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Version Date: April 01, 2021

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Clinical Trial Protocol

Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Parallel Group, Single Ascending Dose Study Following Intravenous Administration of HF1K16 in Healthy Subjects to Evaluate the Safety, Tolerability and Pharmacokinetics of HF1K16

Clinical Study Protocol – HF1K16-101

Version 7.0
01 April 2021

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April 1,2021

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Investigator Signature Page

PROTOCOL TITLE: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Parallel Group, Single Ascending Dose Study Following Intravenous Administration of HF1K16 in Healthy Subjects to Evaluate the Safety, Tolerability and Pharmacokinetics of HF1K16

PROTOCOL NO: HF1K16-101

VERSION: Version 7.0

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCPs) and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: 01 APR 2021

Printed Name: GREG TRALEY

Investigator Title: PI

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Summary of Key Changes

Protocol Sections	Changes Made in Version 7.0 from Version 6.0
Synopsis and Section 9.1: Inclusion Criterion #8.	Updated Inclusion Criterion #8 from: Have clinical laboratory renal (eGFR, creatinine) and liver (AST, ALT, GGT, Total bilirubin) function within normal range (eGFR ≥90 mL/min/1.73 m3) and other clinical laboratory results within normal range or within 5% of normal range and assessed as clinically non-significant by the Investigator at screening and admission. To: Have clinical laboratory renal (eGFR, creatinine) and liver (AST, ALT, Total bilirubin) results within normal range and other clinical laboratory results within normal range or outside normal range assessed as clinically non-significant by the Investigator at screening and admission.
Table 1 Schedule of Events	Added and clarified time windows in footnotes of Schedule of Events.
Section 10.9 Meals	On the day of dosing subjects will be offered a low-fat breakfast at **approximately 30 minutes** prior to dosing to be completed **approximately 5 minutes** prior to dosing. **Subjects are not required to consume the entire meal but should complete the meal in 25 minutes or less.**
Section 13.1.4 Electrocardiograms	Added "Triplicate ECGs will be performed at approximately 1 minute apart."
Section 13.1.5 Clinical Laboratory Assessments	Clarified in section 13.1.5 that the screening period is from Day -28 to Day -1.
Protocol Sections	**Changes Made in Version 6.0 from Version 5.1**
Synopsis and Section 9.1: Inclusion Criterion #8.	Adjusted levels of total cholesterol, HDL, LDL and triglycerides in inclusion criteria to better reflect the healthy population at large. This adjustment is not expected to impact subject safety.

Protocol Sections	Changes Made in Version 5.1 from Version 5.0
Title page, synopsis	Principal Investigator changed from Dr. Frank Lee, MD to Dr. Gregory Tracey, MD.

Protocol Sections	Changes Made in Version 5.0 from Version 4.0
Synopsis, Sections 6.3, 8.1, 8.3, and 11.3 (Table 4)	Based on the FDA's comments to follow Fibonacci sequence for dose escalation, the dose escalation scheme has been updated to 3, 6, 10, and 13 mg/m^2. and provided rationale for starting dose of 3 mg/m^2,
Section 10.6	Per FDA comments, an AUC limit/cap of 16550 ng•hr/mL (i.e. escalation to the next dose should not proceed if the expected AUC will exceed 16550 ng•hr/mL). The limit is based on the mean AUC

	of male and female monkeys at the NOAEL (3 mg/kg) in the 28-day toxicity study.

Protocol Sections	**Changes Made in Version 4.0 from Version 3.0**
Synopsis, Sections 8.1, and 8.3	Based on the FDA's comments to follow Fibonacci sequence for dose escalation, the dose level for Cohort 4 has been reduced from 65 mg/m^2 to 55 mg/m^2
Synopsis and Section 9.1	Per FDA recommendation, adjusted inclusion criterion #8 from: Have clinical laboratory renal (eGFR, creatinine) and liver (AST, ALT, GGT, Total bilirubin) function within normal range (eGFR ≥ 90 mL/min/1.73 m2) and other clinical laboratory results within normal range or outside normal range assessed as clinically non-significant by the Investigator at screening and admission To: Have clinical laboratory renal (eGFR, creatinine) and liver (AST, ALT, GGT, Total bilirubin) function within normal range (eGFR ≥ 90 mL/min/1.73 m2) and other clinical laboratory results within normal range or within 5% of normal range and assessed as clinically non-significant by the Investigator at screening and admission

Protocol Sections	**Changes Made in Version 3.0 from Version 2.0**
Synopsis, Sections 8.1, and 8.3	Based on the FDA's comments to follow Fibonacci sequence for dose escalation, the dose level for Cohort 4 has been reduced from 90 mg/m^2 to 65 mg/m^2
Synopsis and Section 9.2	Per FDA recommendation to exclude subjects with QTc> 450ms. Exclusion criterion #5 updated from "Reported family history of long QTc syndrome" to "Reported family history of long QTc syndrome or a QTc of > 450 ms at screening."
Synopsis and Section 9.1	Per FDA recommendation, addition of eGFR cutoff value of ≥ 90 mL/min/1.73 m^2 to inclusion criterion #8.
Table 1: Schedule of Procedures	Per FDA recommendation triplicate ECGs are included at baseline (pre-dose) and at 1.5 h post start of infusion.

Protocol Sections	**Changes Made in Version 2.0 from Version 1.0**
Section 10.6	Based on the FDA's comments to update DLT definitions to: a. Specify that any one grade ≥ 3 AE will halt dose escalation unless the AE is clearly and incontrovertibly due to extraneous causes.

	b. Specify that any two grade ≥ 2 AEs will halt dose escalation unless the AEs are clearly and incontrovertibly due to extraneous causes. c. Grade 3 asymptomatic laboratory abnormalities that resolved to ≤ grade 1 within 3 days may be excluded from the definition of DLT.
Synopsis and Section 9.1	Updated inclusion criteria #8 based on the FDA's comments to provide details regarding renal and hepatic function. Renal function will be assessed according to laboratory results of eGFR and creatinine within normal ranges and liver function shall be assessed according laboratory results of ALT, AST, GGT, and total bilirubin within normal ranges.
Table 1 Schedule of Procedures and Section 13.1.2	Updated per FDA recommendation to monitor infusion reactions by obtaining vital signs every 15 mins for the first hour and every 30 minutes through 1-hour post infusion (2 hours post start of infusion).

2 SYNOPSIS

Name of Sponsor/Company: HighField Biopharmaceutical Corporation	
Name of Investigational Product: HF1K16	
Name of Active Ingredient: (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1- yl)nona-2,4,6,8-tetraenoic acid	
Title of Study: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential Parallel Group, Single Ascending Dose Study Following Intravenous Administration of HF1K16 in Healthy Subjects to Evaluate the Safety, Tolerability and Pharmacokinetics of HF1K16	
Study center(s): Frontage Clinical Services, Inc.	
Principal Investigator: Gregory Tracey, MD	
Studied period (years): Estimated date first subject enrolled: TBD Estimated date last subject completed: TBD	**Phase of development:** Phase 1
Objectives: **Primary:** • To evaluate the safety and tolerability of HF1K16 following single ascending doses by intravenous administration. **Secondary:** • To characterize the pharmacokinetics of HF1K16 following single ascending doses by intravenous administration.	
Methodology: This is a randomized, double-blind, placebo-controlled, dose escalation study to evaluate the safety, tolerability and pharmacokinetics (PK) of HF1K16 following single ascending dose administration by intravenous (IV) infusion in healthy adult volunteers. Up to 4 dose cohorts are planned. The HF1K16 dose level of each cohort is determined based on the collective nonclinical data of HF1K16 (pharmacology and toxicology). The starting dose of 3 mg/m^2 of HF1K16 represents about a10-fold safety margin based on a body surface area-adjusted dose at the no-observable-adverse-effect level (NOAEL) dose of 10 mg/kg [human equivalent dose (HED): 3 mg/kg] after HF1K16 was administered IV to cynomolgus monkeys once every two days for a total of 14 doses in a 28-day dosing period, and takes into consideration exposure values following oral Vesanoid at the recommended human dose of 45 mg/m^2/day. The starting dose was selected in accordance with scientific standards outlined in the Food and Drug Administration (FDA) Guidance for Industry, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (July 2005). The proposed dose levels of Cohorts 1, 2, 3 and 4 are up to 3 mg/m^2, 6 mg/m^2, 10 mg/m^2 and 13 mg/m^2, respectively.	

A total of up to 32 subjects will be evaluated with 24 subjects randomized to receive active drug and 8 subjects randomized to receive placebo in a double-blind fashion (8 subjects per each dose cohort, with 6 subjects randomized to receive active drug and 2 subjects randomized to receive placebo).

Following a screening period of up to 28 days, eligible subjects will be admitted to the Clinical Research Unit (CRU) on Day -1, one day prior to dosing, remain at the CRU for 3 overnight stays, and be discharged the morning of Day 3, approximately 48 hours post-dose.

[redacted]

Vital sign assessments will be done at screening, pre-dose and 0.5, 2, 6, 24 and 48 hours post-dose relative to the start of infusion. Clinical safety laboratory assessments will be performed at screening, on Day -1 and Day 3. A resting 12-lead electrocardiogram (ECG) will be completed at screening, Day -1, 12, 24 and 48 hours post-dose. A full physical examination will be conducted at screening, and abbreviated physical examinations will be conducted on Day -1 and Day 3. Injection site assessments will be performed prior to and 4 and 24 hours relative to the start of infusion.

A follow-up telephone call will be placed to all subjects on Day 8 (± 2 days) to collect adverse event (AE) and concomitant medication information.

Single dose escalation will not occur until review of the single dose safety and PK data from the previous dose cohort. After the starting dose of HF1K16, dose escalation decisions will be based on safety and tolerability assessments collected up to Day 8, and agreed upon by the Safety Monitoring Committee (SMC) comprised of, at least, the Investigator and the Medical Monitor from the Sponsor.

Number of subjects (planned):

Up to 32 evaluable healthy male and non-childbearing female subjects, 8 subjects (6 active, 2 placebo) per cohort for up to 4 cohorts.

Selection of Subjects:

Inclusion Criteria:

1. Capable of giving informed consent and complying with study procedures;
2. Between the ages of 18 and 55 years, inclusive;
3. Body mass index (BMI) of 18.0 to 32.0 kg/m^2 inclusive and body weight not less than 50 kg;
4. Female subjects must have a negative pregnancy test result at screening and at admission;
5. Female subjects are:
   a. Surgically sterile for at least 3 months prior to screening by one of the following means:
      - Bilateral tubal ligation
      - Bilateral salpingectomy (with or without oophorectomy)
      - Surgical hysterectomy
      - Bilateral oophorectomy (with or without hysterectomy)
   b. Postmenopausal, defined as the following:
      - Last menstrual period greater than 12 months prior to screening, and
      - Postmenopausal status confirmed by serum follicle stimulating hormone (FSH) and estradiol levels at screening;
6. Male subjects must agree to utilize a highly effective method of contraception (condom plus spermicide) during heterosexual intercourse from the time of clinic admission until 12 weeks following the end of study visit, and refrain from donating sperm for this same period;
7. Considered healthy by the Investigator, based on subject's reported medical history, full physical examination, 12-lead ECG, and vital signs;

8. Have clinical laboratory renal (eGFR, creatinine) and liver (AST, ALT, Total bilirubin) function within normal range and other clinical laboratory results within normal range or outside normal range assessed as clinically non-significant by the Investigator at screening and admission;
9. Non-smoker and has not been exposed to any products containing nicotine in the last 6 months;
10. Willing and able to adhere to study restrictions and to be confined at the Clinical Research Unit.

