STATISTICAL ANALYSIS PLAN
for
Protocol UR1-DOT-103

A PHASE 1B OPEN LABEL EVALUATION OF PK AND PD OF DOTINURAD AND THE DRUG-DRUG INTERACTION OF DOTINURAD AND ALLOPURINOL IN U.S. PATIENTS WITH GOUT AND HYPERURICEMIA

Version 1.0: SEP 12, 2023

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REVISION HISTORY

Version	Date	Author	Reasons
1.0	**SEP 12, 2023**	**Mykyta Yakovliev**	Initial version.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
°C	Degrees Celsius
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BLQ	Below the Lower Limit of Quantitation
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-Drug Interaction
dL	Deciliter
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FSH	Follicle-Stimulating Hormone
FU	Follow-up Visit
H	High
HBsAg	Hepatitis B Virus Surface Antigen
HCV	Hepatitis C Virus
kg	Kilogram
L	Low
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min(s)	Minute(s)
N	Normal
NCS	Not Clinically Significant
PD	Pharmacodynamics

Abbreviation or special term	Explanation
PK	Pharmacokinetics
PT	Preferred Term
QD	Once Daily
QTc	The QTc interval is the corrected QT interval, adjusted for heart rate
RBC	Red Blood Cells
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings, and Figures
ULT	Urate Lowering Therapy
WBC	White Blood cells
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods and data handling procedures to be followed during the final reporting and analyses of data collected for the study Protocol UR1-DOT-103.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol 1.1 dated JUN 20, 2023, and eCRF Specifications v2.0 dated JUN 29, 2023.

This is a Phase 1B, open-label, open label, 3-period, multi-center multidose, PK/PD and drug-drug interaction (DDI) study. A total of N=20 eligible patients with gout and hyperuricemia will, following at least 14 days of washout of urate lowering therapy (ULT) and open-label treatment with Colchicine 0.6 mg QD, be assigned to one of 2 cohorts (N=10 patients each to dotinurad 2 mg or to dotinurad 4 mg) and then treated with open-label study medication (given once-daily in the morning).

Content copied exactly from the protocol to this document will be displayed in *Italics*.

2 STUDY DETAILS

2.1 Study Objectives

This study has two objectives:

1. *To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of 7 days of treatment with two doses of dotinurad monotherapy, and*
2. *To evaluate the effect of dotinurad, as monotherapy and in combination with allopurinol, versus allopurinol monotherapy, on the PK of each, and to assess the additive PD effects on serum uric acid and urinary urate excretion in U.S. patients with gout and hyperuricemia.*

The safety/tolerability of each treatment (monotherapy dotinurad, combination of dotinurad and allopurinol, and monotherapy allopurinol) will also be assessed.

To achieve this objective, this study will evaluate the PK, PD, and safety/tolerability of 7 days of treatment with dotinurad monotherapy, followed by 7 days of treatment with concomitant allopurinol and dotinurad, and then followed by 7 days of treatment with allopurinol monotherapy. Two dose regimens of dotinurad (2 and 4 mg, once-daily) will be assessed in combination with allopurinol 300 mg once-daily.

Specific objectives include assessment of coadministration dotinurad and allopurinol dosing over 7 days vs monotherapy dosing of each alone on:

- *Pharmacokinetics (serum and urine);*
- *Uricosuric response (serum uric acid and urinary uric acid excretion);*
- *Safety and tolerability.*

2.2 Study Design

This is a Phase 1B, open-label, 3-period, mulit-center multidose, PK/PD and DDI study. A total of N=20 eligible patients with gout and hyperuricemia will, following at least 14 days of washout of ULT and open-label treatment with Colchicine 0.6 mg QD, be assigned (1:1) to one of 2 cohorts (N=10 patients each to the first cohort, dotinurad 2 mg, or to the second cohort, dotinurad 4 mg) and then treated with open-label study medication (given once-daily in the morning) for 7 days in each of 3 treatment periods (Table 1). Patients will continue with Colchicine 0.6 mg QD until the end of follow-up period.

Two doses of dotinurad (monotherapy and in combination with allopurinol) are being studied (dotinurad 2 mg and dotinurad 4 mg), with allopurinol 300 mg, with both medications given QD in the morning. Patients, Investigators and the Sponsor will not be blinded, and thus will be aware of the treatments given to each patient during each treatment period. Patients will be admitted to the CRU on the evening of Day -2 OR the morning of Day -1 to obtain baseline measurements for blood samples, a 24-hour urine collections (which will end shortly prior to the first dose of dotinurad on Day 1), and other scheduled assessments. Patients will remain in the CRU through the morning of Day 8, receiving daily morning doses of dotinurad on Days 1 through 7. Following the Day 7 dose, patients will undergo 24 hour serum and urine sampling, ending on the morning of Day 8 (prior to

dosing with concomitant dotinurad and allopurinol). Patients will be discharged on the morning of Day 8, after having completed their PK and PD sampling procedures and after having received their first dose of treatment with concomitant dotinurad and allopurinol.

