NONMEM Simulation Dataset

Article Title: Application of population pharmacokinetics to cladribine

Analyte(s): Cladribine

Matrix: Plasma

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Light Blue: compound needing to be changed

Light Gray: units specific to each model

Gold: Covariates

Yellow Filled: NONMEM calculated PK Parameters

Green: Parameter ETAs are affecting

Yellow Highlight: Items in DST that may need their notes changed

# NONMEM Dataset Variables and Descriptions

| **Data Item ID** | **Data Item Description** | **Format** | **Sig Digit Display** | **Input Decimal  Places** | **Units** | **Data Item Notes** |
| --- | --- | --- | --- | --- | --- | --- |
| C | Comment Data Item | C or .  (Text) | N/A | N/A | N/A | * Top row of dataset should contain ‘C’ with variable names in each column * Any observation or dosing records to be excluded should be commented out (Insert ‘C’), otherwise the field should be set to missing (ie, “.”) |
| ID | NONMEM Specific  Subject / Patient Identification Number | (Numerical Integer) | 4 | 0 | N/A | * Each subject has a unique ID value * ID should be sequential starting from 1 to 9,999 subjects throughout the dataset |
| TRT | Treatment Group | Numerical (Integer) | 1 | 0 | N/A | * Each subject is assigned a treatment group. * If all treatments are the same, each subject will have the same treatment group |
| TIME | Numerical Time from First Dose | XX.XXX | 5 | 3 | hr | * Nominal time * Recorded on each record * TIME should be set to missing “.” for any records prior to the first dosing record |
| TAD | Time After Most Recent Dose | XX.XXX | 5 | 3 | hr | * Nominal Time * Recorded on each record * Resets back to 0 for each additional dose after the first dose |
| DOSE | Total Subcutaneous Dosage Administered | XX | 2 to 7 | 0 | mg | * This variable is identical to AMT, but should be propagated forward for each record from the most recent dosing record (for each treatment/PK Visit); for pre-dose values, DOSE should be carried backward. |
| AMT | Total Subcutaneous Dosage Amount Data Item | XX | 2 to 7 | 0 | mg | * If a value is entered into the AMT variable, the DV variables for that record should be set to missing “.” * Values should be positive and only located on the “dosing” records * For observation records, set to missing ‘.’ * Dose is assumed to be administered by subcutaneous route |
| SS | Steady State | 0 = No  1 = Yes | 1 | 0 | N/A | * Used to identify if the records following are for a drug at steady state or not |
| II | Dosing Interval | Numerical (Integer) or “.” | 2 | 0 | hr | * Denotes the time in-between multiple doses * If a single dose is given, the record should be “.” for all observations |
| ADDL | Additional Doses after the First Dose | Numerical | 1 | 0 | N/A | * Number included in the dosing record to denote how many more doses are to be given. * Timing of these additional doses is determined by II. |
| DV | Dependent Variable Data Items | XX.XX | 3 or 4 | N/A | mg/L | * Cladribine plasma levels for a typical patient, including inter-individual variability * If a value is entered into the DV variable, the AMT variable for that record should be set to missing “.” * Each time point at which DV variables are measured should be entered as a new record |
| MDV | Missing Dependent Variable Data Item | 0 = Value in DV  1 = Missing DV | 1 | 0 | N/A | * If there is an observation value defined in the DV data item, the MDV variable should be set to 0 * If there is NOT an observation in the DV data item, the MDV variable should be set to 1. |
| EVID | Event Identification Data Item | 0 = Value in DV  1 = Dosing Event | 1 | 0 | N/A | * If EVID = 0, AMT, RATE, SS, and II must = “.” * If EVID = 1, DV must = “.” |
| CMT | Compartment Number | Numerical  (Integer) | 1 | 0 | N/A | * If CMT = 1, it must be a dosing record * If CMT = 2, it must be an observation record |
| AGE | Age of Subject | XX.X | 3 | 1 | years | * Chronological Age * Should be recorded on all records * Continuous Covariate * Mean: 40 and SD:3.5 for simulated subjects |
| Post Execution Table | | | | | | |
| IPRE | Individual Prediction | XX.XX | 3 or 4 | N/A | mg/L | * If a value is entered into the IPRE variable, the AMT variable for that record should be set to missing “.” * Simulated cladribine level including inter-individual and residual variability |
