on Day 1 (preferably prior to 12pm). Subsequent doses will be given on Day 4 and twice weekly with 3 days between dose 1 and 2 per week (i.e. Sunday/Wednesday, Monday/Thursday, Tuesday/Friday, Wednesday/Saturday). Follow-up doses should be administered within 6 hours of the initial dose time on Day 1. Refer to the Pharmacy Manual for information on proper storage, stability, dosing assignment, dose, and administration of study drug.

5.15 ADVERSE EVENT MONITORING

AE/SAE collection will occur from time of study drug administration to end of study or Participant withdrawal. AEs will be captured during all study visits or between visits as reported by the Participant. Refer to **Section 6 Safety Oversight** for further information.

5.16 PARTICIPANT WITHDRAWAL

Participation in the study is strictly voluntary. A Participant has the right to withdraw from the study at any time for any reason.

Early withdrawals are defined as enrolled Participants who discontinue participation prior to study completion on Day 104. Every effort should be made to complete an Early Withdrawal Visit for a Participant that withdraws from the study prior to completing all study requirements. Refer to **Table 1 Schedule of Assessments** for a description of testing that should occur during the Early Withdrawal Visit. The reasons for early withdrawal will be recorded on the End of Study Electronic Case Report Form (eCRF) and in the final clinical study report. No additional safety assessments or testing will be required if a Participant voluntarily withdraws before receiving the study drug.

The Participant can also be withdrawn from the study by the Investigator for the following reasons:

1. Does no longer meet the protocol inclusion or exclusion criteria
2. The need to take medication which may interfere with study assessments
3. Reasons related to the Participant's safety (AE/SAE) or integrity of the study data
4. Noncompliance with the protocol
5. Difficulty obtaining blood samples
6. Lost to follow-up
7. Pregnancy

   Note: The Participant will be encouraged to remain available for follow-up medical monitoring. Refer to **Section 6.3.7 Pregnancy Reporting**.

8. The Investigator will also withdraw a Participant at the discretion of the Sponsor or if DiaMedica Therapeutics Inc. terminates the study.

The Sponsor will be notified as soon as possible of any early withdrawals before Day 39, so replacement Participants can be enrolled and assigned study drug dose.

Participants who fail to return for required study visits will be contacted by the site in an attempt to have them comply with the protocol. The follow up will consist of two (2) documented phone calls followed by a registered letter before a Participant is considered lost to follow-up.

6 SAFETY OVERSIGHT

Participant safety will be closely monitored throughout the study. Safety oversight will be managed by a Medical Monitor as described in the Safety Management Plan. The entire study may be stopped by DiaMedica Therapeutics Inc. for safety reasons at the recommendation of the Medical Monitor or at any other time.

6.1 DEFINITIONS

6.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (FDA 21 CFR 312.32).

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either severity or frequency after exposure to the study drug.

Adverse Events (AEs) will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A pre-existing disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or social admissions)

6.1.2 Suspected Adverse Reaction (SAR)

An SAR is defined as a subset of all AEs for which there is a reasonable possibility that the drug caused the AE. “Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. SAR implies less certainty about causality than adverse reaction, which means any adverse event caused by a drug (FDA 21 CFR 312.32).

6.1.3 Serious Adverse Event (SAE)/Serious Suspected Adverse Reaction (SSAR)

An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes:

- Death
- Life-threatening adverse event

  Note: An AE or SAR is considered life-threatening if its occurrence places the Participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the Participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA 21 CFR 312.32). Examples of such events include:

- Allergic bronchospasm requiring intensive study drug in an emergency room or at home;
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization; and
- Development of drug dependency or drug abuse.

6.1.4 Unexpected Adverse Event/Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed (FDA 21 CFR 312.32).

6.1.5 Serious Unexpected Suspected Adverse Reaction (SUSAR)

A SUSAR is a suspected adverse reaction that is both serious and unexpected (i.e., an event that meets the definition of a suspected adverse reaction, serious, and unexpected).

6.2 EVALUATION OF ADVERSE EVENTS

6.2.1 Assessment of Severity

AEs and other symptoms will be graded according to the adapted FDA Guidance 2007 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

The Investigator or medically qualified designee will assess severity for each AE reported during the study. The assessment will be based on the Investigator's (or medically qualified designees)

clinical judgment. The severity should be assigned to one of the categories outlined in **Table 3: Toxicity Grading**.

Table 3: Toxicity Grading

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

If an AE worsens in severity, it should be updated in the Adverse Event eCRF to reflect the new grading. If an AE gets milder (less severe), the most severe grading should remain in the AE eCRF until the Participant is recovered and the AE is resolved.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

6.2.2 Local (Injection Site) Adverse Event Intensity

Intensity of the following local injection site AEs should be assessed as described in

Table 4: Grading of Local (Injection Site) Adverse Event Intensity adapted from the FDA guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Table 4: Grading of Local (Injection Site) Adverse Event Intensity

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.2.3 Assessment of Causality

The Investigator or medically qualified designee is obligated to assess the relationship between study drug and the occurrence of each AE. The Investigator or medically qualified designee will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator or medically qualified designee will also consult the Investigator's Brochure in the determination of his/her assessment.