On Days 9, 10, 12, and 13, sites will conduct a daily telehealth visit (phone-call or video-call) to confirm that they have taken dotinurad with allopurinol and to provide a health check and reminder of hydration. On Day 11, patients will have a full safety laboratory assessment (in-clinic), which will include a serum creatinine test for renal function.

Patients will be re-admitted to the CRU on the evening of Day 13 OR early on the morning of Day 14. Following the Day 14 dose of concomitant dotinurad and allopurinol, patients will undergo 24 hour serial blood samples, 24-hour urine collections, and other scheduled assessments, ending on the morning of Day 15 (prior to dosing with allopurinol only). Patients will be discharged on the morning of Day 15 having completed their PK and PD sampling procedures and after having received their first dose of treatment with allopurinol monotherapy.

On Days 16 to 20, patients will conduct a daily telehealth visit to confirm that they have taken allopurinol and to provide a health check and reminder of hydration.

Patients will be re-admitted to the CRU on the evening of Day 20 OR early on the morning of Day 21. Following the Day 21 dose of allopurinol, patients will undergo 24 hour serial blood samples, 24-hour urine collections, and other scheduled assessments, ending on the morning of Day 22.

Patients will be encouraged to be well hydrated by consuming 2L of liquids a day during each day of the study. Patients will have a telephone follow-up on Day 28.

Table 1 provides the overall study design, cohort sequence of treatments, and the treatment periods during this study.

Table 1: Study Design, Cohort Sequence of Treatment, and Treatment Periods

Screening (Days -28 to -15)	Washout of Prior Meds (Days -14 to -1)	Period 1 (Days 1 to 7) In-clinic	Period 2 (Days 8 to 14)	Period 3 (Days 15 to 21)	Follow-Up (Days 22 to 28)
	Colchicine 0.6 mg/day (can start any time at least 2 weeks prior to Day 1)				
Cohort 1	N=10 patients	Dotinurad 2 mg/day	Dotinurad 2 mg/day Allopurinol 300 mg/day	Allopurinol 300 mg/day	Follow-up period and scheduled telehealth call
Cohort 2	N=10 patients	Dotinurad 4 mg/day	Dotinurad 4 mg/day Allopurinol 300 mg/day	Allopurinol 300 mg/day	Follow-up period and scheduled telehealth call

Table 2 provides the schedule of events.

Table 2: Schedule of Events

Period:	**Screening**	**Baseline/ Admission to the CRU**	**Treatment Periods (Days 1 through Day 21)**				**End of Study FU**
Day:	**-28 to -1**	**-2 or --1**	**Period 1: Days 1-7 (In CRU Days 1 through 7)**	**Period 2: Days 8 to 14 (CRU Visit Days 11 and 14)**	**Period 3: Days 15 to 21 (CRU Visit Day 21)**	**Day 22**	**Day 28[1]**
Screening, consent	X						
Inclusion/Exclusion	X	X					
Medical history and screen for HLA-B*5801	X						
Prior/Con med check	X	X	X	X	X	X	X
COVID-19 testing	X	X		X (checkin)	X (checkin)		
Urine drug/alcohol/cotinine test	X	X					
Serology	X	X					
Body weight/height[2]	X	X					
Pregnancy test[3]	X	X			Pre-dose Day 15	X	
Serum uric acid eligibility	X						
Admission to clinic[4]		X (evening Day -2 or morning Day -1)		X (evening Day 13 or morning Day 14)	X (evening Day 20 or morning Day 21)		
Discharge from clinic				Morning Day 8	Morning Day 15	X	
Open-Label Study Treatment			Dotinurad (Days 1 to 7)	Dotinurad & Allopurinol (Days 8 to 14)	Allopurinol (Days 15 to 21)		
Washout of prior uric-acid lowering and treatment with Colchicine 0.6 mg/Day[8]	X (Days -14 to -1)	X	X	X	X		X
Physical examination[5]	X	X		Morning Day 8	Morning Day 15	X	
AE collection			X	X	X	X	X
Clin chem, hematology and urinalysis	X	X	Days 2, 4, 6	Day 8 pre-dose, Day 11 (any time), Pre-dose Day 14		X	
Lipid panel	X					X	
Coagulation	X	X				X	
Vital signs	X	X	Pre-dose daily	Pre-dose Day 14	Pre-dose Day 21	X	
ECG 12-lead	X	X	Pre-dose daily	Pre-dose Day 14	Pre-dose Day 21	X	
Blood samples for PK[6]			Days 1, 4, and 7: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24h Days 3 and 6: Pre-dose	Day 14: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24h	Day 21: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24h		
Blood samples for PD (serum uric acid)	X	0, 2, 4, 6, 12, 24h	Days 1, 4, and 7: Predose, 2, 4, 6, 12, 24h	Day 14: Predose, 2, 4, 6, 12, 24h	Day 21: Predose, 2, 4, 6, 12, 24h		
Trough (pre-dose) blood samples for PD (serum uric acid) and PK			Days 2, 3, 5, and 6 (all pre-dose)				