Exclusion Criteria:

1. Clinically significant reported history of gastrointestinal, cardiovascular, musculoskeletal, endocrine, hematologic, psychiatric, renal, hepatic, bronchopulmonary, neurologic, immunologic, lipid metabolism disorders, or drug hypersensitivity as determined by the Investigator;
2. Known or suspected malignancy;
3. Reported history of pancreatitis or gall stones;
4. Reported history of unexplained syncope, symptomatic hypotension or hypoglycemia;
5. Reported family history of long QTc syndrome or a QTc of > 450 ms at screening;
6. Reported history of chronic diarrhea, malabsorption, unexplained weight loss, food allergies or intolerance;
7. Poor venous access;
8. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) at screening;
9. Donated or lost >500 mL of blood in the previous 3 months prior to screening;
10. Taken an investigational drug or participated in a clinical trial within 30 days (or 5 half-lives) prior to first dose of study drug, whichever is longer;
11. Taken any prescription medications within 14 days or 5 half-lives (whichever is longer) of the first dose of study drug;
12. Taken any prescription or non-prescription drugs and herbal medication known to be CYP450 inducers, inhibitors, and substrates within 14 days prior to screening (See Appendix B);
13. Taken daily Vitamin A supplement within 3 months prior to screening;
14. Major surgery or hospitalization within 6 months prior to screening that in the Investigators opinion would put the subject or study conduct at risk;
15. A history of prescription drug abuse, or illicit drug use within 9 months prior to screening;
16. A history of alcohol abuse according to medical history (≥ 2 drinks per day for male and ≥ 1 drink per day for female) within 9 months prior to screening;
17. A positive screen for alcohol, drugs of abuse at screening or admission;
18. An unwillingness or inability to comply with food and beverage restrictions during study participation;
19. Use of over-the-counter (OTC) medication within 7 days, and/or herbal medications (including herbal teas, garlic extracts) within 7 days prior to first dose of study drug;
20. Have a history of allergic reactions (either spontaneous or following drug administration) to ATRA or to any of the excipients or related compounds, including vitamin A;
21. Any condition or finding that in the Investigators opinion would put the subject or study conduct at risk if the subject were to participate in the study.

Investigational product, dosage, and mode of administration:

HF1K16 is a pegylated liposome formulation of tretinoin [All-Trans Retinoic Acid (ATRA)] supplied as 2 mg/mL, 10 mL/vial. Each subject will be administered a single IV infusion of HF1K16 over a period of approximately 60 minutes.

Duration of Study:

The total duration of participation in the study for each subject is up to 38 days, including a screening period of up to 28 day.

Reference therapy:

Placebo will be sterile saline (0.9% sodium chloride) for IV infusion.

Criteria for evaluation:

Safety:

Safety assessments will include monitoring of AEs, vital signs (blood pressure, pulse rate, respiration rate, oral temperature), clinical laboratory findings (chemistry, including LDL-C, HDL-C, triglycerides, total cholesterol, AST and ALT; coagulation parameters PT/INR and aPTT; hematology and urinalysis), resting 12-lead ECGs, physical examination findings (including evaluation of skin) and injection site assessment.

Pharmacokinetics:

Pharmacokinetic analysis of the plasma concentration time data for free tretinoin and liposome encapsulated tretinoin will be performed using WinNonlin version 8.1 or higher (Certara, Princeton, NJ) and analyzed using non-compartmental methods. Actual dosing and sampling times will be used for analyses. The primary pharmacokinetics parameters of interest are: C_{max}, T_{max}, $t_{1/2}$, AUC_{last}. Additional PK parameters include AUC_{inf}, MRT, CL/F, V_zF and K_{el}.

Statistical methods and Planned Analysis:

Safety:

Adverse events will be summarized by system organ class (SOC) and preferred term (PT). A subject will only be counted once per SOC and once per PT within a treatment. Subject counts and percentages and AE counts will be presented for each treatment and totaled for all treatments. Listings will be presented by subject for all AEs.

Clinical laboratory values at each visit and change from baseline will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L).

Other safety parameters will be listed and summarized using descriptive statistics. Data from placebo-treated subjects in each cohort will be pooled for summary presentations. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of baseline-subtracted free tretinoin and liposome encapsulated tretinoin will be listed and summarized using descriptive statistics. Individual and mean free tretinoin and liposome encapsulated tretinoin concentration-time profiles will be presented graphically.

A dose proportionality regression assessment for log-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} and log-transformed dose will be analyzed using a power model: ln (PK parameter) = $\mu + \beta$ x ln(dose) for free tretinoin or liposome encapsulated tretinoin. The 90% confidence intervals (CI) around the slopes (β) from each of these regression analyses will be obtained from the model and presented. Plots of the log-PK parameter by log-dose (AUC_{0-t}, AUC_{0-inf}, and C_{max}) will be produced.

Statistical tables will be generated using SAS version 9.4 or higher. Disposition of all randomized subjects will be summarized by treatment and listed for each subject. Demographic and baseline characteristics will be listed and summarized for the safety population using descriptive statistics. Each subject's exposure to study drug will be listed. Adverse events will be coded using a standardized Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced Dictionary (March 2020 or later). Tabulations will be prepared including all AEs and all AEs by relationship and severity using Common Terminology Criteria for Adverse Events Version 5.0 [CTCAE v5]. Adverse events resulting in early termination and events meeting regulatory criteria for seriousness will also be tabulated separately. By subject listings of all safety data and concomitant medication use will be generated.
This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

Table 1: Schedule of Procedures

	Screen		Subjects Resident in Clinical Research Unit													FU Tel Call
Day	-28 to -1	-1	Day 1										2		3*	Day 8 ± 2
Hour			0	0.25	0.5	0.75	1	1.5	2	4	6	9	12	24	36	48	
Informed Consent	X																
Eligibility Assessment	X	X															
Demographics	X																
Admission to CRU	[redacted]																
Randomization																	
Medical History																	
Physical Exam[1]																	
Height, Weight, BMI																	
Weight																	
Resting 12-lead ECG[2]																	
Vital signs (BP, PR, RR, Oral Temp)																	
Clinical laboratory tests[3]																	
HIV, Hep B&C screen																	
Drug/alcohol screen																	
Pregnancy test[4]																	
FSH and estradiol[5]																	
Dose administration[6]																	
PK blood samples																	
Injection site assessment																	
AE & ConMeds																	
Discharge from CRU																	

NOTE: all timed procedures are with respect to START of study drug infusion.

AE= adverse event; BP = blood pressure; con med = concomitant medications; CRU = clinical research unit; ECG = electrocardiogram; FU = Follow-up; HIV = human immunodeficiency virus; Hep = Hepatitis; PR = pulse rate; PK = pharmacokinetics; RR = respiratory rate.

*Day 3 is the completion visit. Assessments to be performed on Day 3 prior to discharge from the CRU or at early termination; physical exam, vital sign assessments, clinical laboratory tests and ECG.

[1]A full physical exam will be conducted at screening and an abbreviated physical exam will be conducted on Day -1 and Day 3.

[2]Pre-dose and 1.5 h post infusion start ECGs will be triplicate ECGs (Triplicate ECGs will be performed approximately 1 minute apart).

[3]Clinical laboratory samples include: hematology, chemistry, coagulation parameters PT/INR/aPTT, and urinalysis.

[4]For female subjects – Serum pregnancy test at screening and urine pregnancy test at admission, both must be negative to enroll in the study.

[5]FSH and estradiol levels will be assessed in postmenopausal females to confirm status.

[6]IV infusion will occur at approximately 8:00 am, following completion of a low-fat breakfast. Infusion will over an approximately 60 minute period. Infusion stop time will have a time window of ±5 minutes.

Time windows: Vital signs and ECGs: Pre-dose: within 60 min prior dosing; post-dose to ≤ 12 h: (±15 min); ≥ 24 h: (±30 min).

PK sampling: pre-dose (-60 min), < 2 h (±5 min), 2 to <24 h (±10 min), 24, 36 and 48 h (±15 min).

Injection site assessments: pre-dose (-60 min), ≤ 24 h (±30 min).

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LIST OF TABLES

4 LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine Transaminase
APL	Acute Promyelocytic Leukemia
AST	Aspartate Transaminase
ATRA	All-Trans Retinoic Acid
aPTT	Activated Partial Thromboplastin Time
AUC	Area Under the Curve
AUC_{last}	AUC up to the last measurable concentration
AUC_{inf}	AUC from time 0 to infinity
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Total systemic clearance after oral administration
C_{max}	Maximum Plasma Concentration
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic Cell
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein - Cholesterol
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
INR	International Ratio
IRB	Institutional Review Board
IV	Intravenous
K_{el}	Apparent terminal elimination rate-constant
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LDL-C	Low Density Lipoprotein - Cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	Myeloid Derived Suppressor Cell
MRT	Mean Residence Time
NASH	Non-Alcoholic Steatohepatitis

Abbreviation or special term	Explanation
NOAEL	No Observed Adverse Effect Level
OTC	Over the Counter
PE	Physical Examination
PHI	Patient Health Information
PK	Pharmacokinetic(s)
PT	Prothrombin Time
PT	Preferred Term
RA	Retinoic Acid
RAS	Retinoic Acid Syndrome
RBC	Red Blood Cell
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
TB	Total Bilirubin
T_{max}	Time to maximum plasma concentration
$T_{1/2}$	Terminal Half-Life
ULN	Upper Limit of Normal
WHO	World Health Organization

5 INTRODUCTION

5.1 Background Information

HighField Biopharmaceutical Corporation is developing HF1K16, an investigational pegylated liposome formulation of tretinoin (All-Trans Retinoic Acid, ATRA) for injection for the induction of remission in patients with acute promyelocytic leukemia (APL) and for the treatment of solid tumors through targeting myeloid derived suppressor cells (MDSCs).

Tretinoin is a naturally occurring vitamin A metabolite that participates in many biological processes. The normal physiologic range of retinoid acid (RA) is about 3 nM. At higher concentrations (~1 μM), ATRA can induce terminal differentiation of acute promyelocytic leukemia blasts into mature granulocytes.

Vesanoid® is the capsule formulation for oral administration approved by the Food and Drug Administration (FDA) as the standard of care in combination with chemotherapy for the treatment of APL.[1] There are limitations to the current treatment regime of 25~45 mg/m^2/day (twice daily). The very short half-life of ATRA in circulation causes highly variable drug systemic exposure and a variable peak to trough concentration ratio. Importantly, the natural RA metabolic mechanism may cause up to 3-10 times reduction in C_{max} and AUC at subsequent doses compared to the first dose in some patients. Since most treatments requires twice daily administration of ATRA for 30 days and longer, and ATRA concentration correlates highly with its activity *in vitro*, such catabolism variations may lead to unsustained response and relapse. Notably, the most commonly observed and serious side effect during APL treatment is retinoic acid syndrome (RAS), which requires high doses of dexamethasone to treat while withholding ATRA to relieve symptoms. The cause of RAS is not clear but thought to be unique in APL patients with malignant promyelocytes.