The Investigator will provide the assessment of causality utilizing one of four possible categories: Unrelated, Unlikely, Possible, and Probable.

- **Unrelated:** Clearly and incontrovertibly due to an underlying or concurrent illness or effect of a concomitant therapy and is not related to the study drug does not meet criteria listed under unlikely, possible, or probable. Events that occur prior to dosing will be classified as unrelated.
- **Unlikely:** Does not follow a reasonable temporal relationship from administration. May have been produced by the Participant's medical condition, environmental factors, or other therapies administered.
- **Possible:** Follows a reasonable temporal relationship from administration. May have been produced by the Participant's medical condition, environmental factors, or other therapies administered.

- **Probable:** Clear-cut temporal relationship with improvement on cessation of the study drug. Follows a known pattern of response to the study drug.

6.3 REPORTING OF ADVERSE EVENTS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study drug.

Changes in health or new symptoms occurring during the screening period will be recorded as medical history. All AEs and SAEs will be recorded from study drug administration until study withdrawal (study drug-emergent events). AEs and SAEs related to study participation (e.g., protocol-required assessment) will be recorded from study drug administration. All AEs must be recorded irrespective of whether they are considered related to study drug.

AEs meeting serious criteria MUST be reported within 5 working days to the Sponsor or designee. Prompt notification of SAEs by the Investigator is essential so that the Sponsor may comply with its global regulatory obligations.

When an AE occurs, it is the responsibility of the Investigator to review all documentation relative to the event, including, but not limited to, progress notes, laboratory, and diagnostic reports. The Investigator will then ensure that all relevant information regarding an AE is expediently recorded in accordance with the eCRF guidelines. Investigators should be mindful of expedited reporting requirements for SAEs (refer to **Section 6.3.2 Expedited Reporting of SAEs**). The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, when available, the diagnosis should be reported as the AE and not the individual signs/symptoms. All AEs will be recorded on the AE eCRF and will be followed to adequate resolution.

6.3.1 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the Investigator (or medically qualified designee) at the site as clinically significant or result in clinical sequelae will be recorded as AEs if they meet the definition of an AE (refer to **Section 6.1.1 Adverse Event (AE)**). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

6.3.2 Expedited Reporting of SAEs

Once an Investigator becomes aware that a SAE has occurred in a study Participant, she/he will report the information in EDC within five (5) working days. If the Investigator does not have all

information regarding the SAE, he/she will not wait to receive additional information before reporting the event but rather will update the AE eCRF when additional information is received.

The Investigator or medically qualified designee will always provide an assessment of causality at the time of the initial report as described in **Section 6.2.3 Assessment of Causality**. The Investigator or medically qualified designee may change his/her opinion of causality considering follow-up information and amend the AE eCRF accordingly. The causality assessment is one of the criteria used when determining global regulatory reporting requirements.

Any event that in the opinion of the Investigator may be of immediate or potential concern for the Participant's health or well-being will be reported to the Sponsor's Medical Monitor emergency contact. The Sponsor will provide a list of project contacts for SAE reporting.

6.3.3 Serious Adverse Event Reports to the IRB/EC

The Investigator or designee will promptly report all SAEs to the IRB/EC per their requirements.

6.3.4 Sponsor Expedited Safety Reporting Requirements

The Sponsor must notify FDA and all Investigators of any suspected adverse reaction that is both serious and unexpected (i.e., SUSAR), as soon as possible, but no later than 15 calendar days after initial receipt of the information.

The Sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than seven (7) calendar days after the Sponsor's initial receipt of the information (FDA 21 CFR 312.32 Part C).

6.3.5 Adverse Event Follow-up

After the initial AE report, the investigator is required to proactively follow each Participant and provide further information to the Sponsor on the Participant's condition as deemed appropriate. All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the Participant is lost to follow-up. Once resolved, the appropriate AE eCRF page will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. In the event of a fatal outcome in an SAE, the Investigator will attempt to obtain postmortem findings, including histopathology and provide all additional information in the AE eCRF.

6.3.6 Post-study Adverse Events

A post-study AE is defined as any event that occurs outside of the AE reporting period defined in Investigators are not obligated to actively seek AEs in former study Participants. However, if the Investigator learns of any SAE, including death, at any time after a Participant has been discharged from the study, and he/she considers the event reasonably related to the study drug, the Investigator will promptly notify the Sponsor.

6.3.7 Pregnancy Reporting

Pregnancy is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy reporting form. To ensure Participant safety, each pregnancy should be reported to DiaMedica Therapeutics Inc. within five (5) working days of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the Participant was discontinued from the study. Pregnancy complications and terminations of pregnancy will be reported as a SAE if SAE criteria are fulfilled. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the Participant has completed the study, and considered by the Investigator as possibly related to the study drug, must be promptly reported to DiaMedica Therapeutics Inc. and the IRB.

