GT-032 Statistical Analysis Plan

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: 16 November 2020

Statistical Analysis Plan

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

SAP Status: Final
SAP Version: 1.0
SAP Date: [redacted]

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

Protocol Reference Number: GT-032
[redacted]

Sponsor:
Galectin Therapeutics, Inc.
4960 Peachtree Industrial Blvd., Suite 240
Norcross, GA 30071
United States

Study Site:
Multiple Study Sites

Principal Investigator:
Multiple Principal Investigators

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

λ_z	apparent terminal elimination rate constant
ADaM	Analysis Data Model
A_e	amount of dose excreted in the urine
A_{et1-t2}	amount of dose excreted in the urine over the time interval t1 to t2
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	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
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity
BLQ	below the limit of quantification
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL	total clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CP	Child-Pugh
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
F_e	percentage of dose excreted in the urine
F_{et1-t2}	percentage of dose excreted in the urine over the time interval t1 to t2
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IV	intravenous
LBM	lean body mass
LLOQ	lower limit of quantification
ln	natural log (base e)
MDRD	Modification of Diet in Renal Disease
MELD	Model for End-Stage Liver Disease
MELD(i)	initial Model for End-stage Liver Disease score
n	number of subjects with valid observations
Na	sodium

NC	not calculated
NCA	non-compartmental analysis
PK	pharmacokinetic(s)
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of the maximum observed concentration
t_{last}	time of last measurable concentration
$t_{1/2}$	terminal elimination half-life
V_{ss}	apparent volume of distribution at steady state
V_z	volume of distribution during the terminal phase

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol amendment [redacted] and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK) and safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Galectin Therapeutics, Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Galectin Therapeutics, Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Council for Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- To assess the 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.

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 ($t_{1/2}$)
- 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 adverse events (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. 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:

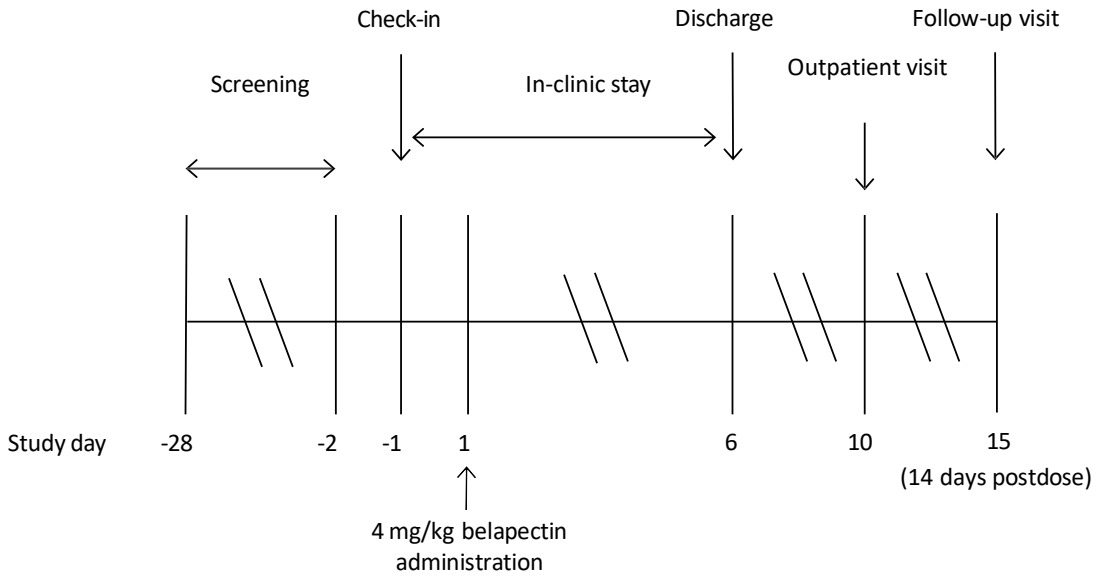
- Group 1: matched healthy subjects with normal hepatic function
- Group 2: subjects with mild hepatic impairment (Child-Pugh Class A [4 x subjects with a score of 5 and 4 x subjects with a score of 6])
- Group 3: subjects with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9])

- 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.

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).

4. SAMPLE SIZE JUSTIFICATION

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.

5. STUDY TREATMENT

All subjects will receive a single dose of 4 mg/kg of lean body mass (LBM) belapectin solution for injection administered intravenously (infused over approximately 60 minutes). The planned treatment will be referred to as 4 mg/kg LBM Belapectin IV.

The TFLs will reflect the actual treatment received.

[redacted] Table 1

[redacted]

6. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

6.1. All Subjects Population

The all subjects population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

6.2. Safety Population

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

6.3. Pharmacokinetic Population

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

7. STATISTICAL METHODOLOGY

7.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they completed all protocol-specified procedures and assessments for the Follow-up visit. Any subject who discontinued the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 2.2.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics and statistical analyses.