In addition to the treatment of APL, ATRA and similar retinoids are also considered to have significant immune-modulating activities towards MDSCs that contribute greatly to cancer growth and progression. Preclinical efficacies of ATRA to induce MDSC differentiation into dendritic cells (DCs) and downregulate their inhibitory effects on cytotoxic T cell activities against cancer have been demonstrated. There are several ongoing clinical trials using ATRA alone or in combination with other drugs to treat cancers other than APL such as pembrolizumab and ATRA combination treatment of advanced melanoma (NCT03200847), ipilimumab and ATRA combination treatment of advanced melanoma (NCT02403778), and a Phase 1 study of tranylcypromine in combination with ATRA for adult patients with acute myelocytic leukemia and myelodysplastic syndromes (NCT02273102). In these studies, the ATRA oral dosage forms are given at 45-150 mg/m^2/day, equivalent to about 20 capsules per day, presumably because ATRA is poorly soluble and has low bioavailability per oral administration.

In order to achieve a better treatment outcome for APL patients and to facilitate studies addressing other unmet medical needs, it is highly desirable to develop a new injectable ATRA formulation with improved PK behavior, a higher therapeutic index, and more specific targeted mechanism towards MDSCs for cancer immunotherapy.

Considering ATRA is very poorly soluble and has short and variable catabolism rates, a liposome formulation of stably encapsulated ATRA is a primary candidate. The liposome technology has been developed for more than 30 years and there are already a few successful anti-cancer and anti-infection drug liposome formulations marketed worldwide. The key advantages include particle size control, drug encapsulation, and pegylation of liposomes to enable longer half-life, slower clearance, smaller volume of distribution, and accumulation of drugs in tumor tissues through the loose newly developed blood vessels.

5.2 Investigational Product

HF1K16 was developed using a proprietary drug loading process to prepare a liposome formulation containing stably encapsulated ATRA. The lipid composition is HSPC/Chol/DSPE-PEG (3:1:1 wt.) at 20 mg/mL and it is the same lipid composition as the FDA-approved liposome product DOXIL®. The recently approved liposome products ONIVYDE® and DSPC/Chol/DSPE-PEG (3:1:0.05 wt.) have a similar lipid composition.

The proposed dosage strength of HF1K16 drug product is 2 mg/mL in 10 mL per Type I glass vial.

6 PRECLINICAL AND CLINICAL DATA

6.1 Pre-Clinical Data

6.1.1 Pharmacology

In vitro and *in vivo* pharmacology studies were conducted using HF1K16 in comparison with hydroxypropyl-β-cyclodextrin-solubilized ATRA in myeloid cancer cells, mouse solid tumor models, and clinical samples isolated from cancer patients. These studies included the differentiation effect on human myeloid cancer cell lines, the differentiation and maturation effects on MDSCs from tumor-bearing mice and clinical samples, and the anti-tumor efficacy and immuno-modulation effects in 4T1 and CT26-bearing Balb/C mouse models.[2]

These pharmacology studies demonstrated that HF1K16 exerted better promotion of myeloid cell differentiation and maturation, had lower toxicity effects for mature myeloid cells and lymphocytes, inhibited tumor growth in the tumor-bearing mouse models and the anti-tumor effect was positively correlated with dose levels. Its pharmacodynamic effect is mainly based on the fact that HF1K16 can promote the maturation of MDSCs into mature dendritic cells and macrophages, thereby activating the T cell cytotoxicity and improving the anti-cancer immune responses. More prominently, using myeloid cells from blood samples or tumor tissues from clinical patients with different tumor types, the addition of HF1K16 resulted in marked phenotypic changes of MDSCs towards maturation and differentiation. The number of MDSCs was reduced, the expression of PD-L1 decreased, dendritic cell-lineage markers increased, and T cell activities improved.

6.1.2 Non-clinical Pharmacokinetics and Tissue Distribution

Non-clinical pharmacokinetics of HF1K16 were evaluated in BALB/c mice, Sprague Dawley rats, Beagle dogs and cynomolgus monkeys.[2] A tissue distribution study was conducted in CT26 tumor bearing mice to demonstrate higher AUC in solid tumor tissues compared to those in the liver, spleen, and other organs. HF1K16's PK profile was distinctively different from that of the oral tretinoin formulations. The drugs encapsulated inside liposomes were cleared more slowly and contributed to sustained drug concentrations for prolonged time duration. The multi-dose exposure variability issue that is associated with the oral route of administration was not observed.

6.1.3 Safety Pharmacology and Toxicology

A single dose of HF1K16 administered by intravenous (IV) injection to BALB/c mice at 72 mg/kg was well tolerated.[2] In an exploratory study in rats, HF1K16 was injected IV for 14 days (once a day) at doses of 5, 25 and 50 mg/kg/day, respectively. A reference control group (positive control) was administrated tretinoin orally at 50 mg/kg/day for consecutive 5 days; the dose was increased to 500 mg/kg/day (Days 6-14). Negative control groups included a solvent control group (5% glucose injection) and the vehicle control group (empty liposomes). There was no mortality/moribundity observed in the control and 5 mg/kg/day and 25 mg/kg/day groups. Moribundity/mortality was found in 2/3 of both males and females of test article group at 50 mg/kg/day HF1K16 on Day 13. The main clinical abnormalities at the high dose were thin

body, abnormalities of digestive tract (watery feces and anal staining) and abnormal skin/hair coat (hair coat rough, hair coat stained, skin exudate, crust, and severe hair loss). Decreased body weight gain or body weight loss was observed at ≥25 mg/kg/day HF1K16 and in the positive control.

The primary clinical pathology findings were decreases in red cell parameters at all doses; prolonged activated partial thromboplastin time (aPTT), increased alkaline phosphatase and globulin, and decreased total protein, albumin, and albumin/globulin ratio at ≥25 mg/kg/day. Cholesterol levels were increased in all groups receiving liposomes. Histopathology was not performed. Toxicity of the positive control was similar in nature to that at the high dose (50 mg/kg/day) of HF1K16.

In an exploratory study in cynomolgus monkeys, two animals were administrated single IV doses of HF1K16 of 1, 3, 10, 30 or 60 mg/kg (doses one week apart except for a 16-day interval between 30 and 60 mg/kg) and one animal served as a control (administered liposomes). There were no notable findings at dose levels of 1, 3, or 10 mg/kg. Following a dose of 30 mg/kg there was a transient decrease in food consumption in one animal, and decreased food consumption was noted in both treated animals with 60 mg/kg. Decreases in lymphocytes and increases in urea and creatinine were observed following doses ≥30 mg/kg, and increases in neutrophils and triglycerides were seen following doses of 60 mg/kg. All groups had increases in total cholesterol. Animals were necropsied at the end of the study (14 days after last dose). There were no significant abnormalities reported in the microscopic examination.

In a 28-day study in monkeys, animals were administered 0 (blank liposomes) 3 or 10 mg/kg HF1K16 by IV injection (once every two days for a total of 14 doses) followed by a 28-day recovery phase. All monkeys survived until their scheduled sacrifice and there were no test article-related effects on body weight, body temperature, ophthalmology, ECG/blood pressure, urinalysis, organ weights or macroscopic examinations.

Clinical observations following doses of 10 mg/kg included dry skin, desquamation, hyperemia, and skin lesion (inguinal/armpit). Slight decreases in food consumption occurred in the high dose males. Non-adverse decreases in red cell parameters (RBC, hemoglobin, hematocrit, and reticulocytes) were observed following doses of 3 mg/kg (females only) and 10 mg/kg. Cholesterol levels were increased in control and treated animals, triglycerides were increased in treated animals. At the high dose, slight increases in fibrinogen, globulin, and albumin/globulin ratio and a slight decrease in albumin were noted but were within the normal background range.

Test article-related microscopic changes in the femur of males following doses of 10 mg/kg consisted of growth plate closed, fibrosis of endosteum and physis, increased osteoblasts and osteoclasts of physis and hemorrhage (all minimal or mild in severity). Vehicle-related changes included foamy macrophage accumulation and vacuolization of vascular wall in many organs/tissues in control and treated groups. Minimal to mild reactions observed in all groups at the last injection site were considered related to mechanical damage. After the 28-day recovery phase, all test article-related or vehicle-related microscopic changes observed in the dosing phase were completely resolved. As the bone changes were fully reversible, the high dose was considered the NOAEL (AUC_{0-t} of 83,800 and 75,600 ng*h/mL in males and females, respectively).

An *in vitro* hemocompatibility study indicated HF1K16 at a concentration of 2.1 mg/mL resulted in no erythrocyte hemolysis or agglutination reaction in rabbit red blood cells.

Genotoxicity, carcinogenicity, and reproductive toxicity studies have not been conducted with HK1K16. However, data on the genotoxicity, carcinogenicity, and reproductive toxicity of tretinoin is available from the Vesanoid® package insert.[1]

6.2 Clinical Data

Tretinoin has been administered to humans as an oral formulation for the treatment of APL, and was first approved in the US as Vesanoid® in 2004.[1]

This is the first study in human in which HF1K16 is administered as in IV infusion.

6.3 Study Rationale and Calculation of Dose

HF1K16 is an investigational pegylated liposome formulation of tretinoin for injection under development for the induction of remission in patients with APL and for the treatment of solid tumors through targeting MDSCs. HF1K16 was developed as a new injectable ATRA formulation to have improved PK behavior, a higher therapeutic index, and more specific targeted mechanism towards MDSCs for cancer immunotherapy.

HF1K16 drug product is a sterile liquid injection containing small unilamellar liposomes with drug substances (ATRA) encapsulated inside the lipid bilayer.

[redacted]

6.4 Potential Clinical Risks

Potential target organs identified from the 14-day rat study and the 28-day toxicity study in monkeys with HK1K16 were skin and bone. Findings in the skin (dry skin, desquamation, hyperemia, and skin lesion in monkeys) were reversible and similar to those found following IV administration of another liposomal formulation of ATRA.[3] The bone findings (femur: growth plate closed, fibrosis of endosteum and physis, increased osteoblasts and osteoclasts of physis and hemorrhage) were found only in males at the high dose, were minimal or mild in severity, and reversible in the 28-day reversal period. The bone findings are consistent with the known effects of vitamin A on bone homeostasis.[4] Bone pain has been reported in patients with high dose vitamin A.[1] Exposure in healthy volunteers in the current study will be limited to a single dose and the anticipated exposure (by AUC) is expected to be well below the exposure obtained in monkeys following doses of 10 mg/kg (the NOAEL with AUC_{0-t} of 83,800 and 75,600 ng*h/mL in males and females, respectively).

Healthy volunteers should be monitored for any skin changes and the occurrence of bone pain.

Increased levels of cholesterol and/or triglycerides were noted in animals that received empty liposomes or HK1K16, and the increases were reversible. Hypercholesterolemia and/or hypertriglyceridemia were seen in Vesanoid®-treated patients. These parameters are easily monitored in humans.

Tretinoin has teratogenic and embryotoxic effects (fetal resorptions, a decrease in live fetuses, gross external, soft tissue and skeletal alterations) which occurred at doses similar to or less than the human dose (on a mg/m^2 basis) and may be expected to cause fetal harm when administered to a pregnant woman. As tretinoin causes teratogenic and embryotoxic effects in animals[1],only females on non-childbearing potential (surgically sterile or postmenopausal) will be enrolled in this study.

The Vesanoid® package[1] insert carries warnings for retinoic acid-APL syndrome and rapidly evolving leukocytosis. It is unknown whether HK1K16 has a potential to cause these effects.

