GT-032 Protocol

Study Title**:** A Single-dose, Open-label, Pharmacokinetic Study of Belapectin (GR-MD-02) in Subjects with Normal Hepatic Function and Subjects with Varying Degrees of Hepatic Impairment

NCT #: NCT04332432

Document Date: 11 November 2020

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Protocol Amendment Status: Final
Original Protocol Date: [redacted]
Protocol Amendment Date: [redacted]
Protocol Version: [redacted]

Investigational Medicinal Product: Belapectin (GR-MD-02)

Protocol Reference Number: GT-032
[redacted]

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SPONSOR APPROVAL

We have read the protocol and approve it:

[redacted]

11NOV2020

Adam E. Allgood, PhafulD, RPh
Vice President, Clinical Development
& Clinical Operations

Date

[redacted]

[redacted]

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

STUDY IDENTIFICATION

Sponsor	Galectin Therapeutics, Inc. 4960 Peachtree Industrial Blvd., Suite 240 Norcross, GA 30071 United States
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[redacted] Medical Monitor	[redacted]
Study Sites	Obtain information from Form Food and Drug Administration (FDA) 1572
Principal Investigator	Obtain information from Form FDA 1572
Sub-investigator(s)	Obtain information from Form FDA 1572
Clinical Laboratory	Obtain information from Form FDA 1572
Bioanalytical Laboratory	[redacted]
Statistician	[redacted]

SYNOPSIS

Study Title

A Single-dose, Open-label, Pharmacokinetic Study of Belapectin (GR-MD-02) in Subjects with Normal Hepatic Function and Subjects with Varying Degrees of Hepatic Impairment

Objectives

The primary objective of the study is:

- To assess the pharmacokinetics (PK) of belapectin following a single intravenous (IV) dose of belapectin in subjects with mild, moderate, or severe hepatic impairment, compared to healthy subjects with normal hepatic function.

The secondary objective of the study is:

- To evaluate the safety and tolerability of a single IV dose of belapectin in subjects with mild, moderate, or severe hepatic impairment, and in healthy subjects with normal hepatic function.

Study Design

This will be a Phase 1, open-label, non-randomized, parallel-group study to determine the effect of hepatic impairment on the PK, safety, and tolerability of a single IV dose of belapectin compared to matched healthy subjects with normal hepatic function.

Subjects will be enrolled into the following groups based on their hepatic function, as determined according to the Child-Pugh system:

- Group 1: matched healthy subjects with normal hepatic function
- Group 2: subjects with mild hepatic impairment (Child-Pugh Class A [4 x subjects with a score of 5 and 4 x subjects with a score of 6])
- Group 3: subjects with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9])
- Group 4: subjects with severe hepatic impairment (Child-Pugh Class C [score of 10 to 14]).

Healthy subjects with normal hepatic function (Group 1) will be demographically matched by age (±10 years), sex, and body mass index (BMI ±20%) to subjects with hepatic impairment (Groups 2, 3, and 4). Subjects with normal hepatic function cannot be matched to more than 1 hepatically-impaired subject within an impairment group; however, subjects with normal hepatic function may be matched to a subject from more than 1 hepatic impairment group.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 6. Subjects will return to the CRU for an outpatient visit on Day 10 and a Follow-up visit on Day 15.

An interim review of preliminary PK, safety, and tolerability data with a minimum of 2 subjects with severe hepatic impairment (Group 4) + 2 matched normal hepatic function subjects (Group 1) will be performed, once they have completed Day 10. It will then be determined whether returning for an outpatient visit on Day 10 will be necessary for the remaining subjects. Amendment to the protocol will also be considered, notably to protect patient safety, and the decision to treat more subjects with hepatic impairment at the same dose of belapectin may be taken.

Number of Subjects

Approximately 40 subjects will be enrolled in the study; approximately 16 subjects in Group 1 and 8 subjects in each of Groups 2, 3, and 4.

Group 2 will also be split into 2 subgroups of 4 subjects; 4 with a Child-Pugh score of 5 and 4 with a Child-Pugh score of 6.

Diagnosis and Main Criteria for Inclusion

Male and female subjects with mild, moderate, or severe hepatic impairment, or with normal hepatic function, aged between 18 and 75 years (inclusive), with a BMI between 18.0 and 45.0 kg/m^2 (inclusive).

Investigational Medicinal Products, Dose, and Mode of Administration

Single dose of 4 mg/kg of lean body mass (LBM) belapectin solution for injection administered intravenously (infused over approximately 60 minutes).

Duration of Subject Participation in the Study

Planned Screening duration: approximately 4 weeks

Planned study duration (Screening to Follow-up): approximately 6 weeks

Endpoints

Pharmacokinetics:

The PK outcome endpoints of belapectin derived from the concentration-time profile following single-dose IV administration are as follows and will be determined wherever possible:

- area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- area under the concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t})
- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})
- terminal elimination half-life ($t_{½}$)
- time of last measurable concentration (t_{last})

- total clearance (CL)
- apparent volume of distribution at steady state (V_{ss})

Other PK parameters, such as amount of dose (A_e) and percentage of dose (F_e) excreted in the urine, may also be reported.