7 DATA COLLECTION AND MANAGEMENT

7.1 DATA MANAGEMENT

All required clinical data for this trial will be collected in web-based standardized electronic case report forms (eCRFs). FDA 21 CFR, Part 11 will be followed as well as other applicable legislation on the handling of electronic data. Participant personal information will be pseudonymized.

A Data Management Plan (DMP) will be developed outlining the procedures used for data review, database cleaning, and issuing and resolving data queries. Procedures for validations and data storage will also be contained within the DMP.

Investigators and designated staff will receive training on eCRF completion and use of the electronic data capture (EDC) system prior to use.

7.2 PARTICIPANT IDENTIFICATION

After obtaining oral and written informed consent by the Participant, Participants will be screened according to the inclusion and exclusion criteria. If all eligibility criteria have been met, Participants will be sequentially assigned to a study drug dosing group and enrolled into the study on Day 1 when study drug administration is complete. Enrolled Participants will be assigned a unique number that will be used to identify them on source documents, eCRFs, and reports. Those who do not meet eligibility criteria or withdraw consent for any reason before completing all screening evaluations will be considered screen failures. Screen failures will not be entered in the eCRFs.

The Investigator or authorized designee at each site will keep a screening and enrollment log of all Participants screened and enrolled to document Participant numbers and reasons for screen failures or withdrawals.

7.3 CASE REPORT FORMS

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation. All protocol-required information collected during the study must be entered by the Investigator or designated representative in the eCRF. Each eCRF should be completed as soon as possible after data are collected (within 72 Hours). An explanation should be given for all missing data.

The completed eCRFs must be reviewed and signed by the Investigator per the Data Management Plan (DMP).

7.4 SOURCE DOCUMENTATION

Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled Participant. No source documentation will be recorded directly on the eCRF. Source documents may include, but are not limited to, admission/discharge records, lab and imaging reports, demographic records, and site visit records.

The Investigator will permit study-related monitoring, audits, IRB/EC review and regulatory authority inspections (refer to **Section 11. Study Monitoring and Auditing**) by allowing direct access to all study source data and documents (ICH E6 Guidance for GCP, section 6.10). In case of electronic source data, access must be allowed or dated printouts must be available prior to the monitoring visits and any audits or inspections. Printouts will not be limited to study drug data but will include all available data related to the identified Participant(s).

7.4.1 Source Documentation Reporting Requirements

It may be necessary from time to time to submit source documents to the Sponsor or designee to allow for timely safety discussions (i.e. expedited reporting of SAEs). All source documents submitted to the Sponsor or its representatives must be de-identified according to local and federal confidentially requirements and identified by the Participant number.

8 STATISTICAL CONSIDERATIONS

The statistical and analytical plan for this study is summarized below. Further details are provided separately in the Statistical Analysis Plan (SAP).

8.1 STATISTICAL DESIGN AND SAMPLE SIZE

8.1.1 General Design

This is an open-label investigation of DM199 in Participants with CKD (3 cohorts), as detailed in **Section 2 Study Design**. The study is intended to assess efficacy, and safety with multiple doses of DM199 SC administration. Approximately thirty Participants in each cohort will be assigned

to receive one of two doses of DM199 administered by a SC injection (2.0, or 5.0 ug/kg). All the Participants in each cohort will be assigned dosing groups in a parallel enrollment strategy.

8.1.2 Sample Size Determination

Approximately 90 evaluable male and female Participants at approximately fourteen sites, as detailed above, are planned for enrollment in the study. The sample size of thirty Participants per study cohort is common and is expected to provide sufficient data to adequately assess the multi-dose primary efficacy and safety evaluations in Participants with CKD. These results are also expected to provide an informative comparison with data that has previously been collected with DM199 in healthy volunteers and Participants with Type 2 diabetes.

8.1.3 Analysis Populations

There are two analysis populations: Safety and modified Intention-to-Treat (mITT).

8.1.3.1 Safety Population

All Participants who receive any amount of study drug will be included in the Safety Population. Participants will be summarized according to the dose they were assigned to receive. Demographic, baseline characteristics, urine concentrations of KLK1, and safety analysis will be conducted using the Safety Population.

8.1.3.2 Modified Intention-to-Treat (mITT) Population

All Participants who receive the study drug and who have the majority of assessments through Day 39 post-dose study assessment, will be included in the mITT population. Participants will be summarized according to the dose they were assigned to receive. Study analysis will be conducted using the mITT population as described in the SAP.

8.1.4 Interim Analyses

Monthly interim analyses may be performed for this study for each cohort.

8.2 STUDY ENDPOINTS

8.2.1 Primary Endpoints

1. Safety as assessed by incidence, severity, and causality of AEs
2. Kidney function assessed by:
    - eGFR using CKD EPI
    - Urine albumin creatinine ratio
    - Blood pressure (vitals)
3. Tolerability as assessed by incidence and severity of AEs

4. PK profile of DM199, assessed in plasma
5. DM199 in urine concentration of KLK1 pre- and post-study drug administration. (The assay to be used cannot differentiate between DM199 and KLK1 in human urine.)