Elevated liver function tests have been reported with Vesanoid® therapy. Similar findings were not seen in animal studies with HK1K16, but routine testing for liver function will be included in the proposed clinical trial.

Possible drug-drug interactions: Vesanoid® (tretinoin) is metabolized by the hepatic P450 system, therefore there is a potential for HF1K16 to have altered PK parameters in subjects administered concomitant medications that are inducers or inhibitors of P450. All such medications will be prohibited during this study.

6.5 Population to be Studied

Healthy male and female subjects 18 to 55 years of age will be enrolled in this study. Females must be of non-childbearing potential, defined as postmenopausal [confirmed by follicle-stimulating hormone (FSH) and estrogen levels at screening] or surgically sterile as documented by a healthcare provider.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of HF1K16 following single ascending doses by intravenous administration.

7.2 Secondary Objective

The secondary objective of this study is to characterize the pharmacokinetics of HF1K16 following single ascending doses by intravenous administration.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design

Up 32 subjects, comprised of up to 4 cohorts of 8 subjects each, will receive a single IV dose of study drug. Six of the 8 subjects in each cohort will receive HF1K16 and 2 subjects will receive placebo in a blinded manner.

Planned treatments are:

- Cohort 1: up to 3 mg/m^2 of HF1K16 or placebo
- Cohort 2: up to 6 mg/m^2 of HF1K16 or placebo
- Cohort 3: up to 10 mg/m^2 of HF1K16 or placebo
- Cohort 4: up to 13 mg/m^2 of HF1K16 or placebo

The duration of study participation for all subjects is up to approximately 38 days, including a screening period of up to 28 days.

After providing written informed consent, subjects will undergo screening for eligibility. Eligible subjects will be admitted to the Clinical Research Unit (CRU) on Day -1, one day prior to dosing, remain at the CRU for 3 overnight stays, and be discharged the morning of Day 3, approximately 48 hours post-dose. Subjects will have a follow-up telephone call on Day 8 ± 2 days to collect AE and concomitant medication information.

[redacted]

Safety assessments will include monitoring of AEs, vital signs (blood pressure, pulse rate, respiration rate, oral temperature), clinical laboratory findings, resting 12-lead ECGs, physical examination findings, including skin assessment, and injection site assessments. Vital sign assessments will be done at screening, pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 6, 24 and 48 hours post-dose relative to the start of infusion. Clinical safety laboratory assessments will be performed at screening, on Day -1 and Day 3. A resting 12-lead ECG will be completed at screening, Day -1and 12, 24 and 48 hours post-dose. A full physical examination will be conducted at screening, and abbreviated physical examinations will be conducted on Day -1 and Day 3. Injection site assessments will be performed prior to and at 4 and 24 hours relative to the start of infusion. Subjects will be discontinued in the event of any AE that may jeopardize the subject's safety and wellbeing.

Safety and tolerability data collected up to Day 8 ± 2 days for each cohort, and PK data, will be evaluated prior to proceeding to the next higher dose cohort. Administration of the next higher dose to a new cohort of subjects will be permitted only if adequate safety, and tolerability data have been demonstrated.

See Table 1 for the details and the timing and scheduling of all study procedures.

8.2 Number of Subjects

Up to 32 subjects, comprised of 8 subjects per cohort for Cohorts 1, 2, 3 and 4.

8.3 Treatment Assignment

Subjects will be assigned to one of four planned dose levels of HF1K16 or placebo to match the active product, administered via IV infusion. The planned assignments are as follows:

Table 2: Treatment Assignment

Cohort	Single Dose HF1K16	Subjects
1	up to 3 mg/m^2 x 1 dose	8 (6 active + 2 placebo)
2	up to 6 mg/m^2 x 1 dose	8 (6 active + 2 placebo)
3	up to 10 mg/m^2 x 1 dose	8 (6 active + 2 placebo)
4	up to 13 mg/m^2 x 1 dose	8 (6 active + 2 placebo)

8.4 Criteria for Study Termination

The Investigator has the right to terminate the study in the interest of subject safety and welfare in consultation with the Sponsor. The Sponsor reserves the right to terminate or amend the study at any time for administrative reasons or if continuation of the protocol would present a potential safety risk to the subjects.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Subject Inclusion Criteria

To participate in the study, subjects must meet all the following eligibility criteria at screening:

1. Capable of giving informed consent and complying with study procedures;
2. Between the ages of 18 and 55 years, inclusive;
3. Body mass index (BMI) of 18.0 to 32.0 kg/m^2 inclusive and body weight not less than 50 kg;
4. Female subjects must have a negative pregnancy test result at screening and at admission;
5. Female subjects are:
   a. Surgically sterile for at least 3 months prior to screening by one of the following means:
      - Bilateral tubal ligation
      - Bilateral salpingectomy (with or without oophorectomy)
      - Surgical hysterectomy
      - Bilateral oophorectomy (with or without hysterectomy)

6. [redacted]
7. Considered healthy by the Investigator, based on subject's reported medical history, full physical examination, 12-lead ECG, and vital signs;
8. Have clinical laboratory renal (eGFR, creatinine) and liver (AST, ALT, Total bilirubin) function within normal range and other clinical laboratory results within normal range or outside normal range assessed as clinically non-significant by the Investigator at screening and admission;;
9. Non-smoker and has not been exposed to any products containing nicotine in the last 6 months;
10. Willing and able to adhere to study restrictions and to be confined at the clinical research center.

9.2 Subject Exclusion Criteria

Subjects will be excluded from study entry if any of the following exclusion criteria are present at screening:

1. Clinically significant reported history of gastrointestinal, cardiovascular, musculoskeletal, endocrine, hematologic, psychiatric, renal, hepatic, bronchopulmonary, neurologic, immunologic, lipid metabolism disorders, or drug hypersensitivity as determined by the Investigator;
2. Known or suspected malignancy;

3. Reported history of pancreatitis or gall stones;
[redacted]
7. Poor venous access;
8. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) at screening;
9. Donated or lost >500 mL of blood in the previous 3 months prior to screening;
10. Taken an investigational drug or participated in a clinical trial within 30 days (or 5 half-lives) prior to first dose of study drug, whichever is longer;
11. Taken any prescription medications within 14 days or 5 half-lives (whichever is longer) of the first dose of study drug;
12. Taken any prescription or non-prescription drugs and herbal medication known to be CYP450 inducers, inhibitors, and substrates within 14 days prior to screening (See Appendix B)
13. Taken daily vitamin A supplement within 3 months prior to screening;
14. Major surgery or hospitalization within 6 months prior to screening that in the Investigators opinion would put the subject or study conduct at risk;
15. A history of prescription drug abuse, or illicit drug use within 9 months prior to screening;
16. A history of alcohol abuse according to medical history (≥ 2 drinks per day for male and ≥ 1 drink per day for female) within 9 months prior to screening;
17. A positive screen for alcohol, drugs of abuse at screening or admission;
18. An unwillingness or inability to comply with food and beverage restrictions during study participation;
19. Use of over-the-counter (OTC) medication within 7 days, and/or herbal medications (including herbal teas, garlic extracts) within 7 days prior to first dose of study drug;
20. Have a history of allergic reactions (either spontaneous or following drug administration) to ATRA or to any of the excipients or related compounds, including vitamin A;
21. Any condition or finding that in the Investigators opinion would put the subject or study conduct at risk if the subject were to participate in the study.

9.3 Prohibitions and Restrictions

Subjects must be willing to adhere to the following prohibitions and restrictions until the end of the study (follow-up telephone call):

- No consumption of alcohol or food containing alcohol from 48 hours prior to Day -1 until the end of study.
- No excessive exercise from 48 hours prior to Day -1 until the end of study.

- No consumption of foods or drinks containing caffeine from 48 hours prior to Day -1 until the end of study.

- No administration of any prescription drugs within 14 days prior to first dose of study drug until the end of study.

9.4 Subject Withdrawal Criteria

Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. The Investigator also has the right to withdraw subjects from the study if it is in the best interest of the subject, or if the subject experiences an AE that warrants premature withdrawal.

Subjects may be withdrawn from the study if they:

- Have entered the study in violation of the protocol
- Use or require the use of prohibited concomitant medication(s)
- Are non-compliant with study procedures

All treated subjects should be followed according to the Schedule of Procedures (See Table 1).

All subjects, even those who have discontinued prematurely, should have all evaluations for the completion visit performed, if possible. All procedures should be documented in the electronic case report form (eCRF). For all subjects who withdraw prematurely, the Investigator will indicate one of the following reasons for withdrawal on the eCRF:

- Adverse event
- Death
- Protocol violation
- Lost to follow-up
- Subject's decision
- Other (reason to be specified by the Investigator)

In case of subjects' discontinuation from the study due to an AE, such subjects will be closely monitored until the resolution or stabilization of the AE. This may include follow-up visits (to complete any procedures or laboratory assessments as needed per the Investigator) or telephone calls after the subject discontinues from the study, and additional information may be requested. The Investigator should document the reason for discontinuation in the source documentation and eCRF.

10 TREATMENT OF SUBJECTS

10.1 Description of Study Drug

HF1K16 drug product is a sterile liquid injection containing small unilamellar liposomes with drug substances (ATRA) encapsulated inside the lipid bilayer.

The proposed dosage strength of HF1K16 Injection is 2 mg/mL in 10 mL per Type I glass vial. The components of HF1K16 Injection (2 mg/mL) are provided in Table 3.

Table 3: Composition of HF1K16 for Injection (2 mg/mL)

[redacted]

10.2 Methods of Assigning Subjects to Dose Groups

Subject treatment assignment will be based on a computer-generated randomization scheme with a ratio of 6:2 (active: placebo).

10.3 Treatment Compliance

Intravenous dose administration will be conducted and monitored by CRU personnel. Subjects will be encouraged to use the restroom prior to the start of infusion. The date and time of start and stop of infusion will be recorded on the eCRF. If an infusion needs to be interrupted, the time of infusion interruption (stop and restart time) will be recorded.

10.4 Blinding

This is a double-blind study with the exception of the CRU pharmacist and the bioanalytical laboratory personnel who perform the interim analyses of plasma study drug concentration determination.

The unblinded clinical site pharmacist or designee will prepare and perform a quality check for each dose for each subject per written dose preparation procedures and according to the randomization schedule, and other applicable local regulations as set forth in the protocol.

Due to the difference in appearance of HF1K16 and placebo solutions, the unblinded pharmacist will place a covering over the IV bags and lines to mask them from CRU staff and subjects.

Subjects, Investigators, persons performing the assessments, clinical operations personnel, data analysts, and the Sponsor will remain blinded to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods:

- Randomization data are kept strictly confidential (e.g., sealed envelopes kept in a locked filing cabinet or placed in a safe) until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: bioanalytical lab personnel involved in the analysis of PK samples, Safety Monitoring Committee (SMC) team members involved in regular review of safety data when it is determined that data need to be unblinded.

- The identity of the treatments will be concealed by the use of coverings over the IV bags and lines to mask them from CRU staff and subjects.

- Preliminary PK concentration data transfer and PK analysis for each cohort safety review will be handled with dummy subject numbers.

10.5 Interim Safety Analysis

Review of all safety and PK data will be done in a blinded manner following completion of each cohort.

10.6 Dose Adjustment and Stopping Criteria

Dose escalation decisions will be based on safety and tolerability assessments (AEs and results from clinical laboratory tests, physical examination findings, injection site assessments, ECGs, and vital signs), as well as PK analysis of each cohort, and agreed upon by the SMC.