Safety:

Safety endpoints include incidence and severity of adverse events (AEs), clinical laboratory parameters (clinical chemistry, hematology, coagulation, and urinalysis), 12-lead electrocardiogram parameters, vital signs parameters, and physical examinations.

Statistical Methods

Pharmacokinetics:

The primary analysis is the evaluation of the PK of belapectin following a single dose in subjects with mild, moderate, or severe hepatic impairment ('Test' groups) compared to matched subjects with normal hepatic function ('Reference' group).

The primary PK parameters are AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, $t_{½}$, and C_{max} for belapectin; all other PK parameters will be regarded as secondary.

If an individual healthy subject is matched to a subject from any or all hepatic impairment groups, a paired t-test will be applied to analyze the natural log-transformed primary PK parameters (C_{max}, t_{max}, $t_{½}$, AUC_{0-t}, and $AUC_{0-\infty}$) for belapectin. The paired t-test will be performed separately for each hepatic impairment group and the corresponding matched healthy controls. Estimates of geometric mean ratios in primary PK parameters between each level of impaired hepatic function versus the matched healthy controls will be presented along with the corresponding 90% confidence intervals for the geometric mean ratios. The p-value assessing the difference between each impairment group and the healthy control group will be presented.

Plasma concentrations and PK parameters will be summarized by group using descriptive statistics (number, arithmetic mean, standard deviation, geometric mean, geometric coefficient of variation, median, minimum, and maximum).

Model for End-Stage Liver Disease (MELD) and MELD sodium (MELD-Na) scores will also be calculated for each subject, to explore the relationship between MELD scores and the PK parameters of belapectin.

Safety:

Safety and tolerability data will be listed, and a listing of the subjects with hepatic impairment and their matched subject with normal hepatic function will be provided. Each AE will be coded using the Medical Dictionary for Regulatory Activities. All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each hepatic function group will be presented by severity and by association with the study drug as determined by the Investigator (or designee). Values for clinical laboratory data, vital signs, 12-lead electrocardiograms and physical examinations will be listed.

No inferential statistical analyses are planned for safety data.

A comparison of the calculation of estimated glomerular filtration rate by the Modification of Diet in Renal Disease (MDRD) versus the Cockcroft-Gault equation will be undertaken in the analysis to evaluate the potential bias caused by increased body weight when using the Cockcroft-Gault equation for creatinine clearance estimation.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
A_e	amount of dose excreted in the urine
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the last measurable concentration
BMI	body mass index
CFR	Code of Federal Regulations
CL	total clearance
C_{max}	maximum observed concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
F_e	percentage of dose excreted in the urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
LBM	lean body mass
ln	natural log (base e)
MDRD	Modification of Diet in Renal Disease
MELD	Model for End-stage Liver Disease score
MELD(i)	initial Model for End-stage Liver Disease score
MELD-Na	Model for End-stage Liver Disease-sodium score
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's method

SAE	serious adverse event
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{last}	time of last measurable concentration
t_{max}	time of the maximum observed concentration
US	United States
V_{ss}	apparent volume of distribution at steady state

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1. Overview

Belapectin (also referred to as galactoarabino-rhamnogalacturonate or GR-MD-02) is a patented pharmaceutically active ingredient prepared from United States Pharmacopeia apple pectin starting material through a proprietary process of controlled hydrolysis and purification.

Belapectin represents a new type of agent for the therapy of patients with non-alcoholic steatohepatitis (NASH) with advanced fibrosis and cirrhosis. [redacted]

Non-alcoholic fatty liver disease (NAFLD), or fatty liver, and NASH are common liver disorders in the United States (US). A subset of individuals with NAFLD are found to have NASH, which is characterized by excessive fat accumulation in hepatocytes (steatosis) with the addition of inflammatory cell infiltrates, evidence of damage to hepatocytes (ballooning degeneration), and the deposition of fibrous tissue. It is estimated that between 3% to 5% of Americans are affected by NASH, with as many as 12.2% in asymptomatic adults. While the prevalence of cirrhosis in NASH is not clearly defined, as many as one third of NASH patients progress to advanced fibrosis. The only therapy available to these advanced patients is liver transplantation. Currently the percentage of liver transplantations performed in the US for NASH is between 10% and 15%, but the numbers are increasing and it has been suggested that it may become the leading cause for liver transplantation over the next 20 years.

Currently, there are no Food and Drug Administration (FDA)-approved therapies for NASH. A number of experimental approaches have been evaluated in clinical trials, or are under evaluation in patients in ongoing clinical trials. Strategies for therapy have been targeted at a number of different sites in the presumed pathogenesis including metabolic syndrome (obesity, insulin resistance, diabetes), anti-oxidants or toxin metabolism, and lipid or bile salt metabolism.

1.2. Nonclinical Pharmacokinetic Drug Interactions

[redacted]

1.3. Summary of Clinical Experience

Three clinical studies in NASH fibrosis were successful in providing information on the design of a Phase 3 clinical trial to demonstrate efficacy of belapectin in NASH cirrhosis patients. An additional Phase 1 drug-drug interaction trial with belapectin and midazolam confirmed no effect on the PK of midazolam. First, and most importantly, all 4 studies showed belapectin to be safe and well tolerated at single and multiple doses up to 8 mg/kg for up to 52 weeks. [redacted]

[redacted]

[redacted]

1.4. Study Rationale

Liver disease can cause alterations in drug disposition and PK, which can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affects plasma protein binding and could influence the process of distribution and elimination.