Any additional analyses will be described in the SAP, as applicable.

8.2.2 Secondary Endpoints

1. Plasma pharmacodynamic biomarkers:
    a. TNF R1
    b. C-reactive protein (CRP)
    c. Matrix metalloproteainase-9 (MMP-9)
    d. Vascular endothelial growth factor (VEGF)
    e. Cystatin C
    f. PGE2
    g. Prostacyclin
2. Urine pharmacodynamic biomarkers
    a. Kim 1
    b. NGAL

8.2.3 Exploratory Endpoints

a. Blood glucose
b. ECG
c. APOL-1 gene cohort I and African Americans in cohort III only (test for both alleles)
d. Sickle cell trait cohort I and African Americans in cohort III only
e. IgA biomarkers cohort II only
    - Serum IgG
    - Plasma IgA
    - Plasma BAFF
    - Plasma APRIL
    - Anti Gd IgA

Any additional analyses will be described in the SAP, as applicable.

8.3 STATISTICAL METHODS

Data will be handled and processed according to the Sponsor representative's Standard Operating Procedures (SOPs), which are written based on the principles of ICH E6 Guidance for GCP.

All data collected on the eCRFs and results of central laboratory analysis will be presented in the data listings. All summaries will present the data by study drug groups and overall (total Participants), as applicable.

Statistical methods will be primarily descriptive in nature. Each cohort will be summarized separately.

The following statistical approaches will be taken:

- Continuous variables: Descriptive statistics will include the number of non-missing values (N), mean, standard deviation (SD), median, minimum, and maximum. Additionally, for urine concentrations of KLK1, the coefficient of variation (CV%), geometric mean and geometric coefficient of variation (geo CV%) values may also be presented.
- Categorical variables: Descriptive statistics will include frequency counts and percentages per category.
- Imputation: All data will be listed in data listings. Missing data will not be imputed but will be analyzed as missing. The handling and presentation of urine concentrations of KLK1 below the limit of quantification (BLQ) will be discussed in the Statistical Analysis Plan.
- Confidence intervals (CIs): CIs will be two-sided and will use 95% confidence levels unless specified otherwise.
- Baseline: Baseline values will be defined as the last non-missing observation for each Participant prior to the administration of the study drug.

Additional statistical analyses other than those described in this section may be performed if deemed appropriate in the SAP.

8.3.1 Baseline Summaries

Demographic and baseline characteristics will be summarized descriptively by study cohort and study drug dose.

8.3.2 Safety

Safety endpoints will be analyzed. Any significant difference will be identified with proper statistical analysis.

8.3.2.1 Adverse Events/Serious Adverse Events

An overall summary of the number and percentage of Participants in each cohort and study drug dose will be presented, as will an overall summary of the number of events in each cohort. The number and percentage of Participants reporting AEs in each cohort above will be summarized by study drug group according to the system organ class (SOC) and preferred term (PT) assigned to the event using the Medical Dictionary for Regulatory Activities (MedDRA).

All AE data will be listed for all Participants. Both the Investigator's verbatim terms and the MedDRA preferred terms will be listed for each Participant. Listings will also include the SAEs, start and end time and date of AEs, relationship to study drug, severity, and action taken for the AEs. A summary of deaths (for all deaths, AE outcome, not AE term, is death) will be provided by number and percentage of Participants by cohort and study drug dose.

8.3.2.2 Physical Examination Findings

Physical examination data for all time points assessed will be summarized, including Investigator assessment of clinical significance for abnormal findings. Shift tables from baseline to Day 95 or early withdrawal may also be generated, as applicable.

8.3.2.3 Vital Signs

Changes from baseline in vital signs at each scheduled timepoint will be summarized by study cohort and study drug dose for the Safety Analysis Population using descriptive statistics (n, mean, SD, median, minimum, and maximum). The baseline value is defined as the last value observed prior to administration of the study drug. The change from baseline is defined as the post-baseline value minus the baseline value. There will not be any imputation for missing values. All vital sign data will be listed individually by each Participant based on the Safety Analysis Population.

8.3.2.4 Clinical Laboratory

All laboratory data will be summarized by cohort and study drug dose at each scheduled timepoint using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The baseline value is the last value observed prior to administration of study drug and any information taken after administration of study drug is regarded as post-baseline information. The change-from-baseline variables will be calculated as the post-baseline value minus the value at baseline. Change from baseline on continuous data will be summarized using descriptive statistics at each scheduled time point by study drug group. For categorical data, change from baseline will be summarized using frequency and proportion at each scheduled timepoint by study drug group.

Individual data listings of laboratory results will be presented for each Participant. Values outside of the laboratory's reference range (i.e., those with low or high values) will be flagged in the laboratory listings.

8.3.2.5 12-lead ECG

A listing will be provided for Investigator-identified ECG abnormalities from safety ECGs. Overall evaluation of safety ECGs will be summarized by study cohort and study drug dose using frequency counts and percentage of Participants as normal or abnormal, and the relevance of the abnormality will be summarized by CS or NCS.

