NONMEM Simulation Dataset

Article Title: Population pharmacokinetic modeling of idelalisib, a novel PI3Kδ inhibitor, in healthy subjects and patients with hematologic malignancies

Analyte(s): idelalisib

Matrix: Plasma

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**Control Stream taken from supplemental material**

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# 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 |
| NTIM | Nominal Time from First Dose | XX.XXX | 5 | 3 | hr | * Nominal time * Time record if there was no deviation from sampling time * Recorded on each record * TIME should be set to missing “.” for any records prior to the first dosing record |
| NTAD | Nominal Time After Most Recent Dose | XX.XXX | 5 | 3 | hr | * Nominal Time * Time record if there was no deviation from sampling time * Recorded on each record * Resets back to 0 for each additional dose after the first dose |
| TIME | Numerical Time from First Dose | XX.XXX | 5 | 3 | hr | * Actual 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 | * Actual Time * Recorded on each record * Resets back to 0 for each additional dose after the first dose |
| DOSE | Total Oral 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 Oral 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 |
| DV | Dependent Variable Data Items | XX.XX | 3 or 4 | N/A | ng/mL | * Simulated idelalisib level including inter-individual and residual 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 |
| WT | Weight of Subject | XX.X | 3 | 1 | kg | * Individual simulated patient weight * Continuous Covariate * Mean: 75 and SD:10 for simulated subjects |
| PAT | Patient Disease Status | 1 = Patient with malignancy  2 = Healthy volunteer | 1 | 0 | N/A | * Individual simulated patient disease status * Categorical Covariate * Categorical Probability: 0.5 |
| Post Execution Table | | | | | | |
| IPRE | Individual Prediction | XX.XX | 3 or 4 | N/A | mg/L | * Idelalisib plasma levels for a typical patient, including inter-individual variability * If a value is entered into the IPRE variable, the AMT variable for that record should be set to missing “.” |
| 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 for PAT=1 & THETA8 for PAT = 2 * Empirical Bayesian Estimate of the individual’s idelalisib 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 idelalisib 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 |
| Q | Distributional Clearance from Central to Peripheral Compartment | XXX | 3 | N/A | L/hr | * THETA3 for PAT=1 & THETA9 for PAT=2 * Empirical Bayesian Estimate of the individual’s idelalisib distributional clearance from central to peripheral compartment * 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 Volume | XXX | 3 | N/A | L | * THETA4 * Empirical Bayesian Estimate of the individual’s idelalisib peripheral compartment 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 | Oral Absorption  Rate Constant | XXX | 3 | N/A | 1/hr | * THETA5 * Empirical Bayesian Estimate of the individual’s idelalisib absorption rate constant * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| ALAG1 | Lag Time | XXX | 3 | N/A | hr | * THETA6 * Empirical Bayesian Estimate of the individual’s idelalisib absorption lag time * Value should be positive and the same for all records for a particular individual * Propagated forward on all records for each respective ID |
| F1 | Effect of Dose on Bioavailability | XXX | 3 | N/A | N/A | * THETA7 * Empirical Bayesian Estimate of the individual’s idelalisib 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 |
| SWT | Effect of Body Weight on Clearance | XXX | 3 | N/A | N/A | * THETA10 * Logarithmic relationship between body weight and individual clearance |
| Vss | Volume Distribution at Steady State | XX.XX | 3 or 4 | N/A | L | * Vss = V2 + V3 * 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 / (BETA) * Propagated forward on all records for each respective ID |
| MRT | Mean Residence Time | XX.XX | 3 or 4 | N/A | hr | * Calculated as 1 / (BETA) * Propagated forward on all records for each respective ID |
| AREA | Area Under the Curve | XXX.XX | 4 or 5 | N/A | ng\*hr/L | * Calculated as (F1\*DOSE / CL)\*1000 * Propagated forward on all records for each respective ID |
| AUMC | Area Under the First Moment Curve | XXX.XX | 4 or 5 | N/A | ng\*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 Q |
| 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 KA |
| ETA6 | Between Subject Variability | X.XXX | 4 | N/A | N/A | * Exponential relationship of individual variability for ALAG1 |