This study will assess the PK of belapectin in subjects with mild, moderate, or severe hepatic impairment according to 3 different Child-Pugh categories: mild, moderate, or severe impairment[2,3], compared to matched healthy control subjects.

There are a number of methods used to categorize the severity of hepatic impairment. The Child-Pugh classification is the most widely used and is an acceptable method supported by regulatory agencies (including the US FDA and the European Medicines Agency [EMA]).[4,5]

1.5. Benefit-risk Assessment

Subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatment, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with belapectin may be found in the IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To assess the PK of belapectin following a single IV dose of belapectin in subjects with mild, moderate, or severe hepatic impairment, compared to healthy subjects with normal hepatic function.

The secondary objective of the study is:

- To evaluate the safety and tolerability of a single IV dose of belapectin in subjects with mild, moderate, or severe hepatic impairment, and in healthy subjects with normal hepatic function.

2.2. Endpoints

2.2.1. Primary Endpoints

The PK outcome endpoints of belapectin derived from the concentration-time profile following single-dose IV administration are as follows and will be determined wherever possible:

- area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- area under the concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t})

- maximum observed concentration (C_{max})
- time of the maximum observed concentration (t_{max})
- terminal elimination half-life ($t_{½}$)
- time of last measurable concentration (t_{last})
- total clearance (CL)
- apparent volume of distribution at steady state (V_{ss})

Other PK parameters, such as amount of dose (A_e) and percentage of dose (F_e) excreted in the urine, may also be reported.

2.2.2. Secondary Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, coagulation, and urinalysis test results
- 12-lead electrocardiogram (ECG) parameters
- vital signs measurements
- physical examinations.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, open-label, non-randomized, parallel-group study to determine the effect of hepatic impairment on the PK, safety, and tolerability of a single IV dose of belapectin compared to matched healthy subjects with normal hepatic function.

Subjects will be enrolled into the following groups based on their hepatic function, as determined according to the Child-Pugh system (see Section 4.3 for more details):

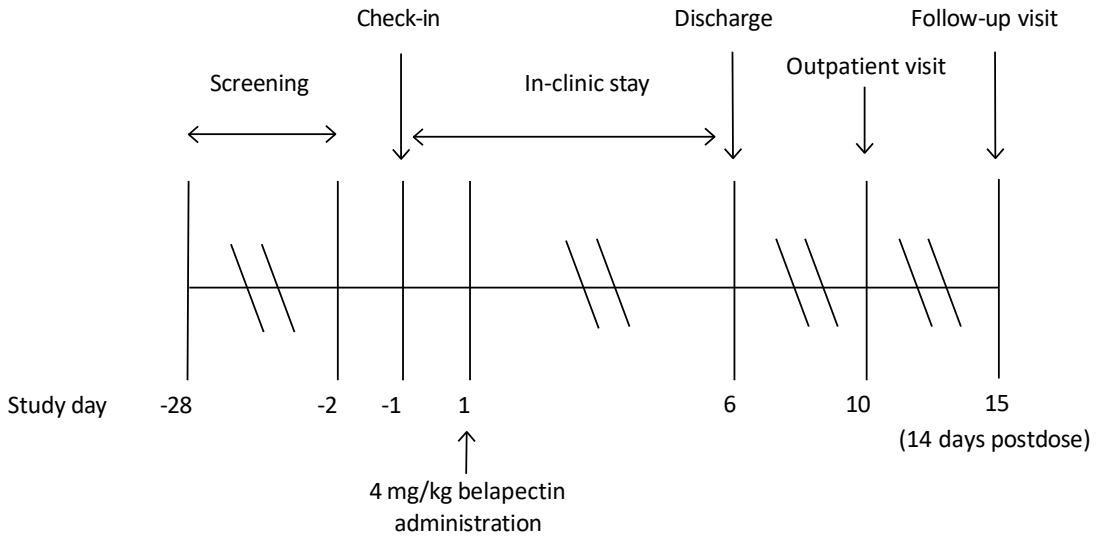
- Group 1: matched healthy subjects with normal hepatic function
- Group 2: subjects with mild hepatic impairment (Child-Pugh Class A [4 x subjects with a score of 5 and 4 x subjects with a score of 6])
- Group 3: subjects with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9])
- Group 4: subjects with severe hepatic impairment (Child-Pugh Class C [score of 10 to 14]).

Healthy subjects with normal hepatic function (Group 1) will be demographically matched by age (±10 years), sex, and body mass index (BMI ±20%) to subjects with hepatic impairment (Groups 2, 3, and 4). Subjects with normal hepatic function cannot be matched to more than

1 hepatically-impaired subject within an impairment group; however, subjects with normal hepatic function may be matched to a subject from more than 1 hepatic impairment group.

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 6. Subjects will return to the CRU for an outpatient visit on Day 10 and a Follow-up visit on Day 15. An interim review of preliminary PK, safety, and tolerability data from a minimum of 2 subjects with severe hepatic impairment (Group 4) + 2 matched normal hepatic function subjects (Group 1) will be performed once they have completed Day 10. It will then be determined whether returning for an outpatient visit on Day 10 will be necessary for the remaining subjects. Amendment to the protocol will also be considered, notably to protect patient safety, and the decision to treat more subjects with hepatic impairment at the same dose of belapectin may be taken.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 6 weeks.