The data to be evaluated will be safety data collected through to Day 8. If for any reason there is not a minimum amount of data available for at least 6 subjects, the site will enroll replacement subjects until the minimum data threshold for dose escalation is met. Replacement numbers will be utilized in order to ensure that the treatment ratio (6:2) is maintained.

AUC limit/cap of 16550 ng•hr/mL (i.e. escalation to the next dose should not proceed if the expected AUC will exceed 16550 ng•hr/mL). The limit is based on the mean AUC of male and female monkeys at the NOAEL (3 mg/kg) in the 28-day toxicity study.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be used to grade AEs.

The trial stopping criteria (that is no increase in the dosing schedule) will be based on the safety data reviewed by the SMC and agreement prior to higher dosing any additional subjects if:

- Any one Grade ≥ 3 AE unless the AE is clearly and incontrovertibly due to extraneous causes. ;
- Any two Grade ≥ 2 AEs unless the AEs are clearly and incontrovertibly due to extraneous causes
- If a serious AE (SAE) attributed to the study drug is observed, the study will be stopped, and the SMC will review all safety and PK data available up to that point in time. If in this case the SMC recommends dose de-escalation to the previously tolerated dose, or the addition of another cohort at an intermediate dose level below the dose level causing the SAE, before proceeding the Institutional Review Board (IRB) will be notified and must approve restarting the study after reviewing the additional safety measures submitted to the IRB as a protocol amendment.

Grade 3 asymptomatic laboratory abnormalities that resolved to ≤ Grade 1 within 3 days may be excluded from the definition of DLT. It should be made clear that these are guidelines only and the Investigator together with the SMC can stop dosing for an individual, a cohort, or the study at any time if considered necessary. In such instances the reasons for stopping should be clearly documented.

For subjects with normal baseline liver biochemistries that exhibit new elevations in transaminases greater than 3 times the upper limit of normal (ULN), repeat measurements should be performed within 48-72 hours if possible. If elevations persist, subjects should be evaluated for other causes of transaminase elevations and with tests of hepatic function. If no other cause is found, then the subject needs to be closely monitored.

Close observation is defined as follows:

- Repeating liver biochemistry tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultation.
- Other less common causes also may need to be considered, such as acute viral hepatitis, autoimmune or alcoholic hepatitis, NASH, hypoxic/ischemic hepatopathy; and biliary tract disease.

Per FDA Guidance for Industry - Drug Induced Liver Injury: Premarketing Clinical Evaluation, drug will be discontinued, and the subjects followed until resolution of symptoms or signs in the following situations:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (TB >2x ULN or INR >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Considering gastroenterology or hepatology consultations.

10.7 Safety Monitoring Committee

A SMC will be established to ensure the continuing safety of the study subjects. The SMC will consist of, at a minimum, the Investigator or delegate and the Sponsor's Medical Representative.

For each cohort, the SMC will review all of the blinded safety information including AEs, vital signs, physical examination finds, injection site assessments, standard 12-lead ECG data, safety laboratory results, as well as blinded PK data. In addition to data obtained from the current and most recent cohort, the SMC will conduct rolling reviews of all safety data that has been observed in all preceding cohorts, as needed.

The decision to advance to the next planned dose level, to implement a change in the planned dose level of the next cohort, and/or to evaluate if additional cohort(s) at lower dose level(s) should be enrolled will be documented in writing, signed, and submitted to the IRB.

10.8 Prior and Concomitant Medications and Substances

All prescription medications and OTC products, including herbal products, taken within 30 days prior to dosing or during the study period will be documented in the subject's source documentation and the eCRF. The only other medications (prescription or OTC) that subjects may be allowed to use during the study will be those necessary for the treatment of an AE in the opinion of the Investigator.

10.9 Meals

Standardized meals supplied by the CRU will be provided for all subjects. On the day of dosing subjects will be offered a low-fat breakfast at approximately 30 minutes prior to dosing to be completed approximately 5 minutes prior to dosing. Subjects are not required to consume the entire meal but should complete the meal in 25 minutes or less. On days that subjects are domiciled at the CRU meals will be offered according to the standard procedures of the CRU Water will be allowed *ad libitum* with the exception of 1 hour prior to and 2 hours post-dose on day of dosing. Soft drinks (sodas) without caffeine, non-citrus fruit juices or water will be offered with meals.

11 STUDY DRUG MATERIALS AND MANAGEMENT

11.1 Study Drug Packaging and Labeling

HF1K16 for Injection is stored as sterile liquid (2 mg/mL) in Type 1 glass vials at 2-8°C.

The placebo will be sterile saline (0.9% sodium chloride) for injection.

Product will be labeled according to applicable regulatory requirements. The label will include at least the following information:

- Name and address of Sponsor
- Protocol number or other identifier to reference the study
- Storage conditions
- Statement: Caution: New Drug—Limited by Federal (or US) law to investigational use

11.2 Study Drug Storage and Accountability

All investigational drug supplies will be stored in a secure, locked area, under the responsibility of the Investigator or other authorized individual.

Study drug must be stored at 2 - 8°C based on the available stability data.

The Investigator or designee must maintain accurate records of the receipt of all study drug, including date received, lot number, expiration date if applicable, amount received, condition of the package and the disposition of all study drug.

Current dispensing records will also be maintained including the date and amount of study drug dispensed and the identity of the subject receiving the study drug.

11.3 Study Drug Preparation and Dosing

The clinical site pharmacist or designee will prepare the study drug according to the randomization scheme, maintain the drug packaging and labeling log, and keep the blinding for treatment assignment per the randomization scheme. Study drug will be administered to subjects by CRU staff at approximately 8:00 a.m., following completion of a low-fat breakfast.

HF1K16 for Injection doses will be calculated based on subject weight measured at admission, and diluted in sterile saline (0.9% sodium chloride) according to Table 4. All calculations will be documented in the pharmacy log. The preferred injection site for IV infusion is the antecubital region of the upper extremity. Doses will be administered using an IV infusion pump over a period of approximately 60 minutes at 2.5 mL/min, with details to be provided in a separate manual. Dose date and time, including any unscheduled stop times, and site of injection will be documented in the eCRF.

11.4 Study Drug Handling and Disposal

All unused study drug and supplies must be returned to the Sponsor or disposed according to Sponsor's instruction after the study is completed and the drug accountability log is reconciled.

12 PHARMACOKINETIC ASSESSMENTS

Blood sampling time points are listed in Table 1.

Deviations from planned blood sample collection times are acceptable based on logistical and operational considerations as follows:

- 0 h/pre-dose: within 60 minutes prior to dosing
- <2 hours post-dose: ± 5 minutes
- 2 hours to ≤ 24 hours: ± 10 minutes
- 24, 36 and 48 hours: ± 15 minutes

Every effort will be made to collect PK samples at the protocol-specified time. Other assessments e.g. ECG, vital signs etc. may be taken before or after PK sample collection.

12.1 Pharmacokinetic Blood Collection and Processing

Blood samples determination of plasma concentrations of free tretinoin and liposome encapsulated tretinoin will be collected into tubes containing K_2-EDTA, immediately inverted gently several times and placed in wet ice until centrifugation. Within 30 minutes after collection, samples will be centrifuged at approximately 4°C for 15 minutes at approximately 2500 x g and plasma will be transferred into two polypropylene screw-cap tubes (approximately 1 mL/tube), stored on dry ice until transferred to a freezer and stored at ≤-70°C.

The actual sample collection date and time will be recorded on the eCRFs. Details of blood sample collection and processing will be described in a separate manual.

12.2 Specimen Labeling

Labels will be affixed to the cryovial and polypropylene tubes in a manner that will prevent the label from being detached after being wet or frozen. The labels will contain at a minimum the subject number, cohort number, nominal day, and nominal collection time, as appropriate.

The site will provide a sample inventory page, listing the information above for each sample. The sample inventory page will also include the treatment cohort for each series of tubes.

12.3 Sample Shipping Instructions

All plasma samples will be kept frozen and shipped on dry ice to the designated laboratory in two separate shipments. Upon notification by the designated laboratory that the first shipment of samples (the primary aliquot of each sample) was received, the second aliquot of each sample may be shipped.

12.4 Bioanalytical Methodology

Plasma samples will be analyzed using validated, specific, and sensitive methods of liquid chromatographic separation with tandem mass spectrometric detection (LC-MS/MS) for concentrations of free tretinoin and liposome encapsulated tretinoin by the designated bioanalytical lab.

12.5 Pharmacokinetic Parameters

The plasma concentration time data for free tretinoin and liposome encapsulated tretinoin will be analyzed using non-compartmental methods. Actual dosing and sampling times will be used for PK analyses. The primary PK parameters of interest are: C_{max}, T_{max}, $t_{1/2}$, AUC_{last}. Additional PK parameters include AUC_{inf}, MRT, CL/F, V_zF and K_{el}.

13 ASSESSMENT OF SAFETY

For specific timing of assessments, see Table 1.

13.1 Safety Parameters

13.1.1 Demographic/Medical History

Demographic characteristics (age, sex, race, and ethnicity) will be collected at the screening visit. Medical history will be reviewed and collected at the screening visit and updated at admission. The subject may be asked to sign a medical release form allowing contact with the subject's doctor for more information about subject's medical history or in case of an AE.

13.1.2 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate and oral temperature will be measured after the subject has rested in the supine position for at least 5 minutes.

Vital signs will be monitored for infusion reactions, and will be taken at screening, pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 6, 24 and 48 hours post-dose relative to the start of infusion

Vital signs may be repeated for clinically significant abnormal vital signs at the discretion of the Investigator.

13.1.3 Physical Examination, Height, Weight, and Body Mass Index

A full physical examination includes assessment of general appearance and evaluation of dermatological system, head, eyes, ears/nose/throat, neck, lymph nodes, lungs, heart, abdomen, neurological, skin and musculoskeletal system.

An abbreviated physical examination includes assessment of the heart, lungs, abdomen, skin and the neuromuscular system. A symptom-directed physical examination may be performed at any time. All physical examinations will be performed by qualified personnel.

Physical examinations may be repeated at any time during the study in the interest of subject safety, at the discretion of the Investigator.

At the screening visit, height (centimeters) and weight (kilograms) will be measured and BMI will be calculated. Weight will be measured at admission.

13.1.4 Electrocardiogram

A standard resting 12-lead ECG will be performed after the subject has rested in the supine position for at least 5 minutes. Parameters assessed will include ventricular rate (bpm), PR interval (msec), QRS complex and duration (msec), ST Segment, T wave, QT interval (msec) and QTcF interval (msec).

Post-dose ECGs must be evaluated for safety by the Investigator or his/her designee. The final conduction intervals entered into the eCRF will be those generated by the ECG machine, unless deemed significantly inaccurate by the review performed by the Investigator or designee. In these cases, the over-read intervals will be documented in the eCRF. The Investigator will also record an overall assessment of the ECG.

Triplicate ECGs will be performed at approximately 1 minute apart.

Clinically significant abnormal ECGs may be repeated at the discretion of the Investigator.

13.1.5 Clinical Laboratory Assessments

Hematology, blood chemistry including LFTs and coagulation parameters, and urinalysis evaluations will be performed on all subjects. The list of clinical laboratory assessments is included in APPENDIX A. LABORATORY ASSESSMENTS.

