STATISTICAL ANALYSIS PLAN

Specific to the non-compartmental analysis of study:

Study title : A bioequivalence study to compare the pharmacokinetics of two formulations of hydroxycarbamide® in healthy volunteers

Protocol number:	SIK-FR-21-1
Drug name:	hydroxycarbamide
Drug development phase:	Phase I
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PhInC reference:	PH20064
Version - date:	Version 1.0 - 16/09/2021
NCT Number:	05025072

This study was conducted in full compliance with applicable Good Clinical Practices and regulations, including archiving.
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1 ANALYSIS SETS

1.1 ENROLLED SET

The enrolled set will include all enrolled participants. This set is not discussed in this SAP.

1.1.1 Safety set

All randomised participants who receive at least 1 dose of IMP will be included in the safety analysis. This set is not discussed in this SAP.

1.1.2 PK set

The PK set will include all participants from Safety Set who completed the study (completed all study periods and EOS) without major protocol deviations or events implying bias for the PK evaluation as outlined in the paragraph below.

The following events will be considered relevant events likely to imply a bias for the PK evaluation:

- Participant experienced emesis within 2.4 hours post-dose (2 times expected median time of t_{max})
- Missing sample(s) at time point(s) around the expected t_{max} of hydroxycarbamide
- Intake of concomitant medication which is expected to affect the PK of hydroxycarbamide.

Moreover, under certain circumstances, it may be justified to exclude participant's data from the bioequivalence assessment for one or all treatments after the review of the plasma concentration data due to an unforeseeable event implying bias for the PK evaluation. This includes, but is not limited to:

- Missing concentrations due to bioanalytical reasons around the t_{max}
- Participant experienced diarrhoea of moderate or severe intensity during the study and it is judged likely to have affected the PK evaluation

In such cases where the decision the exclude a participant or participant's data was taken after bioanalysis, bioequivalence assessment will be performed with and without the participant's data, unless specified otherwise in the study protocol.

2 PRESENTATION OF RESULTS

2.1 GENERAL SPECIFICATION

The individual data listings, descriptive statistics and figures will be generated in Word or rtf format and presented in the PK report. Apart from those described in this document, specific tables may be generated for direct insertion in the PK report.

2.2 GENERAL RULES FOR STUDY DATA

2.2.1 General rules

All data derived for PK analysis will be presented in the individual data listings.

All listings will be presented sorted by treatment and participant number.

Concentrations will be presented using the same number of significant digits or decimals as the data provided by the bioanalytical laboratory. PK parameters will be presented using a precision of 2 decimals (for terminal

elimination rate-constant (k_e) additional decimals could be added), except for PK parameters derived directly from observed concentrations (*e.g.* C_{max}) which will be presented using the same number of significant digits or decimals as raw data.

Descriptive statistics will be presented with the same number of significant digits or decimals as the individual data except for coefficient of variation (CV%), which will be presented with only one decimal.

2.2.2 Handling of drop-outs and missing data

Missing data will not be replaced, descriptive statistics and statistical analysis will be performed on the basis of the available data only.

In case of missing actual time of sampling, the scheduled time will be used for derivation of PK parameters.

All data recorded on discontinued participants will be listed.

3 PHARMACOKINETIC ANALYSIS

3.1 ANALYSIS DATASET

Source datasets required for the PK analysis will be transferred from this CRO responsible of CDISC activities (*i.e.* SDTM mapping and ADaM generation) to PhinC using specifications described in a separate data transfer agreement (DTA).

3.2 PK ENDPOINTS

Derivation of PK parameters will be carried out by PhinC Development using Phoenix WinNonlin® (Version Phoenix 8.1 or higher – Certara – Princeton – USA). PK parameters in plasma will be calculated using non-compartmental methods.For each calculation of the PK parameters and characteristics the following rules will be applied:

- All the plasma concentrations validated by the bioanalytical laboratory and provided to the pharmacokineticist will be used for the PK analysis.
- The actual blood sampling time points related to the preceding administration will be used.
- At time points in the lag-time between time zero and the first concentration equal or above limit of quantification (LOQ), concentrations below LOQ (BLQ) will be set to zero (0). Concentrations BLQ between 2 concentrations equal or above LOQ will be considered as missing. Trailing concentrations BLQ will not be used in calculations.
- For plasma concentration above the upper limit of quantification and reported as above limit of quantification (ALQ) in the final plasma concentration tables, ALQ will be replaced by the first measurement for the PK analysis.
- Not reported (NR) concentration will be excluded from the PK analysis.
- If pre-dose concentration is less than or equal to 5% of C_{max} value in a PK profile, the participant's data can be included in all PK measurements and calculations without any adjustments. If the pre-dose value is greater than 5% of C_{max}, the participant will be dropped from all statistical evaluations (no additional bioequivalence evaluation including the participant will be required).

The following PK parameters of hydroxycarbamide will be calculated for each treatment (period) and each participant:

C_{max} The observed maximum concentration in plasma measured in a participant after dosing identified by inspection of the plasma drug concentration *vs.* time data.

t_{max} The time at which C_{max} is apparent, identified by inspection of the plasma drug concentration *vs.* time data by Phoenix WinNonlin®.

k_e The terminal plasma elimination rate-constant will be estimated from log-linear regression analysis of the terminal phase of the plasma concentration-time profile. The number of points included in the terminal phase will be determined by visual inspection of the semi-log plots of the plasma concentration-time profiles. A minimum of 3 data points, including the last measured data point and excluding C_{max}, are available for the regression). The correlation coefficient for the goodness of the fit of the regression line through the data points (r^2) must be 0.90 or higher, for the value to be considered reliable. No derived parameters ($t_{1/2}$, AUC_{extra} or $AUC_{0-\infty}$) will be determined with unreliable elimination rate constants (hence, considered as not calculable – NC).

$t_{1/2}$ The apparent terminal elimination half-life will be calculated as $\ln 2/k_e$, where k_e is the elimination rate constant as defined above.

AUC_{0-t} The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration (AUC_{0-t}) will be calculated using a linear trapezoidal method (at least 3 time points with quantifiable concentration).

$AUC_{0-\infty}$ The AUC from time 0 to infinity will be calculated as $AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty}$, where AUC_{0-t} is the area under the concentration-time curve as defined above and $AUC_{t-\infty} = C_t/k_e$, where C_t is the measured concentration at time of the last quantifiable concentration t. The extrapolated part of $AUC_{0-\infty}$ must be lower than 20% for the value be considered as reliable. $AUC_{0-\infty}$ determined with percentage of extrapolation above 20% will be flagged in the listing. Those values will not be excluded from descriptive statistics or bioequivalence evaluation.

AUC_{extra} % of AUC extrapolated

3.3 POPULATIONS ANALYZED

The PK analysis will be performed on the PK analysis set

3.4 STATISTICAL METHODS

PK statistical analysis will be carried out by PhinC Development using the SAS® package (release 9.4) or using Phoenix WinNonlin® version 8.1.

The k_e dependent parameters ($AUC_{0-\infty}$, $t_{1/2}$ and AUC_{extra}) will not be determined with $r^2 < 0.9$ and will not be taken into account in statistics.

3.4.1 Descriptive statistics

Individual analyte concentrations will be presented by treatment and time point. Descriptive statistics for the concentrations will be presented as N (number of subjects in the PK set [by treatment]), n (number of observations), mean, SD, CV%, median, minimum (Min) and maximum (Max) values and geometric mean (GM), and will be calculated if at least 2/3 of the values per time-point are non-missing. For descriptive statistics calculations, concentrations BLQ will be set to zero (0) before the first concentration equal or above LOQ and considered as missing after.

Individual PK parameters will be presented by participant and treatment.

Descriptive statistics of PK parameters will be presented by treatment. Descriptive statistics of the PK parameters will be presented as N, n, mean, SD, CV%, median, Min and Max values, as well GM and will be calculated if N≥3.

In the tables of individual PK parameters, all the deviations from planned analysis will be mentioned by flagging the abnormal results (e.g. percentage of extrapolated AUC > 20%).

Measured concentration *vs.* actual time curves will be produced in graphic for each participant on both linear/linear and log/linear scales. Mean (±SD) plasma concentration *vs*. time curves will be presented by treatment using theoretical blood sampling times.