The start of the study is defined as the date the first subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in Appendix 5.

3.2. Discussion of Study Design

A single-dose, parallel design is the standard design to investigate the PK of a drug in subjects with hepatic impairment. A parallel design is required to include subjects with

hepatic impairment and matched control subjects with normal hepatic function. The study will be open-label as the endpoints are not considered subjective.

Matched control healthy subjects with normal hepatic function will be enrolled in this study to serve as a reference group for interpretation of the results. A range of hepatic impairments have been included to enhance the ability to detect and characterize the effects of hepatic function on the PK of belapectin. Based on non-clinical and clinical data, and the known PK profile of belapectin, the duration of the treatment period is considered adequate to achieve the study objectives. Intravenous administration has been chosen as this is the intended clinical route of administration.

The FDA and EMA Guidelines recommend 'the number of subjects enrolled should be sufficient to detect clinically relevant PK differences'.[4,5] In this study, 8 subjects with mild hepatic impairment (4 with Child-Pugh score of 5 and 4 with a Child-Pugh score of 6), 8 subjects with moderate hepatic impairment, 8 subjects with severe hepatic impairment, and approximately 16 subjects with normal hepatic function will be enrolled. The PK profiles and safety and tolerability between each hepatic impairment group and their matching healthy subjects (in terms of sex, age, and BMI) will be compared.

3.3. Selection of Doses in the Study

[redacted]

3.4. Discontinuation of Study Drug for an Infusion-related Reaction

[redacted]

[redacted]

There were no incidences of any of the above in 3 additional clinical trials with belapectin.

Study drug infusions will be discontinued based on the following criteria:

- If a subject develops an AE during infusion of study drug, the infusion should be interrupted for approximately 10 minutes
- If the AE improves or resolves, then the infusion can be restarted
- If the AE does not improve or resolve, then symptomatic medication may be administered, and the AE should be reassessed after 30 minutes
- If the AE improves or resolves within 30 minutes, then the infusion can be restarted
- If the AE recurs when the study infusion is restarted, then the infusion should be terminated
- If the AE does not improve or resolve within 30 minutes, then the infusion will be terminated
- Any infusion-site reactions or infusion-related events should be recorded as an AE. Refer to Section 7.2.1 for criteria for defining the severity of an AE. All infusion-related (S)AEs must be recorded in electronic data capture (EDC).

Study drug may also be withheld if clinically indicated. Please contact the Medical Monitor regarding resumption of belapectin dosing.

4. SELECTION OF STUDY POPULATION

If a subject has not met all eligibility criteria, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 2 times at the discretion of the Investigator in consultation with the Sponsor.

Rescreen subjects must first be documented as screen failures, and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day Screening window will begin. Subjects will retain the same subject identification number assigned at the original Screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures including informed consent must be repeated.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit, unless otherwise stated:

All Subjects

1. Males or females, of any race, between 18 and 75 years of age, inclusive.
2. Body mass index between 18.0 and 45.0 kg/m^2, inclusive.

[redacted]

3. Females of childbearing potential will not be pregnant or lactating and must have a negative result on an approved pregnancy test at Screening and Check-in. Females of childbearing potential must agree to use contraception by a method of proven reliability (including abstinence) for the duration of the study, as detailed in Appendix 3.
4. Males will agree to use contraception, as detailed in Appendix 3.
5. Male subjects must not donate sperm from Check-in (Day -1) until 90 days after the Follow-up visit.
6. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

Subjects with Normal Hepatic Function Only

7. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in (Day -1), as assessed by the Investigator (or designee).
8. Matched to subjects with mild, moderate, or severe hepatic impairment in sex, age (±10 years), and BMI (±20%).

Subjects with Hepatic Impairment Only

9. Documented chronic stable liver disease based on Child-Pugh score and classification (Child-Pugh Class A [mild], B [moderate], or C [severe]; see Table 1 for details) at Screening and Check-in (if the classification differs when assessed at Check-in compared to Screening, enrollment of the subject into a hepatic category will be based on the score at Screening):
    - 'Documented' is defined by at least 1 of the following: medical history, physical examination, hepatic ultrasound, computed axial tomography scan, magnetic resonance imaging, and/or liver biopsy.
    - 'Chronic' is defined as >6 months.
    - 'Stable' is defined as no clinically significant change in disease status within the last 1 month (30 days) , as documented by the subject's recent medical history (eg, no worsening of clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time, at the discretion of the Investigator [or designee] or Medical Monitor).
10. Subjects with mild, moderate, or severe hepatic impairment may have medical findings consistent with their hepatic dysfunction as determined by medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations at Screening and Check-in (Day -1), as assessed by the Investigator (or designee).
11. Non-hepatic, abnormal clinical laboratory evaluations must not be clinically relevant, as judged by the Investigator (or designee) and Medical Monitor.
12. Currently on a stable medication regimen, defined as not starting new drug(s) or changing drug dose(s) within 30 days of administration of study drug (Day 1).

[redacted]

Concomitant medications administered within 30 days prior to administration of study drug (Day 1) must be approved by the Investigator (or designee), Sponsor, and Medical Monitor.