7.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.

- Missing values will not be imputed unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

7.1.2. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 7.1.3).

7.1.3. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded prior to the start of the infusion. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the start of the infusion.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The mean change from baseline will be defined as the mean of the individual changes from baseline for all subjects.

See Section 7.1.2 for more detail on handling repeat and unscheduled readings in the calculations.

7.2. Subject Disposition and Population Assignment

Subjects' hepatic function, disposition and population assignment will be listed.

A summary table by hepatic function will be provided, based on the all subjects population.

7.3. Screening Demographics

The screening demographics including age, sex, child-bearing potential, race, ethnicity, height, body weight, and BMI will be listed. A listing displaying the matching of subjects will be included.

A summary table by hepatic function will be provided, based on the safety population.

The CP total score will be summarized for subjects with hepatic impairment only. The CP score will not be assessed for subjects with normal hepatic function. For these subjects, the serum bilirubin, serum albumin and international normalized ratio results obtained from the

clinical laboratory evaluations will be used to derive the respective CP component scores, and these scores will be listed as derived.

7.4. Prior and Concomitant Medication

Prior medication will be defined as medication which starts and ends prior to the start of the infusion. Concomitant medication will be defined as medication that starts during or after the start of the infusion or starts but does not end prior to the start of the infusion.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary Global, Format B3, Version March 2020 (or later if upversioned during the study). Prior and concomitant medications will be listed.

7.5. Pharmacokinetic Assessments

7.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined from the individual plasma belapectin concentration-time profiles obtained following single IV dosing with 4 mg/kg LBM by non-compartmental methods performed using the validated software program, Phoenix WinNonlin (Certara USA Inc, Version 8.1 or higher):

Parameter	Definition
AUC_{0-t}	area under the concentration-time curve from time 0 to the last measurable concentration
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity, calculated as $100*(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty}$
C_{max}	maximum observed concentration
t_{max}	time of the maximum observed concentration
t_{last}	time of last measurable concentration
$t_{1/2}$	terminal elimination half-life
CL	total clearance
V_z	volume of distribution during the terminal phase, calculated as $V_z = \frac{CL}{\lambda_z}$
V_{ss}	apparent volume of distribution at steady state

Additional plasma PK parameters may be determined where appropriate.

Pharmacokinetic parameters will be calculated for each subject using actual doses and actual sampling times after start of infusion. If an actual time is missing, the nominal time will be used.

[redacted]The units of concentration and resulting PK parameters, with amount or concentration in the units provided, will be presented as they are received

from the analytical laboratory by default, but the units can be changed appropriately [redacted] if the reading is too small or too big.

The C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}. Area under the concentration-time curve (AUC) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up/log down rule).

The following PK parameters will be determined, where possible, from the urine concentrations of belapectin following single IV dose administration of 4 mg/kg LBM.

Parameter	Definition
$A_{et1\text{-}t2}$	amount of dose excreted in the urine over the time interval t1 to t2
CL_R	renal clearance
$F_{et1\text{-}t2}$	percentage of dose excreted in the urine over the time interval t1 to t2

The amount of dose excreted in the urine (A_e) and F_e will be calculated by time interval and cumulatively. The A_e for each urine collection interval will be calculated as the product of urine concentration and urine volume. Cumulative A_e will be calculated by summing the A_e values for each collection interval over the collection period or dosing interval.

Urine concentrations below the lower limit of quantification (LLOQ) will be treated as numerical 0 for the calculation of A_e and F_e.

The F_e will be calculated for each urine collection interval and cumulatively as follows:

$$F_e = \frac{A_e}{Dose} \times 100\%$$

The CL_R will be calculated as follows:

$$CL_R = \frac{A_{e,0-x}}{AUC_{0-x}}$$

Where 0-x represents the same time interval for both A_e and AUC. Where the planned AUC cannot be calculated CL_R may be calculated using another appropriate AUC and A_e over the same time intervals.

7.5.1.1. Criteria for Handling Concentrations Below the Limit of Quantification and Missing for Non-Compartmental Analysis and Individual Plot

For the non-compartmental analysis (NCA) and individual plot, if a BLQ value occurs before the first measurable concentration, it will be assigned a value of 0, otherwise it will be treated as missing. The following rules apply with the situation defined below:

- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless they are considered to be a true characteristic of the profile of the drug.

- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

- If a predose concentration is missing, these values will be set to 0 by default.

7.5.1.2. Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is ≥0.7. In cases where the constant λ_z is not assigned, the values of associated variables (i.e., $t_{1/2}$, $AUC_{0-\infty}$, CL, V_{ss}, and V_z) will not be calculated and the PK handover will mark them as not calculated (NC). In case the percent of $AUC_{0-\infty}$ extrapolated exceeds 30%, $AUC_{0-\infty}$ and related PK parameters (CL, V_z) will be listed and flagged, but will be excluded from PK parameter summary statistics and formal statistical analysis, at the discretion of the Sponsor or pharmacokineticist.