Period:	Screening	Baseline/ Admission to the CRU	Treatment Periods (Days 1 through Day 21)				End of Study FU
Day:	-28 to -1	-2 or --1	Period 1: Days 1-7 (In CRU Days 1 through 7)	Period 2: Days 8 to 14 (CRU Visit Days 11 and 14)	Period 3: Days 15 to 21 (CRU Visit Day 21)	Day 22	Day 28[1]
24-hour urine[7] for PK and PD (urine dotinurad, creatinine, urate)		Day -1: 2, 4, 6, 12, 24h	Days 1, 4, and 7: 2, 4, 6, 12, 24h	Day 14: 2, 4, 6, 12, 24h	Day 21: 2, 4, 6, 12, 24h		

abbreviations: AE = adverse event; FU = follow-up visit; h = hour; PD = pharmacodynamics; PK = pharmacokinetics.

Note: Where assessments fall at the same timepoints, the order of priority is: dose administration, then PK blood samples, then any other assessments.

1. *The follow-up visit will occur approximately 7 calendar days after discharge from the CRU via a scheduled telehealth phone call.*
2. *Height will be measured at screening only.*
3. *Pregnancy testing in females with child bearing potential; urine except for Day -1 which will be in serum. A positive urine pregnancy test must be confirmed with a serum pregnancy test.*
4. *Patients will be admitted to the clinic on the morning of Day -1 and will be discharged on the morning of Day 8. For periods 2 and 3, they are admitted either the evening before or the morning of the final dosing for each Period (eg, evening of Day 13 or morning of Day 14) and will remain resident until discharge the following morning after their Hour 24 serial blood samples and 24 hour urine collections for each Period.*
5. *Full physical examination at screening and Day -1; abbreviated (symptom-driven) physical examination at discharge for Day 8 and Day 15.*
6. *Predose PK draw to be collected within 30 minutes prior to first dosing at each period. Subsequent PK draws should be ±5 minutes of specified time for times up to 3 hours post dose and ±10 minutes thereafter.*
7. *Patients can urinate between the designated timepoints. Site will collect the urine sample and combine in the appropriate bins. Eg, Hour 0-2 means urine produced between hour 0 and hour 2. Precisely at hour 2, patients will be instructed to collect urine sample, with that sample stored in the Hour 0-2 container. For this study, the bins are 0-2, 2-4, 4-6, 6-12, 12 to 24 hours post dosing.*
8. *Colchicine treatment will start at the time patients start washout of their prior uric-acid-lowering medications (eg, allopurinol). This will be at least 14 days prior to starting treatment but can be longer (up to 28 days) at the discretion of the PI.*

2.3 Determination of Sample Size

A sample size of n=10 patients per dotinurad dose level is sufficient to determine whether a PK or PD difference exists for those endpoints (both as a monotherapy and coadministered with allopurinol). This is based on observed coefficients of variation of PK parameters for prior dotinurad studies, as well as previous publications of similar studies with allopurinol. Specifically, studies of dotinurad in Japanese patients have demonstrated low variability of PK and PD endpoints and have therefore required a small number of patients to demonstrate clear study outcomes.

Thus, a total of N=20 patients will therefore be sufficient to assess the PK and PD characteristics of two different dose levels of dotinurad in a drug-drug interaction study design.

2.4 Randomization

This is non-randomized study.

2.5 Blinding

This is an open-label (non-randomized) study. Patients, investigational staff (including the PI), the Sponsor, and other study personnel will be aware of the treatments being given to the patients. Because the primary objectives of this study are focused on PK and PD assessments, all measured by serum and urine sampling (and thus are objective), open-label treatment is scientifically reasonable.

3 DATA ANALYSIS CONSIDERATION

3.1 General Considerations

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be provided in the specific detailed sections of this SAP.

The statistical analyses will be performed using SAS Version 9.4 (or higher). The domain (Study Data Tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, listings, and figures (TLFs). All TLFs will be produced in landscape format.

Each dose group will be presented separately in summaries and analyses as appropriate. Continuous variables will be summarized by dose group and time point (as applicable) using the following descriptive statistics: number of observations (n), mean, standard deviation (SD), minimum, median, and maximum. Categorical variables will be summarized by dose group and time point (as applicable) using frequency counts and percentages. Changes from baseline for continuous outcomes will be presented as their corresponding continuous measures for postbaseline visits as applicable. All study data will be listed by dose group, subject, and time point (as applicable).