13. Anemia secondary to hepatic disease will be acceptable, if hemoglobin is > 9 g/dL and anemia symptoms are not clinically significant as judged by the Investigator (or designee) and Medical Monitor.
14. Subjects must have a platelet count $\geq 35 \times 10^9$ platelets/L.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit, unless otherwise stated:

All Subjects

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
4. Alcohol consumption of > 21 drinks per week for males and > 14 drinks for females.
5. Positive urine drug screen at Screening and/or Check-in (Day -1), that is not otherwise explained by permitted concomitant medication or ingestion of poppy seeds, or positive alcohol test result (breath or urine in accordance with standard practice at each CRU) at Screening or Check-in (Day -1).
6. Positive human immunodeficiency virus test.
7. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 30 days, or 5 half-lives (whichever is longer), prior to dosing.
8. Ingestion of Seville orange- or grapefruit-containing foods or beverages within 7 days prior to Check-in (Day -1).
9. Receipt of blood products within 2 months prior to Check-in (Day -1).
10. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
11. Poor peripheral venous access.
12. Have previously completed or withdrawn from this study or any other study investigating belapectin, and have previously received belapectin.
13. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

Subjects with Normal Hepatic Function Only

14. History of alcoholism or drug/chemical abuse within 2 years prior to Check-in.
15. Subject has creatinine clearance <90 mL/minute as calculated by using the Cockcroft-Gault equation:
    a. [1.23 × (140 - age) × (weight in kg)] ÷ (serum creatinine in μmol/L) – if male.
    b. [1.04 × (140 - age) × (weight in kg)] ÷ (serum creatinine in μmol/L) – if female.
16. Confirmed supine blood pressure > 140 mmHg or < 90 mmHg and/or supine diastolic blood pressure > 90 mmHg or < 50 mmHg, or resting (supine) heart rate < 45 bpm or > 100 bpm at Screening or Check-in (Day -1), with a QT interval corrected for heart rate using Fridericia's method (QTcF) > 450 ms for male subjects and > 470 ms for female subjects.
17. Use or intend to use any prescription medications/products other than prescribed hormone replacement therapy or contraception within 14 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in (Day -1), unless deemed acceptable by the Investigator (or designee).
19. Use or intend to use any nonprescription medications/products including vitamins and minerals within 7 days prior to Check-in (Day -1), unless deemed acceptable by the Investigator (or designee).
20. Positive serology test results for hepatitis A, hepatitis B antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibodies.
21. Clinically significant abnormal laboratory values (clinical chemistry, hematology, coagulation, and urinalysis), as determined by the Investigator (or designee).
22. Significant history or clinical manifestation of hepatic disorder, as determined by the Investigator (or designee).
23. History or presence of liver disease or liver injury as indicated by any clinically significant deviations from normal reference ranges in liver function tests, unless approved by the Investigator (or designee).
24. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in (Day -1), or positive cotinine test at Screening or Check-in.

Subjects with Hepatic Impairment Only

25. Cirrhosis etiology of primary biliary cholangitis or primary sclerosing cholangitis.
26. History of alcoholism or drug/chemical abuse within 6 months prior to Check-in.
27. Evidence of hepatorenal syndrome and/or creatinine clearance < 45 mL/min, as calculated using the Cockcroft-Gault equation:
    a. [1.23 × (140 - age) × (weight in kg)] ÷ (serum creatinine in μmol/L) – if male.

   b. [1.04 × (140 - age) × (weight in kg)] ÷ (serum creatinine in µmol/L) – if female.

28. Confirmed supine blood pressure > 150 mmHg or < 90 mmHg and/or supine diastolic blood pressure > 90 mmHg or < 50 mmHg, or resting (supine) heart rate < 45 bpm or > 100 bpm at Screening or Check-in (Day -1), with a QTcF > 480 ms for male and female subjects.
29. Use or intend to use any prescription medications/products within 14 days of study drug administration, with the exception of:
    a. stable medication regimen, as approved by the Investigator (or designee), Sponsor, and Medical Monitor; see inclusion criterion 12
    b. prescribed hormone replacement therapy
    c. prescribed contraceptive (see Appendix 3).
30. Values outside the normal range for liver function tests that are not consistent with their hepatic condition, as determined by the Investigator (or designee).
31. Positive serology test results for hepatitis A, hepatitis B DNA (hepatitis B DNA levels will be analyzed if subject tests positive for HBsAg or hepatitis B core antibodies), or hepatitis C RNA (hepatitis C RNA levels will be analyzed if subject tests positive for hepatitis C antibodies).
32. Clinically significant abnormal physical examination, vital signs, and/or ECG findings that are not consistent with their degree of hepatic dysfunction, as determined by the Investigator (or designee).
33. Recent history, or the treatment of, esophageal bleeding (within the 180 days prior to Screening), unless banded.
34. History of hepatic shunt surgery or presence of a portosystemic shunt.
35. History of paracentesis within 7 days prior to screening. Paracentesis will not be permitted throughout the study.
36. Current functioning organ transplant or awaiting organ transplant.
37. Evidence of severe ascites needing paracentesis/not controlled by medication.
38. Current symptoms or recent history of hepatic encephalopathy (Grade 2 or above) at Screening.
39. Smoke more than 10 cigarettes, or use the equivalent tobacco- or nicotine-containing products (including vaping), per day or inability to refrain from tobacco/nicotine use 2 hours predose until 4 hours postdose.
40. Unstable diabetes as evidenced by hemoglobin A1c > 9%.