The total volume of blood collected for safety laboratory assessments will be approximately 50 mL.

The results of clinical laboratory tests conducted at the screening visit and on Day -1 must be assessed by the Investigator or designee to determine each subject's eligibility for participation in the study. Screening labs (Day -28 to Day -1) may be repeated at the discretion of the Investigator or designee. If subjects' values are out of range and the Investigator deems the out of range value is clinically significant, the Investigator must discuss and agree upon individual cases with the Sponsor's Medical Monitor prior to enrollment. Clinical laboratory values from samples collected after administration of the first dose that are out of range and considered clinically significant by the Investigator will be recorded as an AE.

Any significant abnormalities should be fully investigated. Whenever possible, the etiology of the abnormal findings will be documented on the eCRF. Laboratory results with clinically significant abnormal values may be repeated for verification. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. In particular if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests will be performed if possible and resolution or stability of the abnormality will be recorded in the source documentation.

Any clinically significant laboratory abnormalities that are either serious (e.g., require medical intervention or result hospital admission) or unexpected will be promptly reported to the Sponsor representative. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be reported to the Sponsor

Virus serology (HIV, hepatitis B surface antigen (HBsAg) and hepatitis C antibody will be assessed at the screening visit and must be negative to qualify enrollment.

Drug and alcohol tests will be conducted at the screening visit and admission. Results must be negative to qualify enrollment prior to dosing.

Pregnancy test for all female subjects will be performed at the screening visit and prior to administration of the first dose. Postmenopausal status of females will be confirmed by screening serum FSH and estradiol levels.

13.1.6 Injection Site Assessments

Injection site assessments will be performed prior to and 4 and 24 hours relative to the start of infusion.

Local skin reactions will be scored after visual inspection of the injection site, recording redness (erythema), bleeding, bruising, edema, and itching.

The dermal response score will be based on a visual irritation scale (0-7) that rates the degree of erythema, edema, and other signs of cutaneous irritation will be recorded in the eCRF using the following scale:

- 0 = no evidence of irritation
- 1 = minimal erythema, barely perceptible
- 2 = definite erythema, readily visible; minimal edema or minimal papular response
- 3 = erythema and papules
- 4 = definite edema
- 5 = erythema, edema and papules
- 6 = vesicular eruption
- 7 = strong reaction spreading beyond application site

13.2 Adverse Events

Adverse events will be recorded beginning immediately after the Informed Consent Form (ICF) is signed. Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Investigator (and/or designee) must document all AEs reported by the subject from the time subjects give consent through the follow-up/completion visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized, and the Investigator will document available follow-up information on the subject's source documentation and eCRF.

13.2.1 Definitions of Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An AE is any symptom, sign, illness, or experience that develops or

worsens in severity during the course of the study. Adverse events reported after consent but before the first dose of study drug are still to be documented by the Investigator but will be considered non-treatment-emergent AEs. Adverse events will be considered treatment-emergent if the onset date is after the first dose of study drug. The severity of each AE will be graded by the Investigator using the National Cancer Institute (NCI) CTCAE v5.0 as follows:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Grade 2**: Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL);
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;
- **Grade 4**: Life-threatening consequences; urgent intervention indicated;
- **Grade 5**: Death related to AE.

Abnormal results of laboratory tests or diagnostic procedures are considered AEs if the abnormality:

- Is associated with clinical signs or symptoms
- Is considered by the Investigator to be of clinical significance
- Results in study withdrawal
- Fulfills any of the criteria for a serious AE (SAE), as described in this section
- Requires treatment

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above

The term “life threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE form and documented in the eCRF.

The Investigator must assess the relationship between the AE and the study drug by using the following definitions:

- Not related (lack of temporal relationship or alternate etiology readily apparent).
- Probably not related (temporal relationship exists, but the event is not known to be associated with the study drug or related mechanism of action; alternate etiologies are more likely than the study drug).
- Probably related (temporal relationship exists, the event may be associated with the study drug or related mechanism of action; alternate etiologies are possible but unproven).
- Related (temporal relationship exists, the event is known to be associated with the study drug or related mechanism of action and alternate etiologies are less likely than action of the study drug).

13.2.2 Recording Adverse Events

All AEs (regardless of seriousness or relationship to study drug) including those from the time of consent to the follow-up/completion visit are to be recorded in the subjects’ source documents and on the corresponding page(s) in the eCRF. Whenever possible, symptoms, signs, and laboratory abnormalities should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, severity, action taken with respect to study drug, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug, according to the definitions noted. All medications administered to treat an AE must be recorded in the subject’s source documentation and documented in the eCRF.

13.2.3 Reporting of Serious Adverse Events

Reporting of SAEs will be conducted in accordance with the appropriate regulatory guidelines. All SAEs that occur from the time of consent to the study completion/follow-up visit must be reported, whether or not the event is considered associated with the study drug. The Investigator must complete an SAE Reporting Form and submit it by fax or email with other relevant source documentation to the Sponsor within 24 hours of awareness of the event to:

Name: Yongchao Dai

Mobile: +8617788560109

Email: daiyc@hf-biopharm.com

The Investigator must also provide with urgent priority (upon receipt of a request) other relevant documentation (e.g., copies of diagnostic test results, hospital discharge summary, and/or

autopsy report) and send this information by fax or email to the Sponsor. All SAEs must be recorded in the subject's source documentation and documented in the eCRF. Medications administered in association with the SAE must be documented in the eCRF and in the subject's source documentation. The Investigator must also promptly notify the IRB of SAEs, including any follow-up information, in accordance with local institutional policy and applicable regulatory requirements. Regulatory authorities will be notified of any AE that is both serious and unexpected, regardless of relationship to study drug, in accordance with the appropriate local regulatory guidelines. Notification of the event will be made by written, expedited safety report.

13.2.4 Adverse Event Follow-up

The Investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated. The Investigator should follow up on the outcome of any AE until the event has resolved or stabilized.

This implies that follow-up may continue after the subject discontinues from the study, including additional clinical laboratory assessments or other procedures, and that additional information may be requested.

Any SAE brought to the attention of the Investigator within 30 days after cessation of study drug and considered by him/her to be caused by the study drug with a reasonable possibility, should be reported through the SAE reporting process.

14 STATISTICAL METHODOLOGY

Complete details of the statistical analyses will be documented in the Statistical Analysis Plan (SAP) and will be completed prior to unblinding of the study data. This document will present more detail of the analysis populations, summary statistics, statistical analyses, and any changes to the proposed statistical analyses specified in the protocol. All statistical analyses (other than PK parameter estimation) will be performed using SAS version 9.3 or higher. All participant data will be listed for the Randomized Population. All safety assessments will be summarized for the Safety Population. All baseline and demographic characteristics will be summarized for the randomized participants. Data from subjects treated with placebo will be pooled in summary analyses.

14.1 Sample Size Determination

This is an early development study, and therefore no statistical considerations were involved in the sample size determination for this study. It is expected that the sample size of 8 subjects (6 subjects receiving active drug and 2 subjects receiving placebo) in each cohort should be adequate for evaluation of tolerability and PK parameters in this study.

14.2 Analysis Populations

The Randomized Population will be defined as all enrolled participants assigned a randomization number. The Safety Population will be defined as all randomized subjects who receive at least one dose of study drug. The Pharmacokinetic Population will be defined as all subjects who receive active drug, have no major protocol violations, and have sufficient PK data to obtain reliable estimates of the key PK variables. Subjects in the PK population will be referred to as evaluable subjects.

14.3 Pharmacokinetics

Pharmacokinetics:

Individual plasma concentrations and PK parameters of free tretinoin and liposome encapsulated tretinoin will be listed and summarized using descriptive statistics. Individual and mean free tretinoin and liposome encapsulated tretinoin concentration-time profiles will be presented graphically.

All PK parameters except T_{max} will be listed by treatment and subject, and summarized by treatment with descriptive statistics (n, mean [arithmetic and geometric], SD, min, median, max, and CV% [arithmetic, and geometric]). T_{max} will be described utilizing n, min, median, and max, and $t_{1/2}$ will be summarized using n, arithmetic mean and SD, CV%, min, median, and max.

A dose proportionality regression assessment for log-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} and log-transformed dose will be analyzed using a power model: ln (PK parameter) = $\mu + \beta$ x ln(dose) for free tretinoin or liposome encapsulated tretinoin. The 90% confidence intervals (CI) around the slopes (β) from each of these regression analyses will be obtained from the model and presented. Plots of the log-PK parameter by log-dose (AUC_{0-t}, AUC_{0-inf}, and C_{max}) will be produced.

14.4 Demographic Characteristics

Demographic characteristics will be listed and summarized for the subjects randomized in the study using descriptive statistics.

14.5 Exposure to Study Drug

Each subject's exposure to study drug will be listed and summarized using descriptive statistics for each dose for the Safety Population.

14.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Enhanced dictionary.

14.7 Safety Analyses

Adverse events will be summarized by system organ class (SOC) and preferred term (PT). A subject will only be counted once per SOC and once per PT within a treatment. Subject counts and percentages and AE counts will be presented for each treatment and totaled for all treatments. Listings will be presented by subject for all AEs.

Clinical laboratory values at each visit and change from baseline will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L).

Other safety parameters will be listed and summarized using descriptive statistics. For vital signs and 12-lead ECGs, values outside the normal ranges will be flagged in the listings and change from baseline will be summarized. No formal statistical analysis of safety data is planned.

14.8 Interim Analyses

Safety will be assessed for each dose cohort by a SMC composed of the Investigator and Sponsor's representative, which will meet after each cohort or ad hoc as required before dose escalation to the next higher dose. The SMC will review the safety data of the subjects (clinical laboratory results, physical examination and skin irritation findings, vital signs and ECG findings, and AEs) and PK data prior to finalizing the decision for next dose escalation. The decision will be documented in writing, signed, and submitted to the IRB.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Study Monitoring

At regular intervals during the study, the site will be contacted through monitoring visits, letters, and telephone calls by a Sponsor representative to review study progress, Investigator and subject compliance with study protocol requirements, and any emergent problems. During monitoring visits, the following points will be reviewed in accordance with all applicable regulatory requirements and Standard Operating Procedures (SOPs): original medical records and other source documents, the Investigator site file, screening logs, subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, documentation and reporting of endpoints, study drug allocation, subject compliance with the study drug regimen, study drug accountability, concomitant therapy use, and quality of data. In addition, other required regulatory documents will be reviewed, including but not limited to: IRB composition and correspondence, laboratory certification(s), delegation of authority, and Investigator and study personnel curricula vitae.

15.2 Sponsor's Responsibility

The Sponsor or its designee is responsible for the following:

1. Selecting qualified Investigators
2. Providing Investigators with the information they need to properly investigate
3. Ensuring proper monitoring of the investigation
4. Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding AEs or risks associated with the medication being studied

The Sponsor has delegated some responsibilities to a Contract Research Organization (CRO).

15.3 Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may inspect the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs and must fully cooperate with the Inspector(s). Inspections will be conducted at a reasonable time and in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review, or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

16 QUALITY CONTROL AND QUALITY ASSURANCE

A quality control and quality assurance plan, addressing aspects of the trial that may affect data integrity or the protection of human subjects, may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

17 ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki, Tokyo 2004 and applicable local regulatory requirements and law.

Copies of these materials are available from the Sponsor and the CRO designee by request. The purpose of these regulations, legal obligations and guidance is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to protect subject safety and ensure the integrity of the findings.
- The potential benefits of the research justify the risks.

The Investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care, and for the control of the medications under investigation.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study related duties and functions. The Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible to conduct or work on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct work on studies sponsored by the Sponsor. The Investigator is required to immediately disclose to the Sponsor in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by US FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The rest of this section of the protocol describes in more detail the specific GCP-defined responsibilities the Investigator assumes by agreeing to participate in this study.

17.1 Ethics Review

The Investigator (or designee) must submit this study protocol, the Sponsor-approved ICF, patient information sheets if applicable, subject recruitment materials, and other appropriated documents to the appropriate IRB, and following review of the submitted materials is required to

forward to the Sponsor(or designee) a copy of the written and dated approval/favorable opinion signed by the Chairman, along with a list of the IRB composition.

The approval/favorable opinion should clearly state the trial (study number, protocol title, and version number), the documents reviewed [Protocol, ICF, Investigator's Brochure (IB), etc.] and the date of the review. The study will not commence at the study site until the Sponsor has received a copy of this written and dated approval/favorable opinion.

During the trial, any amendment to the protocol and the ICF (as appropriate) should be submitted to the IRB. The IRB should also be informed of any event likely to affect the safety of subjects or the continued conduct of the trial, in particular any change in safety. Additionally, all updates to the IB will be sent to the IRB. A progress report will be sent to the IRB and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by IRB or local regulations.

The Investigator will notify the IRB of the conclusion of the clinical study within one month of completion or termination of the study. The final report sent to the IRB will also be sent to the Sponsor, along with the completed eCRFs and all necessary regulatory documents, thereby fulfilling the Investigator’s regulatory responsibility.

The Investigator will maintain a copy of all correspondence with the IRB, including copies of approved documents. The Investigator will also maintain a copy of the IRB membership list, including members’ occupation and qualifications (or a statement confirming compliance with GCP requirements for committee composition). An IRB General Assurance Number may be accepted in lieu of a membership roster.

17.2 Ethical Conduct of the Study

This study will be conducted in accordance with GCP as delineated by Title 21 CFR Parts 50, 56, and 312, and the ICH guidelines and directives. Participating Investigators, including members of the Committees and National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

Before the first subject is enrolled in the study, all ethical, regulatory, and legal requirements must be met.

An Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

17.3 Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from all subjects or subject’s legally authorized representative, as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's source documentation prior to any testing under this protocol, including screening tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and the Sponsor to use and disclose patient health information (PHI) in compliance with local law.

The original signed consent form will be retained with the study records.

18 DATA HANDLING AND RECORDKEEPING

18.1 Data Collection

All data obtained for analysis in the clinical study described in this protocol will be documented in the eCRF. Data reported in the eCRFs should be consistent with and substantiated by the subject's medical record and original source documents. Any discrepancies must be explained. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable. If a field is blank because the item was not done, the field will be marked "Not Done." If the item is unknown, the field will be marked "Unknown."

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

18.2 Case Report Form Completion

Data within the eCRF will be monitored by the Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the CRO and the Sponsor may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The final, completed eCRF for each subject must be signed and dated by the Investigator to signify that the Investigator has reviewed the eCRF and certifies it to be complete and accurate.

18.3 Database Management, Data Clarification, and Quality Assurance

A designated CRO will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document and provide it to the Sponsor for approval. The DMP will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, dataflows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Concurrent medications entered into the database will be coded using a WHO Anatomical Therapeutic Chemical dictionary. Coexistent diseases and AEs will be coded using MedDRA.

Quality control procedures will be conducted prior to database lock according to the designated CRO SOPs.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between the Sponsor, the Trial Statistician, the Data Manager, and the Quality Assurance Auditor according to designated CRO SOPs.

18.4 Inspection of Records/Source Documents

According to the ICH guidelines for GCP, the Sponsor or designee must verify data entered in the eCRF entries against the source documents, except for the pre-identified source data directly documented in the eCRF (if applicable). The ICF will include a statement by which the subject allows the Sponsor's duly authorized personnel, the IRB, and the regulatory authorities to have direct access to source data that supports the data in the eCRF (e.g., subject's medical file, appointment books, and original laboratory records). These personnel, bound by professional secrecy, must keep confidential all personal medical information.

The objective of source document verification (SDV) is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that the source documents are an accurate and verifiable reflection of the subject's participation in the study and that all relevant information that is recorded in the source document is accurately entered into the eCRF.

Where source documents serve as the basis for deriving data for the trial, SDV should ensure that these documents are correctly labeled and filed, and that the data derived from them are correct. All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not Title 21 CFR Part 11 compliant, they are not considered a valid source for this study. All progress notes must be dated and signed by the Investigator at the time of the visit. The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

1. Information to confirm that the subject exists (e.g., initials, date of birth, sex)
2. Confirmation that the subject satisfies the inclusion/exclusion criteria
3. Confirmation that the subject is taking part in the clinical trial
4. Confirmation of the informed consent process
5. Visit dates and documentation of protocol assessments and procedures
6. Information concerning all AEs
7. Details of concomitant and investigational medications

Source document verification is not a substitute for clinical trial monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, SDV has been carried out, and the study timelines and enrollment goals and requirements have been met.

18.5 Retention of Records

The Investigator must maintain all study documentation as confidential and take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study documents at least 2 years after the last approval of a marketing application/new drug application for the indication investigated or at least 2 years

have elapsed since the formal discontinuation of clinical development of the investigational product (e.g., the Investigational New Drug application is withdrawn). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with The Sponsor

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

19 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or designee) or produced during the trial including, but not limited to, the protocol, the eCRFs, the IB, and the results obtained during the course of the trial (if applicable), are confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor

However, submission of this protocol and any other necessary documentation to the IRB is expressly permitted, the IRB members having the same obligation of confidentiality.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site.

All study drug, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor, and responsible ethics committee(s) or regulatory authorities.

Subjects will be identified only by unique subject numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the subject are to remain at the site. This information will not be transferred to the Sponsor or be contained in regulatory filings. In the event of inspections by authorized agencies, this subject identification may be disclosed.

All study data at the site will be stored on secure, limited-access servers, protected by firewalls and anti-virus software. Access is limited and granted using a strict series of domain group policies.

19.1 Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the eCRF or in any study reports and these reports will be used for research purposes only. The Sponsor, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject’s personal medical data confidential.

The Sponsor will protect individual subject information to the fullest extent possible during this trial. At no time will a subject become identified in any publication or presentation.

However, the subject may have to become identified in the event of a regulatory authority auditor inspection in order to verify the accuracy of the data. Access to subject information is at

the discretion of the Sponsor and cannot occur prior to database lock or other specified events as determined solely by the discretion of the Sponsor

20 STUDY PROTOCOL AMENDMENTS

The Investigator will not make any changes to this protocol without prior written consent from the Sponsor, and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears necessary as the study progresses will be fully discussed by the Investigator(s) and the Sponsor. The written amendment must be submitted to the chairperson of the IRB identified with this responsibility. Except for administrative amendments, Investigators must await IRB approval of protocol amendments before implementing the change(s).

Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within 5 days. The Sponsor will ensure submission of any protocol amendments to the appropriate regulatory agencies.

When, in the judgment of the chairperson of the local IRB, the Investigators, and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject; the currently approved written ICF will require similar modification. In such cases, the Investigator will obtain repeat informed consent from subjects enrolled in the study before expecting continued participation.

21 PUBLICATION POLICY

All information concerning the product as well as any information such as clinical indications for the study drugs, their formula, their formulation, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor, or designee, and are unpublished, are confidential and must remain the sole property of the Sponsor

The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor or designee will prepare a final report on the study. The Investigator may not publish or present any information on this study without first presenting the information to the Sponsor for review.

22 REFERENCES

[redacted]

APPENDIX A. LABORATORY ASSESSMENTS

<table>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Urinalysis</th></tr>
<tr><td>Hemoglobin (Hgb)
Hematocrit (Hct)
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count with differential

Coagulation
International Normalized Ratio (INR)
Prothrombin Time (PT)
Partial Thromboplastin Time (aPTT)</td><td>Blood urea nitrogen (BUN)
Creatinine
Ferritin
Alkaline phosphatase
Aspartate transaminase (AST)
Alanine transaminase (ALT)
eGFR
Gamma-glutamyl transferase (GGT)
Bilirubin (total, direct, and indirect)
Lactic dehydrogenase (LDH)
Glucose
Albumin
Total protein
Bicarbonate
Phosphate
Sodium
Magnesium
Potassium
Chloride
Calcium
Total cholesterol
Triglycerides
HDL-C
LDL-C
Urate</td><td>pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Blood
Nitrites
Leukocytes
Urobilinogen
Microscopic urine analysis</td></tr>
<tr><td>Urine/Saliva Drug Screen</td><td colspan="2">Serology Screen</td></tr>
<tr><td rowspan="3">Amphetamines
Barbiturates
Cannabinoids
Cocaine metabolites
Opiates
Benzodiazepines
Alcohol breath test</td><td colspan="2">Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg)
Hepatitis C antibody (IgG),</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td colspan="2">Serum pregnancy test (females, screening only)
Urine pregnancy test (females, admission only)
FSH, Estradiol (postmenopausal females, screening only)</td></tr>
</table>

APPENDIX B. CYP450 ENZYME INDUCERS, INHIBITORS AND SUBSTRATES

INDUCERS - CYTOCHROME P450 (CYP) ENZYMES DRUG TABLE							
CYP_1A2	**CYP_2B6**	**CYP_2C8**	**CYP_2C9**	**CYP_2C19**	**CYP_2D6**	**CYP_2E1**	**CYP_3A4**
Carbamazepine Clotrimazole Phenobarbital Phenytoin Primidone Psoralen Smoking	Barbiturates Mephenytoin Phenobarbital Phenytoin Primidone Roflumilast	Carbamazepine Phenytoin Rifabutin Rifampin	Aprepitant Barbiturates Carbamazepine Primidone Rifampin Vigabatrin	Barbiturates Norethindrone Phenytoin Rifampin	Carbamazepine Ethanol Phenobarbital Phenytoin Primidone Rifampin	4- methylpyrazole Ethanol Isoniazid	Amprenavir Barbiturates Carbamazepine Clotrimazole Dexamethasone Efavirenz Ethosuximide Griseofulvin Modafinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin Prednisone Primidone Rifabutin Rifampin Rifapentine Ritonavir Topiramate