In addition, a summary shift table comparing baseline interpretation (normal, abnormal-NCS, abnormal-CS) to the Investigator interpretation at Days 1 and 95 or early withdrawal will also be presented.

8.3.3 Pharmacokinetic (PK) Parameters

Blood samples will be collected at 13 different times as detailed in **Table 1** to allow for a complete PK profile characterization and to provide sufficient data for complete non-compartmental analysis. (see **Table 1: Schedule of Assessments)**. A validated ELISA assay will be used to measure DM199 concentration in plasma samples and the results will be analyzed by validated software tools (e.g. Phoenix WinNonlin v. 6.3). For each study Participant the following PK parameters will be calculated from the concentration time-course data: AUC_{0-t} (area under the curve from time 0 (time of dosing) to the last time point measurable), AUC_{0-inf} (AUC from time point 0 to extrapolated to infinity), C_{max} (maximum observed concentration), AUC_{0-24} (AUC from time point 0 to 24 hour post-dose), T_{max} (the first time when C_{max} was observed), $T_{1/2,app}$ (apparent elimination half-life), CL/F, mean residence time (MRT), and V_z/f (the apparent oral volume of distribution). Both arithmetic mean geometric mean values will be used to describe the combined results from all Participants from each dose group.

8.3.4 Urine Concentrations of KLK1 Measurements

Urine concentrations of KLK1 will be analyzed using the Safety Population when a validated assay is available. Urinary KLK1 concentrations will be summarized by study drug group at the times detailed in **Table 1**.

8.3.5 Pharmacodynamic Parameters

PD endpoints will be analyzed and used to evaluate any exposure-response relationship.

PD endpoints will be summarized using descriptive statistics for each study cohort and study drug dose for all time points assessed, including change from baseline for all post-dose assessments, as applicable.

Additional exploratory analysis may be performed as necessary to further assess primary and secondary study endpoints and may include additional sub-groups as needed. The PD data may also be examined in conjunction with the urine concentration of KLK1 data for any correlations, as applicable.

9 RISK/BENEFIT ANALYSIS

9.1 POTENTIAL RISKS

Previous pre-clinical and clinical studies have shown DM199 to be generally safe and well-tolerated, with postural hypotension as a drug-related side effect demonstrated at high doses, much greater than being used in this study (refer to **Section 1.2 Summary of Nonclinical Studies** and **Section 1.3 Summary of Clinical Studies**). ACEi medications may be additive in nature with DM199 at higher doses as it relates to hypotension, but this is not expected at the doses to be administered in this study. The effects of the study drug on human pregnancy and the unborn fetus are unknown.

Refer to the IB for full study drug information including a comprehensive listing of known safety information.

9.2 ALTERNATIVE STUDY DRUGS

The primary treatment for CKD is the strict control of blood pressure with angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEi) drugs. However, these treatments are not kidney specific and as such can result in poorly tolerated side effects (e.g., hypotension, hyperkalemia, and cough). The treatment for IgA and DM Type II are disease specific and do not improve kidney function.

9.3 POTENTIAL BENEFITS

The impact of DM199 in patients with CKD is unknown, however, DM199 is hypothesized to improve kidney function by restoring and stimulating the KKS, which maintains a sufficient level of BK in the kidney and associated vasculature. BK has well-known activity as a vasodilator and is a primary pathway for the beneficial effect of ACEi in CKD. ACEi are also known to increase renal blood flow after acute administration to humans, likely related to the endogenous BK activity. Since DM199 is expected to stimulate the same pathway we anticipate that DM199 will also acutely increase renal blood flow and may improve eGFR and reduce AUCR.

As with all study drugs, the long-term results of using DM199 are not known at this time.

9.4 RISK MINIMIZATION

DM199 is being evaluated for use as intended in treating CKD in the patient populations defined herein. This protocol is specifically designed to manage and minimize risk through careful Participant selection, training of Investigators, adherence to the pre-determined assessment schedule to assess Participant clinical status, and regular clinical monitoring visits by trained and qualified Sponsor-appointed personnel.

10 RESPONSIBILITIES

10.1 SPONSOR RESPONSIBILITIES

The Sponsor of this study is DiaMedica Therapeutics Inc. A clinical project team will be developed and trained to perform the obligations of the Sponsor as required by FDA 21 CFR, Part 312, Subpart D and will adhere to DiaMedica Therapeutics Inc. internal procedures (as applicable), FDA 21 CFR, parts 11, 54, 56, 312, all other applicable regulations, and ICH E6 Guidance for GCP.

DiaMedica Therapeutics Inc. designee will be responsible for ensuring the study is conducted in accordance with the clinical study protocol and applicable federal regulations (FDA 21 CFR, Part 312, Subpart D).