4.3. Child-Pugh Classification

Per EMA and FDA guidance[4,5], hepatic impairment will be classified according to the Child-Pugh system (Table 1), and the parameters to determine Child-Pugh classification for subjects with hepatic impairment will be collected at Screening and re-collected at Check-in (Day -1). If the Child-Pugh classification of a subject differs between Screening and Check-in

(Day -1), the Child-Pugh classification documented at Screening will be utilized for enrollment.

Table 1: Child-Pugh Assessment of Hepatic Function

	Points Scored for Observed Findings		
	1	**2**	**3**
Hepatic encephalopathy grade[a]	0	1 or 2[b]	3 or 4[b]
Ascites[c]	Absent	Slight	Moderate to severe
Serum bilirubin, mg/dL (µmol/L)	< 2 (< 34)	2 to 3 (34 to 50)	> 3 (> 50)
Serum albumin, g/dL (g/L)	> 3.5 (> 35)	2.8 to 3.5 (28 to 35)	< 2.8 (< 28)
International normalized ratio	< 1.7	1.7 to 2.3	> 2.3

Chronic hepatic impairment is classified into Child-Pugh Class A to C, employing the added score of the 5 parameters described.
Mild hepatic impairment (Child-Pugh Class A) = 5 or 6 points
Moderate hepatic impairment (Child-Pugh Class B) = 7 to 9 points
Severe hepatic impairment (Child-Pugh Class C) = 10 to 14 points

a. In the current study, hepatic encephalopathy will be graded according to the following criteria:
   Grade 0: normal consciousness, personality, neurological examination, or normal encephalogram
   Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves; or hepatic encephalopathy controlled with medication
   Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves
   Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves
   Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cps delta activity
b. Subjects with hepatic encephalopathy Grade 2 or above will not be enrolled into the study.
c. Subjects with evidence of severe ascites will not be enrolled into the study. Ascites will be graded according to the following criteria:
   Absent: no ascites is detectable by manual examination or by ultrasound investigation (if performed)
   Slight: ascites palpitations doubtful, but ascites measurable by ultrasound investigation (if performed); or ascites controlled by 1 medication
   Moderate: ascites detectable by palpitations and by ultrasound investigation (if performed); or ascites controlled by 2 or more medications
   Severe: necessity of paracentesis; does not respond to treatment (not admitted into the study)

4.4. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number prior to dosing.

The subject number will consist of a 3-digit site number followed by a 3-digit identification number. The identification number will be assigned in ascending order at each site (eg, Subjects 101-101, 101-102, 101-103 at site 101). The identification number will start at 101 for subjects with normal hepatic function (Group 1). The identification number will start at 201, 301, or 401 for subjects with mild, moderate, or severe hepatic impairment (Groups 2, 3, and 4), respectively.

Subjects will be identified by Screening identification number and/or subject number on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 5). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the Investigator, Medical Monitor, and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.6. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Medical Monitor if any of the following criteria are met:

- AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The solution for injection provided [redacted] belapectin (in phosphate buffered saline) will be supplied by the Sponsor (or designee), along with the lot numbers and Certificates of Analysis. Belapectin will be provided in [redacted] sterile vials and stored according to the instructions on the label.

[redacted]

Investigational medicinal products will be stored at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The IMPs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

5.2. Study Treatment Administration

Each dose of belapectin (4 mg/kg LBM) will be administered intravenously. Food and water will not be restricted; standardized meals will be provided whilst subjects are resident in the CRU.

Subjects will be dosed in numerical order.

5.3. Randomization

This is a non-randomized study. All subjects will receive the same treatment.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered by suitably qualified study site staff.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of belapectin solution received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused belapectin solution will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent, unless otherwise stated (see inclusion criterion 12, Section 4.1).

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone replacement therapy, and oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

Standard meals will be provided whilst subjects are resident in the CRU. Subjects may consume water ad libitum throughout the study.

Foods and beverages containing grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until Follow-up on Day 15.

Caffeine-containing foods and beverages will not be allowed from 48 hours prior to Check-in until Follow-up on Day 15.

Consumption of alcohol will not be permitted from 72 hours prior to Check-in until Follow-up on Day 15.

6.3. Smoking

Subjects with normal hepatic function will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

Subjects with hepatic impairment will not be permitted to smoke > 10 cigarettes, or use the equivalent tobacco- or nicotine-containing products (including vaping), per day. Subjects will not be permitted to smoke or use tobacco- or nicotine-containing products (including vaping) for 2 hours predose until 4 hours postdose.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days prior to Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during

this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood samples (for belapectin assay)
- urine samples (for belapectin assay)
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Sample Collection and Processing

Blood samples [redacted] will be collected for PK analysis (Section 8.3) by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 5. For the blood samples collected, after sample analyses described in Section 8.3, remaining samples may be used for additional exploratory analyses.

Urine samples will be collected into preweighed polyethylene containers over the time intervals indicated in the Schedule of Assessments in Appendix 5.