| PRED | Population Prediction | XX.XX | 3 or 4 | N/A | mg/L | * Population level observation * Propagated forward on all records for each respective ID |
| IWRE | Individual Weighted Residual | X.XX | 3 | N/A | N/A | * Difference between that individual’s observation and the population level observation, including residual variability and weighted by the value of the observation |
| IRES | Individual Residual | X.XX | 3 | N/A | mg/L | * Difference between that individual’s observation and the average observation of the population, including residual variability |
| WRES | Weighted Residual | X.XX | 3 | N/A | N/A | * Difference between that individual’s observation and the population level observation, weighted by the value of the observation |
| RES | Residual | X.XX | 3 | N/A | mg/L | * Difference between that individual’s observation and the population level observation |
| CL | Individual Clearance Estimate | XXX | 3 | N/A | L/hr | * THETA1 * Empirical Bayesian Estimate of the individual’s cladribine clearance * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| V2 | Central Compartment Volume | XXX | 3 | N/A | L | * THETA2 * Empirical Bayesian Estimate of the individual’s cladribine central volume * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| Q3 | Distributional Clearance from Central to Peripheral Compartment 1 | XXX | 3 | N/A | L/hr | * THETA3 * Empirical Bayesian Estimate of the individual’s cladribine distributional clearance from central to peripheral compartment 1 * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| V3 | Peripheral Compartment 1 Volume | XXX | 3 | N/A | L | * THETA4 * Empirical Bayesian Estimate of the individual’s cladribine peripheral compartment 1 volume * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| Q4 | Distributional Clearance from Central to Peripheral Compartment 2 | XXX | 3 | N/A | L/hr | * THETA5 * Empirical Bayesian Estimate of the individual’s cladribine distributional clearance from central to peripheral compartment 2 * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| V4 | Peripheral Compartment 2 Volume | XXX | 3 | N/A | L | * THETA6 * Empirical Bayesian Estimate of the individual’s cladribine peripheral compartment 2 volume * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| KA | Subcutaneous Absorption  Rate Constant | XXX | 3 | N/A | 1/hr | * THETA7 * Empirical Bayesian Estimate of the individual’s cladribine absorption rate * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| Vss | Volume Distribution at Steady State | XX.XX | 3 or 4 | N/A | L | * Vss = V2 + V3 + V4 * Propagated forward on all records for each respective ID |
| T12 | Terminal Half-life | XX.XX | 3 or 4 | N/A | hr | * Calculated as 0.693 / (L3) * Propagated forward on all records for each respective ID |
| MRT | Mean Residence Time | XX.XX | 3 or 4 | N/A | hr | * Calculated as 1 / (L3) * Propagated forward on all records for each respective ID |
| AREA | Area Under the Curve | XXX.XX | 4 or 5 | N/A | mg\*hr/L | * Calculated as DOSE / CL * Propagated forward on all records for each respective ID |
| AUMC | Area Under the First Moment Curve | XXX.XX | 4 or 5 | N/A | mg\*hr2/L | * Calculated as AREA \* MRT * Propagated forward on all records for each respective ID |
| ETA1 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for CL |
| ETA2 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for V2 |
| ETA3 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for Q3 |
| ETA4 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for V3 |
| ETA5 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for Q4 |
| ETA6 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for V4 |

# Appendices

**APPENDIX A: Covariate Derivation**

Covariate parameters **age and weight** were resampled from the NHANES 2013-2014 data. A linear regression model was fit to 31 children from the original 261202 data to determine the relationship between age/weight and **VWF**. Resampled ages and weights were then used to derive VWF using the regression model.

Sample Age Category Distributions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Age Range | Proportion\* | n = 50 | n = 75 | n = 100 |
| 0 to < 6 | 0.22 | 11 | 16 | 22 |
| < 6 to 12 | 0.44 | 23 | 34 | 44 |
| < 12 to <16 | 0.33 | 16 | 25 | 34 |

\*Proportions were maintained from the original concept CDP.