- Qualifying Investigators and providing Investigators with appropriate information for study conduct
- Ensuring proper monitoring of study progress by monitors qualified by training and experience
- Securing compliance to the protocol and applicable regulations
- Providing all Investigators with an Investigator's Brochure and ensuring that the necessary regulatory agencies and participating Investigators are promptly informed of significant new findings that might affect the Participant's willingness to participate in the study or newly identified risks with respect to the study drug
- Obtaining financial disclosure information from participating Investigators prior to study commencement and a commitment from Investigators to promptly update the information if relevant changes occur during the study and for one year following study completion
- Maintaining adequate study records and permitting review of these records in the event of a regulatory inspection
- Verifying proper oversight of the receipt, shipping, and disposition of all study drug throughout the study period

10.2 INVESTIGATOR RESPONSIBILITIES

Investigators are responsible for ensuring the investigation is conducted in accordance with the protocol and applicable federal regulations (FDA 21 CFR, Part 312, Subpart D). Investigators are also responsible for:

- Obtaining initial IRB/EC review prior to commencing the clinical study as required by FDA 21 CFR, Part 56
- Protecting the safety, rights, and welfare of study Participants
- Obtaining informed consent of study Participants prior to any study related activities
- Ensuring study drug is only provided to qualified study Participants enrolled in the trial and is securely stored in a locked, limited access area
- Record retention as defined in federal regulations FDA 21 CFR, Part 312.62 (a) and (b), and ICH E6 Guidance for GCP, including disposition of study drug and adequate and accurate case histories
- Submitting accurate reports as defined in federal regulations FDA 21 CFR, Part 312.64, including:
  - Progress reports submitted at least annually to the IRB/EC and Sponsor or designee,
  - Safety reports (refer to **Section 6.3 Reporting of Adverse Events**),
  - Final report submitted to the IRB/EC and Sponsor or designee upon completion of the Investigator's participation in the study, and
  - Financial disclosure if any relevant changes occur during the course of the study and for one year following completion of the study (FDA 21 CFR, Part 54)

- Permit access to study records for monitoring and auditing activities (refer to **Section 11. Study Monitoring and Auditing**)
- Ensuring that all persons assisting with the trial are adequately qualified, informed about the protocol and any amendments, the study drug, and their trial-related duties and functions

11 STUDY MONITORING AND AUDITING

Monitoring activities will be conducted according to the protocol, ICH E6 Guidance for GCP, FDA 21 CFR, Part 312, and regulatory guidance relevant to this clinical study. Procedures for conducting monitoring will be documented in a Clinical Monitoring Plan.

11.1 MONITORING AND SOURCE DOCUMENT VERIFICATION

Investigators and institutions involved in the study will permit study-related monitoring by providing direct access to all study records. Periodic monitoring will be completed on site and/or by remote visit from representatives designated by DiaMedica Therapeutics Inc. who will check the eCRFs for completeness and accuracy and verify them with source documents. Visits are also intended to review site compliance, administrative records, and to confirm that all adverse events have been reported as required by the protocol. In addition to the monitoring visits, frequent communications (letter, telephone, and e-mail) by the study monitors will ensure that the investigation is conducted according to the protocol, regulatory requirements, and good clinical practice.

Study close-out will be performed by the study monitor upon closure of the study. The close-out visit will consist of reconciliation of all remaining data inconsistencies, obtaining current status determination for all unresolved adverse events, and review of administrative records. In addition, the monitor will perform final study drug reconciliation for all products received, used, shipped, or disposed of during the study.

11.2 ON-SITE AUDITS/INSPECTIONS

The Investigator should promptly notify the Sponsor and/or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

The Investigator will permit trial related audits and inspections by the IRB/EC, government regulatory agencies, and external auditors. Direct access to source documents, eCRFs, and other study documents for on-site audits or inspections must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that all Participant identifiers are removed on the copies to ensure confidentiality.

12 STUDY ADMINISTRATION

12.1 REGULATORY AND ETHICAL CONSIDERATIONS

This clinical study will be conducted in accordance with this protocol, FDA 21 CFR, parts 312, 50, 54, and 56, the Declaration of Helsinki, ICH E6 Guidance for GCP, applicable federal and local regulatory requirements, and the conditions of approval imposed by the reviewing IRB/EC.

12.2 PROTOCOL AND AMENDMENT APPROVALS

Prior to initiation of the study at the study sites, written FDA and IRB/EC approval of the protocol that is based on applicable regulations and the principles of ICH E6 Guidance for GCP will be obtained. In addition, any written information and/or advertisements to be used for Participant recruitment will be approved by the IRB/EC prior to use.

Protocol amendments will be submitted to regulatory authoritie(s) by the Sponsor or designee if required by applicable regulation (FDA 21 CFR, Part 312.30) and approved by each site IRB/EC prior to adoption at study sites.