Procedures for collection, processing, and shipping of blood and urine samples will be detailed in a separate document.

The maximum blood volume to be withdrawn per subject will not exceed 450 mL.

7.1.2. Analytical Methodology

Plasma and urine concentrations of belapectin will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in a separate document.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study treatment until study completion. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an Investigator's (or designee's) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion.

7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 5. Clinical laboratory evaluations are listed in Appendix 2.

All subjects will be asked to provide urine samples for drugs of abuse screen and will undergo a breath or urine alcohol test at the times indicated in the Schedule of Assessments in Appendix 5. Subjects with normal hepatic function will also be tested for cotinine.

For all female subjects of childbearing potential, a pregnancy test will be performed at the time indicated in the Schedule of Assessments in Appendix 5. For all postmenopausal female subjects, a follicle-stimulating hormone (FSH) assessment will be performed at the times indicated in the Schedule of Assessments in Appendix 5.

All measurements will be performed singly and may be repeated once if outside the relevant clinical reference range. An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.2.3. Vital Signs

Supine blood pressure, supine pulse rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 5. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.2.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 5. Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF > 500 ms
- QTcF change from the baseline (predose) is > 60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.2.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 5.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 40 subjects will be enrolled in the study.

No formal sample size determination has been performed. The sample size determination is based on historical studies of a similar nature and was not based on power calculations to detect statistically significant differences among groups. Eight evaluable subjects per hepatic impairment group (ie, mild, moderate, or severe) and approximately 16 evaluable subjects with normal hepatic function are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of belapectin under various degrees of hepatic function.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received a dose of belapectin and have evaluable PK data.

8.2.2. Safety Population

The safety population will include all subjects who received a dose of belapectin.

8.3. Pharmacokinetic Analyses

The plasma PK parameters of belapectin will be calculated using standard noncompartmental methods.

The primary PK parameters are AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, and C_{max} for belapectin. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis.

Evaluation of PK of belapectin will be performed following a single dose in subjects with mild, moderate, or severe hepatic impairment ('Test' groups) compared to matched subjects with normal hepatic function ('Reference' group).

If an individual healthy subject is matched to a subject from any or all hepatic impairment groups, a paired t-test will be applied to analyze the natural log-transformed primary PK parameters (C_{max}, $t_{½}$, AUC_{0-t}, and $AUC_{0-\infty}$) for belapectin. The paired t-test will be performed separately for each hepatic impairment group and the corresponding matched healthy controls. Estimates of geometric mean ratios in primary PK parameters between each level of impaired hepatic function versus the matched healthy controls will be presented along with the corresponding 90% confidence intervals for the geometric mean ratios. The p-value assessing the difference between each impairment group and the healthy control group will be presented.

Plasma concentrations and PK parameters will be summarized by group using descriptive statistics (number, arithmetic mean, standard deviation, geometric mean, geometric coefficient of variation, median, minimum, and maximum).

Model for End-Stage Liver Disease (MELD) scores will also be calculated for each subject, to explore the relationship between MELD scores and the PK parameters of belapectin.

Subjects receive an initial MELD score (MELD[i]) equal to: 0.957 x ln(creatinine mg/dL) + 0.378 x ln(bilirubin mg/dL) + 1.120 x ln(international normalized ratio) + 0.643

Note: ln = natural log (base e)

Laboratory values less than 1.0 will be set to 1.0 when calculating a subject's MELD score.

The following subjects will receive a creatinine value of 4.0 mg/dL:

- Subjects with a creatinine value greater than 4.0 mg/dL
- Subjects who received 2 or more dialysis treatments within the prior 7 days
- Subjects who received 24 hours of continuous veno-venous hemodialysis within the prior 7 days.

The maximum MELD score is 40. The MELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10.

The MELD(i) score is then re-calculated as follows to obtain a MELD-sodium (MELD-Na) score:

MELD-Na = MELD(i) + 1.32*(137-Na) – [0.033*MELD(i)*(137-Na)]

Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.

8.4. Safety Analysis

Safety and tolerability data will be listed, and a listing of the subjects with hepatic impairment and their matched subject with normal hepatic function will be provided. Each AE will be coded using the Medical Dictionary for Regulatory Activities. All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each hepatic function group will be presented by severity and by association with the study drug as determined by the Investigator (or designee). Values for clinical laboratory data, vital signs, 12-lead ECGs and physical examinations will be listed.

No inferential statistical analyses are planned for safety data.

A comparison of the calculation of estimated glomerular filtration rate by the Modification of Diet in Renal Disease (MDRD) versus the Cockcroft-Gault equation will be undertaken in the analysis to evaluate the potential bias caused by increased body weight when using the Cockcroft-Gault equation for creatinine clearance estimation.

8.5. Interim Analysis

No interim analyses are planned for this study.

An interim review of preliminary PK, safety, and tolerability data with a minimum of 2 subjects with severe hepatic impairment (Group 4) + 2 matched normal hepatic function subjects (Group 1) will be performed once they have completed Day 10. It will then be determined whether returning for an outpatient visit on Day 10 will be necessary for the remaining subjects. Amendment to the protocol will also be considered, notably to protect patient safety, and the decision to treat more subjects with hepatic impairment at the same dose of belapectin may be taken.