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INHIBITORS - CYTOCHROME P450 (CYP) ENZYMES DRUG TABLE

CYP_1A2	CYP_2B6	CYP_2C8	CYP_2C9	CYP_2C19	CYP_2D6	CYP_2E1	CYP_3A4
Amiodarone	Thiopeta	Anastrozole	Amiodarone	Cimetidine	Abiraterone	Disulfiram	Amiodarone
Atazanavir	Ticlopidine	Ezetimibe (p)	Atazanavir	Citalopram	Amiodarone		Amprenavir
Cimetidine		Gemfibrozil	Cimetidine	Delavirdine	Asenapine		Aprepitant
Ciprofloxacin		Montelukast	Clopidogrel	Efavirenz	Buproprion		Atazanavir
Citalopram		Nicardipine	Cotrimoxazole	Felbamate	Celecoxib		Boceprevir
Clarithromycin		Sulfinpyrazone	Delavirdine	Fluconazole	Chloroquine		Cimetidine
Diltiazem		Trimethoprim	Disulfiram	Fluoxetine	Chlorpheniramine		Ciprofloxacin
Enoxacin			Efavirenz	Fluvastatin	Chlorpromazine		Clarithromycin
Erythromycin			Fenofibrate	Fluvoxamine	Cimetidine		Cyclosporine
Estradiol			Fluconazole	Indomethacin	Cinacalcet		Danazol
Fluvoxamine			Fluorouracil	Isoniazid	Citalopram		Delavirdine
Interferon			Fluoxetine	Ketoconazole	Clemastine		Diltiazem
Isoniazid			Fluvastatin	Lansoprazole	Clomipramine		Efavirenz
Ketoconazole			Fluvoxamine	Modafinil	Cocaine		Erythromycin
Methoxsalen			Gemfibrozil	Omeprazole	Darifenacin		Ethinyl Estradiol
Mibefradil			Imatinib	Oxcarbazepine	Desipramine		Ezetimibe (p)
Tegaserod			Isoniazid	Probenecid	Diphenhydramine		Fluconazole
			Itraconazole	Ticlopidine	Doxepin		Fluoxetine
			Ketoconazole	Topiramate	Doxorubicin		Fluvoxamine
			Leflunomide		Duloxetine		Gestodene
			Lovastatin		Escitalopram		Imatinib
			Methoxsalen		Febuxostat		Indinavir
			Metronidazole		Fluoxetine		Isoniazid
			Mexiletine		Fluphenazine		Itraconazole
			Modafinil		Halofantrine		Ketoconazole
			Nalidixic acid		Haloperidol		Methylprednisolone
			Norethindrone		Hydroxychloroquine		Mibefradil
			Norfloxacin		Hydroxyzine		Miconazole
			Omeprazole		Imatinib		Mifepristone
			Contraceptives		Levomepromazine		Nefazodone
			Paroxetine		Methadone		Nelfinavir
			Phenylbutazone		Metoclopramide		Nicardipine
			Probenecid		Mibefradil		Nifedipine
			Sertraline		Midodrine		Norethindrone
			Sulfamethoxazole		Moclobemide		Norfloxacin
			Sulfaphenazole		Nefazodone		Norfluoxetine
			Sulfonamides		Norfluoxetine		Oxiconazole
			Tacrine		Paroxetine		Posaconazole
			Teniposide		Perphenazine		Prednisone
			Ticlodipine		Propafenone		Quinine
			Tipranavir		Propoxyphene		Ranolazine
			Troleandomycin		Propranolol		Ritonavir
			Voriconazole		Quinacrine		Roxithromycin

			Zafirlukast Zileuton		Quinidine Ranitidine Ranolazine Ritonavir Sertraline Tegaserod Terbinafine Thioridazine Ticlopidine Tipranavir Tripelennamine		Saquinavir Sertraline Telaprevir Telithromycin Troleandomycin Verapamil Voriconazole Zafirlukast Zileuton
Herbals CYP_1A2	**Herbals CYP_2B6**	**Herbals CYP_2C8**	**Herbals CYP_2C9**	**Herbals CYP_2C19**	**Herbals CYP_2D6**	**Herbals CYP_2E1**	**Herbals CYP_3A4**
			Allium sativum *Bergamottin* *Harpagophytum procumbens* *Lycium barbarum*	*Allium sativum* *Harpagophytum procumbens*	*Alpinia glanga* *Alstonia scholaris* *Andrographis paniculata* *Catharanthus roseus* *Cimicifuga racemosa* *Cinnamomum burmannii* *Eleutherococcus senticoccus* *Glycyrrhiza glabra* *Hydrastis canadensis* *Melaleuca leucadendron* *Panax ginseng* *Panax quinquefolius* *Piper nigrum* *Punica granatum* *Rheum palmatum* *Santalum album* *Strychnos ligustrina* *Syzygium aromaticum* *Tinospora crispa* *Zingiber aromaticum*	*Piper Methysticum*	*Allium sativum* *Ammi visnaga* *Azadirachta indica* *Cimicifuga racemosa* *Harpagphytum procumbens* *Hydrastis canadensis* *Naringenin compounds* *Panax ginseng* *Panax quinquefolius* *Strychnos ligustrina* *Uncaria tomentosa*

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SUBSTRATES - CYTOCHROME P450 (CYP) ENZYMES DRUG TABLE

CYP_1A2	CYP_2B6	CYP_2C8	CYP_2C9	CYP_2C19	CYP_2D6	CYP_2E1	CYP_3A4
Acetaminophen	Bupropion	Amiodarone	Amitriptyline	Amitriptyline	Alprenolol	Acetaminophen	Abiraterone
Amitriptyline	Cyclophosphamide	Amodiaquine	Carvedilol	Carisoprodol	Amitriptyline	Disulfiram	Alfentanil
Asenapine	Clopidogrel	Benzphetamine	Celecoxib	Cilostazol	Amphetamine	Theophylline	Alfuzosin
Bendamustine	Efavirenz	Carbamazepine	Chlorpheniramine	Citalopram	Aripiprazole		Aliskiren
Caffeine	Ifosfamide	Cerivastatin	Chloramphenicol	Clomipramine	Asenpine		Almotriptan
Chlordiazepoxide	Ketamine	Docetaxel	Clomipramine	Clopidogrel	Atomoxetine		Alprazolam
Chlorpromazine	Methadone	Everolimus	Clopidogrel	Cyclophosphamide	Bufuralol		Amitriptyline
Clopidogrel	Sertraline	Febuxostat	Desogstrel	Desipramine	Bisoprolol		Amiodarone
Clozapine		Fluvastatin	Diclofenac	Diazepam	Captopril		Amlodipine
Cyclobenzaprine		Isotretinoin	Dronabinol	Escitalopram	Carvedilol		Amprenavir
Febuxostat		Phenytoin	Febuxostat	Esomeprazole	Cevimeline		Aprepitant
Flutamide		Pioglitazone	Fluoxetine	Formoterol	Chlorpheniramine		Aripiprazole
Imipramine		Retinol	Flurbiprofen	Hexobarbital	Chlorppromazine		Astemizole
Leflunomide		Repaglinide	Fluvastatin	Imipramine	Chlorpropamide		Atazanavir
Mexiletine		Rosiglitazone	Formoterol	Indomethacin	Cinacalcet		Atorvastatin
Nabumetone		Tolbutamide	Glibenclamide	Lacosamide	Clemastine		Bepridil
Naproxen		Torsemide	Glimepiride	Lansoprazole	Clomipramine		Bexarotene
Nortriptyline		Verapamil	Glipizide	Loratidine	Clozapine		Boceprevir
Olanzapine		Zopiclone	Hexobarbital	Mephenytoin (s)	Codeine		Bromocriptine
Propafenone			Ibuprofen	Mephenytoin (r)	Cyclobenzaprine		Budesonide
Propranolol			Imipramine	Mephobarbital (r)	Darifenacin		Buprenorphine
Ranitidine			Indomethacin	Moclobemide	Debroquine		Buspirone
Roflumilast			Irbesartan	Nelfinavir	Desipramine		Cafergot
Riluzole			Irinotecan	Milutamide	Dexfenfluramine		Caffeine
Tacrine			Ketamine	Notripytline	Dextromethorphan		Cannabinoids
Theophylline			Lomoxicam	Omeprazole	Diphenhydramine		Carbamazepine
Tizanidine			Losartan	Pantoprazole	Dolasetron		Cerivastatin
Zileuton			Mefenamic acid	Pentamidine	Donepezil		Cevimeline
Zolpidem			Meloxicam	Phenobarbital	Doxepin		Chlordiazepoxide
			Mephenytoin	Phenytoin	Duloxetine		Cilostazol
			Montelukast	Progesterone	Encainide		Cinacalcet
			Nateglinide	Proguanil	Fenfluramine		Citalopram
			Omeprazole	Propranolol	Fluphenazine		Clarithromycin
			Phenylbutazone	Rabeprazole	Fentanyl		Clindamycin
			Piroxicam	Ranitidine	Flecainide		Clomipramine
			Quetiapine	Sertraline	Fluoxetine		Clonazepam
			Rosiglitazone	Teniposide	Fluvoxamine		Clopidogrel
			Sertraline	Thioridazine	Formoterol		Clorazepate
			Sildenafil	Tolbutamide	Galantamine		Clozapine
			Sulfamethoxazole	Voriconazole	Guanoxan		Cocaine
			Sulfinpyrazone	Warfarin (r)	Haloperidol		Codeine
			Suprofen		Hydrocodone		Colchicine
			Tamoxifen		Hydroxyzine		Cyclophosphamide

			Tienilic acid Tolbutamide Torsemide THC Testosterone Valdecoxib Vardenafil Valsartan Voriconazole Warfarin (s) Zafirlukast Zileuton		Iloperidone Imipramine Indoramin Lidocaine Maprotiline Meperidine Methadone Methamphetamine Methoxyamphetamine Metoclopramide Metoprolol Mexiletine Minaprine Mirtazapine Morphine Nebivolol Nortriptyline Olanzapine Ondansetron Oxycodone Paroxetine Perhexiline		Cyclosporine Dapsone Darifenacin Darunavir Delavirdine Desogestrel Dextromethorphan Diazepam Dihdroergotamine Disopyramide Diltiazem Docetaxel Dofetilide Dolasetron Domperidone Donepezil Doxorubicin Dronabinol Dutasteride Efavirenz Eplerenone Propafenone Propoxyphene Propranolol Quetiapine Quinidine Ranolazine Risperidone Ritonavir Sertraline Sparteine Tamoxifen Thioridazine Timolol Tolterodine Tramadol Trazadone Tripelennamine Tropisetron Venlafaxine Ergotamine Erlotinib Erythromycin Esomeprazole Eszoplicone Ethinylestradiol Ethosuximide Etonogestrel

							Etoposide Everolimus Exemestane Felodipine Fentanyl Finasteride Fexofenadine Flurazepam Flutamide Fluticasone Galantamine Haloperidol Hydrocodone Iloperidone Imatinib Imipramine Indinavir Irinotecan Isradipine Itraconazole Ketamine Ketoconazole Lansoprazole Letrozole Lercanidipine Lidocaine Loratadine Lopinavir Lovastatin Methadone Midazolam Mifepristone Mirtazapine Modafinil Mometasone Montelukast Nateglinide Nelfinavir Nevirapine Nicardipine Nifedipine Nisoldipine Nitrendipine Norethindrone Ondansetron Omeprazole Oxybutynin Oxycodone

							Paclitaxel Pantoprazole Pioglitazone Propafenone Propranolol Quetiapine Quinidine Quinine Rabeprazole Ramelteon Ranitidine Ranolazine Repaglinide Rifampin Rifaximin Ritonavir Rivaroxaban Rofulmilast Salmeterol Saquinavir Saxagliptin Sertraline Sibutramine Sildenafil Simvastatin Sirolimus Solifenacin Sorafenib Sufentanil Sunitinib Steroids Tacrolimus Tadalafil Tamoxifen Telaprevir Telithromycin Temazepam Temsirolimus THC Theophylline Tiagabine Ticagrelor Tinidazole Tipranavir Tolterodine Toremifene Tramadol Trazadone

							Triazolam Trimetrexate Valdecoxib Valproic acid Vardenafil Verapamil Vinblastine Vincristine Voriconazole Warfarin (r) Zaleplon Zileuton Ziprasidone Zolpidem Zonisamide

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