12.3 PROTOCOL DEVIATION MANAGEMENT

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the Participant, Investigator, or site staff. All deviations will be tracked and should be reported to the IRB/EC in accordance with their reporting policy. Examples of deviations include, but are not limited to:

- Failure to obtain informed consent from Participants or legally authorized representatives before performing study-specific procedures
- Failure to adhere to study inclusion and exclusion criteria
- Failure to comply with dosing requirements, including administering study drug outside of the time frame specified in the protocol
- Use of medications that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Failure to adhere to test requirements, including testing not done, incorrect tests done, or not done within the time frame specified in the protocol
- Incorrect storage of study drug
- Failure to update the ICF when new risks become known
- Failure to obtain IRB/EC approvals for the protocol and ICF revisions

The Investigator or designee must document and explain in the Participant's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study Participants without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation or change, and the reasons for it, should be submitted to the IRB/EC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

12.4 COMPLIANCE OVERSITE AND STUDY SITE TERMINATION

The Sponsor and its designated representatives will review and monitor Investigator compliance and determine if there is a need to secure compliance based on the severity and/or trends in non-compliance to the signed agreement, protocol, applicable regulations, or any conditions of approval imposed by the reviewing IRB/EC or regulatory agency (FDA 21 CFR, Part 312.56). Depending on the severity and/or trend in non-compliance, the Investigator may receive a formal warning or retraining through a site visit or conference call.

DiaMedica Therapeutics Inc. retains the right to suspend or terminate the participation of a site and/or Investigator for any of, but not limited to, the following reasons:

- Failure to secure informed consent from Participants or legally authorized representatives
- Repeated non-compliance with the protocol, applicable regulations, or requirements set forth by the IRB/EC
- Inability to successfully implement the protocol
- Falsification of data, or any other breech of ethics or scientific principles
- Administrative decision such as low enrollment rates or enrollment targets met

Written notice will be submitted to the Investigator in advance of such suspension or termination. The Sponsor will also notify the IRB/EC and Regulatory Authorities as required by regulation. A suspended or terminated site may not be reinstated without approval of the reviewing IRB/EC and Regulatory Authorities, as required by regulation.

The study drug will be immediately returned to the Sponsor or designee, unless this action would jeopardize the rights, safety, or welfare of the Participant(s).

The Principal Investigator (PI) at any investigational site reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

12.5 PARTICIPANT CONFIDENTIALITY

All data and records generated during this study will be kept confidential in accordance with institutional and IRB/EC policies on Participant privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Information about trial Participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996

(HIPAA). Those regulations require a signed Participant authorization informing the Participant of the following:

- What protected health information (PHI) will be collected from Participants in this Trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research Participant to revoke their authorization for use of their PHI.

In the event that a Participant revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of Participant authorization.

Only the Participant number and initials will be displayed with Participant data provided to the Sponsor or designee. Participant names will not be provided. If the Participant name appears on any document (e.g., laboratory report), it must be eliminated/redacted on the copy of the document supplied to the Sponsor or designee. Study findings stored on a computer will be kept in accordance with local data protection laws. Participants will be informed that representatives of the Sponsor or its representatives, IRB/EC, or regulatory authorities may review their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

12.6 ONGOING INFORMATION FOR IRB/EC AND REGULATORY AUTHORITIES

The Sponsor must submit the following to all Investigators, the IRB/EC, and regulatory agencies:

- Information on serious or unexpected AEs from any investigational site, as required
- Expedited safety reports, in accordance with local and national regulations
- Periodic reports on the study progress (at least annually)

12.7 RECORD RETENTION

All study documents must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified (FDA 21 CRF, Part 312.62). Beyond this period, the Investigator must obtain approval in writing from the Sponsor before the destruction of any records.

The documents to be retained include but are not limited to:

- Original signed informed consent documents for all Participants
- Participant identification code list, screening log, and enrollment log

- Record of all essential communications relating to the conduct of this study between the Investigator and the IRB/EC, Sponsor or designee, Medical Monitor, Safety Review Committee, and other Investigators
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated trial-related duties, together with their roles in the study and their signatures and dates of participation
- Disposition of the study drug
- Study drug accountability records
- All other source documents (Participant medical records, hospital records, laboratory records, etc.)
- A copy of completed case report forms
- All other documents as listed in Section 8 (Essential Documents for the Conduct of a Clinical Trial) of the ICH Guidance E6: Good Clinical Practice: Consolidated Guidance

The Sponsor must be contacted if the Investigator plans to leave the investigational site to ensure that arrangements for a new Investigator or records transfer are made prior to the Investigator's departure.

All study documents will be retained by the Sponsor as defined in FDA 21 CFR, Part 312.57.

12.8 FINANCIAL DISCLOSURE

Before the start of the study, the Investigator and each Sub-Investigator will disclose to the Sponsor any proprietary or financial interests he or she may hold in the study drug or the Sponsor company as outlined in the financial disclosure form provided by the Sponsor (FDA 21 CFR, Part 54). The Investigator and each Sub-Investigator also agree to update this information in case of significant changes during the study or within one year of study completion. The Investigators and each of the Sub-Investigators also agree that, where required by law or regulation, the Sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

12.9 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are outlined in a separate agreement. The Sponsor has taken out an insurance policy covering their legal responsibility.

12.10 STUDY TERMINATION

Although DiaMedica Therapeutics Inc. has every intention of completing the study, DiaMedica Therapeutics Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last Participant completes the Day 104 assessment.