9. REFERENCES

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the Follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be

completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the CRU. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the study site to the Sponsor, Medical Monitor assigned by the Sponsor, and the responsible Institutional Review Board (IRB).

The Sponsor and Medical Monitor will be notified in writing (eg, facsimile) within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported.

Subsequently, a written confirmation or summary of the AE (using FDA Form 3500A or equivalent) will be sent to the Sponsor within 3 working days of the original notification.

The IRB will be notified of any FDA-reportable AEs within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

The responsibility for reporting SAEs will be transferred to the Sponsor 30 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Gamma-glutamyl transferase Glucose Potassium Sodium Total bilirubin[a] Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Coagulation profile: Activated partial thromboplastin time International normalized ratio Prothrombin time	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis A Hepatitis B DNA level[c] Hepatitis B surface antigen Hepatitis C antibody Hepatitis C RNA level[d]Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Cotinine test[b]	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Subjects with normal hepatic function only.
[c] Subjects with hepatic impairment only: Hepatitis B DNA levels will be analyzed if a positive result is reported for either hepatitis B surface antigen or hepatitis B core antibodies.
[d] Subjects with hepatic impairment only: Hepatitis C RNA levels will be analyzed if a positive result is reported for hepatitis C antibodies.

Appendix 3: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Women aged > 60 years old whose FSH values are not ≥ 40 mIU/L may be included at the discretion of the Investigator and in consultation with the Sponsor.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the ICF until 90 days after the Follow-up visit. Primary (non-barrier) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant

- hormonal or non-hormonal intrauterine device
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from Check-in (Day -1) until 90 days after the Follow-up visit.

Male Subjects

Male subjects will be surgically sterile for at least 90 days, with documented azoospermia, or when sexually active with female partners of childbearing potential will be required to use a male condom with spermicide (including vasectomized males) from Check-in until 90 days after the Follow-up visit. Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of dosing until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European Directive 2001/20/EC for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with CRU personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving

their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and

verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any Screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed in a separate agreement.

Appendix 5: Schedule of Assessments

Schedule of Assessments

Study Procedures	Screening (Days -28 to -2)	In-Clinic Stay							Outpatient Visit[a]	Follow-up Visit
		Day -1 (Check-in)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 (Discharge)	Day 10	Day 15
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographic data	X									
Medical history	X	X[b]								
Child-Pugh classification[c]	X	X								
Hemoglobin A1c[c]	X									
Urinary drug screen	X	X								
Alcohol breath or urine test[d]	X	X								
Cotinine test[e]	X	X								
Serology	X									
Pregnancy test[f]	X	X								X
FSH[g]	X									
Height and body weight	X[h]	X								
Study residency:										
Check-in		X								
Check-out								X[i]		
Nonresidential visit	X								X	X
Study drug administration:										
Belapectin			X							
Pharmacokinetics:										
Blood sampling[j]		X	X	X	X	X	X	X	X	X
Urine sampling[k]		X	X	X	X	X	X	X		

Schedule of Assessments

Study Procedures	Screening (Days -28 to -2)	In-Clinic Stay							Outpatient Visit[a]	Follow-up Visit
		Day -1 (Check-in)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 (Discharge)	Day 10	Day 15
Safety and tolerability:										
Adverse event recording	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication monitoring	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations	X	X				X		X		X
Vital signs (blood pressure, pulse rate, and body temperature)	X	X	X	X	X			X	X	X
12-lead electrocardiogram	X	X	X					X		X
Full physical examination	X	X								
Symptom-directed physical examination								X[l]	X	X

Abbreviations: ECG = electrocardiogram; FSH = follicle stimulating hormone; PK = pharmacokinetic(s).

a. Following review of preliminary PK data for the first 2 subjects in Group 4 + 2 matched subjects in Group 1, the PK sampling timepoints will be confirmed or revised and it will be determined whether returning for an outpatient visit on Day 10 will be necessary for the remaining subjects.
b. Interim medical history.
c. Subjects with hepatic impairment only.
d. May be performed in either urine or breath. At Screening, a positive alcohol test may be repeated once. At Check-in (Day -1), a positive alcohol test may not be repeated.
e. Subjects with normal hepatic function only.
f. In female subjects of childbearing potential; performed in serum at Screening and urine at all other timepoints.
g. Post-menopausal females only.
h. Height measured at Screening only.
i. Subjects will check-out of the Clinical Research Unit following the 120-hour post-dose PK blood samples.
j. Blood samples for PK will be taken on Day -1, and on Day 1 at predose and 3 hours postdose (post-end of infusion), and then at 24 and 36 hours postdose (Day 2), 48 hours (Day 3), 72 hours (Day 4), 96 hours (Day 5), 120 hours (Day 6), 216 hours (Day 10), and 336 hours (Day 15) postdose. The sample collected at 3 hours postdose will have a sampling window of ± 1 hour. The samples collected from 24 through 336 hours postdose will have a sampling window of ± 2 hours. Times of all PK samples will be recorded to the nearest minute.

k. Urine samples for PK will be taken on Day -1 (spot sample), at pre-dose (spot sample) on Day 1 and at the following intervals: 2 to 4, 4 to 24, 24 to 36, 36 to 48, 48 to 72, 72 to 96, and 96 to 120 hours post-dose.
l. Assessed prior to discharge on Day 6.