The following regression-related diagnostic PK parameters will be determined:

Parameter	Units	Definition
λ_z	h^{-1}	apparent terminal elimination rate constant
λ_z Upper	H	end of exponential fit
λ_z Lower	H	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

The time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives.

7.5.1.3. Calculation of Area Under the Concentration-time Curve

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the LLOQ. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

- If $AUC_{0-\infty}$ cannot be determined reliably for all subjects, an alternative AUC measure, such as AUC to a fixed timepoint, may be used in the statistical analysis.

- For any partial AUC determination (i.e. AUC over a specific time interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the pharmacokineticist.

7.5.1.4. Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and the CSR.

- Quantifiable predose concentration values will be considered anomalous and set to missing for the PK analysis.

7.5.2. Presentation of Pharmacokinetic Data

7.5.2.1. Presentation Pharmacokinetic Plasma Drug Concentration Data

For the PK concentration summary and mean plot, all BLQ values will be set to 0. The following rules apply with the situations defined below:

- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be listed but excluded from PK concentration summary unless they are considered to be a true characteristic of the profile of the drug.

- If there are less than 3 values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as NC.

- If any of the values at a certain timepoint are BLQ, the geometric mean and geometric coefficient of variation (CV) will be denoted as NC.

- In case of missing predose measurement for the first dose, the missing data will be set as 0. For the other cases, the missing data is not imputed and will be excluded from the analysis.

Actual sampling times that are outside the sampling window will be listed and used for PK parameter calculations, but will be excluded from summary of concentrations. [redacted] 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.

7.5.2.2. Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all no result and NC values in a data series will be set to missing.

7.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by hepatic function, sex, and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales. The +SD bars will only be displayed on the linear scale.

Summary tables by hepatic function and sex will be provided for all PK parameters, with the exception of regression-related PK parameters. Separate summary tables by hepatic function, sex, and time interval will be provided for excretion parameters and cumulative excretion parameters. Mean (+SD) cumulative percentage of dose excreted will be plotted on the linear scale.

The primary PK parameters are $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, and $t_{1/2}$ 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 (ln)-transformed[3] primary PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, C_{max}, and $t_{1/2}$) 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.

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.

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.

The relationship between the primary PK parameters ($AUC_{0-\infty}$, AUC_{0-t}, C_{max}, and $t_{1/2}$) with the MELD and MELD-Na scores will be assessed graphically using scatter plots. Regression lines, R^2 values, and p-values for 0 slope will be presented to assess relationships.

7.6. Safety and Tolerability Assessments

7.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities Version 23.0 (or higher if upversioned during the study).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the start of the infusion, or starts prior to the start of the infusion and increases in severity after the start of the infusion.

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the start of the infusion for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by hepatic function
- TEAEs by severity and hepatic function
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by hepatic function.
- Treatment-related TEAEs by severity and hepatic function.

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and hepatic function
- Preferred term and hepatic function

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the start of the infusion.

- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, the study treatment relationship will not be derived.

- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the start of the infusion is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, the severity of the TEAE will not be included in summary statistics.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

7.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and boxplots by hepatic function and timepoint will be provided for clinical chemistry, hematology, and coagulation parameters, with changes from baseline.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, <x and ≤x values will be set to 0, whereas >x and ≥x values will be set to x.

7.6.3. Vital Signs Parameters

All vital signs parameters, with changes from baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by hepatic function and timepoint will be provided for all vital signs parameters, with changes from baseline.

7.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters will be listed; any value outside the clinical reference range will be flagged.

Boxplots by hepatic function and timepoint will be provided for all 12-lead ECG parameters.

All 12-lead ECG interpretations performed by the investigator (or designee) will be listed.

7.6.5. Other Assessments

A comparison of the calculation of estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD)[4] versus the Cockcroft-Gault equation[5] 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.

The MDRD equation is defined by the following formula:

MDRD formula (mL/min/1.73m^2) = 175 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

The Cockcroft-Gault equation is defined by the following formula:

- *Cockcroft-Gault formula = [1.23 × (140 - age) × (weight in kg)] ÷ (serum creatinine in µmol/L) – if male*
- *Cockcroft-Gault formula = [1.04 × (140 - age) × (weight in kg)] ÷ (serum creatinine in µmol/L) – if female.*

A summary table by hepatic function will be provided for eGFR and creatinine clearance estimation.

Medical history will be listed.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

7.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

8. INTERIM ANALYSES

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. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

10. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

3. Keene ON. The log transformation is special. *Stat Med*. 1995;14(8):811-819.

4. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 2010. Guidance for industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling.

5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

11. APPENDICES

Appendix 1: Document History

Status, Version	Date of Change	Summary/Reason for Changes
[redacted]	[redacted]	[redacted]

NA = not applicable

16.1.9.2. Quality Tolerance Limit Definitions

Not applicable.