12.11 FINAL REPORT

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study report is prepared and provided to the regulatory agency as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study report in marketing applications meet the standards of ICH E3: Structure and content of clinical study reports.

Upon completion of the clinical study report, the Sponsor will provide Investigators with the full summary of the study results. Each Investigator is encouraged to share the summary results with the study Participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

12.12 PUBLICATION

No publication of the results shall take place without the express consent of DiaMedica Therapeutics Inc. Prior to submitting for any publication, presentation, use for instructional purposes or otherwise disclosing the study results generated by the sites (collectively, a "publication"), the Investigator shall provide DiaMedica Therapeutics Inc. with a copy of the proposed publication and allow DiaMedica Therapeutics Inc. a period of at least 60 days (or for abstracts, at least ten working days) to review the proposed publication. Proposed publications shall not include DiaMedica Therapeutics Inc.'s confidential information. At the request of DiaMedica Therapeutics Inc., the submission or other disclosure of a proposed publication will be delayed for a sufficient length of time to allow DiaMedica Therapeutics Inc. to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed publication. If a written contract for the conduct of the study which includes publication provisions inconsistent with the statement is executed, that contract's publication provisions shall apply rather than this statement.

13 REFERENCES

1. American Heart Association Hypertension Guidelines toolkit for HealthCare Providers. http://aha-clinical-review.ascendeventmedia.com/books/aha-high-blood-pressure-toolkit/16/ Accessed 1 August 2019.
2. Center for Drug Evaluation and Research (CDER) at the United States Food and Drug Administration. Draft Guidance for Industry: Pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labeling. http://www.fda.gov/ucm/groups/fdagov-public/@fdagovdrugs-gen/documents/document/ucm204959.pdf. Updated 22 March 2010. Accessed 28 November 2016.
3. Kakoki, M., and Smithies, O. The kallikrein-kinin system in health and in diseases of the kidney. *Kidney Int*. 2009. 75;1019–1030.
4. Pérez-Blanco, F.J., Manzanares-Olivares, L., Domínguez-Vicent, J.R., Moreno-Terribas, G., and Rodríguez-Cuartero, A. (1997). Urinary kallikrein excretion in early diabetic nephropathy. Clin. Nephrol. *47*, 64–65.

5. Naicker, S., Naidoo, S., Ramsaroop, R., Moodley, D., and Bhoola, K. (1999). Tissue kallikrein and kinins in renal disease. Immunopharmacology *44*, 183–192.
6. Chiang, W.-C., Lin, S.-L., Chen, Y.-M., Wu, K.-D., and Tsai, T.-J. (2008). Urinary kallikrein excretion is related to renal function change and inflammatory status in chronic kidney disease patients receiving angiotensin II receptor blocker treatment. Nephrology (Carlton) *13*, 198–203.
7. Yu, H., Song, Q., Freedman, B.I., Chao, J., Chao, L., Rich, S.S., and Bowden, D.W. (2002). Association of the tissue kallikrein gene promoter with ESRD and hypertension. Kidney Int. *61*, 1030–1039.
8. Azizi, M., Boutouyrie, P., Bissery, A., Agharazii, M., Verbeke, F., Stern, N., Bura-Rivière, A., Laurent, S., Alhenc-Gelas, F., and Jeunemaitre, X. (2005). Arterial and renal consequences of partial genetic deficiency in tissue kallikrein activity in humans. J. Clin. Invest. *115*, 780–787.
9. Chao, J., Bledsoe, G., Yin, H., and Chao, L. (2006). The tissue kallikrein-kinin system protects against cardiovascular and renal diseases and ischemic stroke independently of blood pressure reduction. Biol. Chem. *387*, 665–675.
10. Margolis, H.S., Geller, R., Pisano, J.J., and Sjoerdsma, A. (1971). Altered urinary kallikrein excretion in human hypertension. Lancet *2*, 1063–1065.
11. Zinner S., et al. Stability of Blood Pressure Rank and Urinary Kallikrein Concentration in Childhood: An Eight-Year Follow-Up. Circulation Vol 58, No 5, November 1978. 908-915.
12. Hua, H., Zhou, S., Liu, Y., Wang, Z., Wan, C., Li, H., Chen, C., Li, G., Zeng, C., Chen, L., et al. (2005). Relationship between the regulatory region polymorphism of human tissue kallikrein gene and essential hypertension. J Hum Hypertens *19*, 715–721.
13. Yu, H., Song, Q., Freedman, B.I., Chao, J., Chao, L., Rich, S.S., and Bowden, D.W. (2002). Association of the tissue kallikrein gene promoter with ESRD and hypertension. Kidney Int. *61*, 1030–1039.
14. Dutra, R.C. (2017). Kinin receptors: Key regulators of autoimmunity. Autoimmun Rev *16*, 192–207.
15. Maneva-Radicheva L et al. Autoimmune diabetes is suppressed by treatment with recombinant human tissue Kallikrein-1. PLoS One. 2014 Sep 26;9(9).