Unless specified otherwise, in the analysis of categorical variables, the denominator for percentages will be the number of subjects in the appropriate analysis population and dose group. The total number of patients in the study group (N) under the stated set of subjects will be displayed in the header of summary tables.

Means and medians will be presented with one more decimal place than the number of decimal places recorded in the data to at most 3 decimal places. Standard deviations and confidence intervals limits will be presented with two more decimal places than the number of decimal places recorded in the data to at most 3 decimal places. Inferential statistics, including p-values, will be presented with 3 decimal places. In case when p-value rounded to 3 decimal places is equal to 0.000, then "<0.001" will be presented instead. PK and PD concentrations will be reported to the number of decimal places recorded in the data. Parameter summaries will be presented to a decimal precision that provides at least 3 significant digits. Percentages will be presented with one decimal place. A percentage of 100 calculated to any number of decimal places will be reported as 100%; a percentage of 0 calculated to any number of decimal places will be reported as 0. Minimum and maximum will be presented with the number of decimal places as the original data.

All study data will be included in the study data listings. If not stated otherwise listings will be displayed by patient in chronological order.

3.2 Handling of Missing/Partial Data

3.2.1 Medications and Adverse Events with Missing or Partial Dates

To handle missing or partial medication/AE start/end date and time, the following rules will be applied to identify concomitant medications/ treatment-emergent adverse events (TEAEs) and associated periods. This imputation will be used only for the identification of concomitant medications/ treatment-emergent adverse events (TEAEs) and associated periods – start/end date and time for medications and AEs will be listed as collected without any imputations.

1. For partial start dates:
    a. If the year is unknown, there will be no imputation and the date will be assigned a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the any study treatment administration date, then the month, day, hours, and minutes of the earliest matching study treatment administration date will be imputed.
    b. Otherwise, month, day, hours, and minutes will be assigned as "January 01, 00:00."
3. If the day is unknown, then:
    a. If the month and year matches the month and year of the any study treatment administration date, then the day, hours, and minutes of the earliest matching study treatment administration date will be imputed.
    b. Otherwise, day, hours, and minutes will be assigned as "01, 00:00".
4. If the hours are unknown, then:
    a. If the day, month, and year matches the day, month, and year of the any study treatment administration date, then the hours, and minutes of the earliest matching study treatment administration date will be imputed.
    b. Otherwise, hours, and minutes will be assigned as "00:00".
5. If the minutes are unknown, then:
    a. If the hours, day, month, and year matches the hours, day, month, and year of the any study treatment administration date, then the minutes of the earliest matching study treatment administration date will be imputed.
    b. Otherwise, hours, and minutes will be assigned as "00".

For partial end dates:

1. If the year is unknown, there will be no imputation and the date will be assigned a missing value.
2. If the month is unknown, then it will be imputed to be "December."
3. If the day is unknown, then it will be imputed to be the last day of the month.
4. If the hours are unknown, then they will be imputed to be "23".
5. If the hours are unknown, then they will be imputed to be "59".

After implementing the rules above, to determine whether a medication/AE with missing start or end date and time are concomitant/TEAE and associated period, the following algorithm will be used:

1. If the start date\time and stop date\time are both missing, then the medication/adverse event will be considered concomitant/TEAE without associated period.
2. If the start date\time is missing but the stop date\time is not missing and is on or after the date and time of the first study treatment administration, then the medication/adverse will be considered concomitant/TEAE without associated period.
3. If the start date\time is missing but the stop date\time is not missing and it is before the date and time of the first study treatment administration, then the medication will be considered as prior.
4. If the start date\time is not missing, then medication/AE will be considered as concomitant (prior)/TEAE and associated with a specific treatment period according to definitions of prior and concomitant medications, TEAE and analysis treatment period provided in Section 4.

4 DEFINITIONS AND DERIVATIONS

Investigational Products

Table 3: Investigational Product

	Investigational Product	
Product Name:	Allopurinol	Dotinurad
Dosage Form:	tablet	tablet
Unit Dose:	300 mg	1 mg
Route of Administration:	Oral	Oral
Physical Description:	white, round	white, round
Manufacturer:	Various	Fuji Yakuhin Co. Ltd

Study Treatment

There are following study treatments for this study:

- Dotinurad monotherapy (2 mg for Cohort 1, 4 mg for Cohort 2);
- Allopurinol monotherapy (300 mg);
- Combination of dotinurad (2 mg for Cohort 1, 4 mg for Cohort 2) and allopurinol (300 mg).

They are received as the following according to Period:

- Period 1 – Dotinurad monotherapy (2 mg/day for Cohort 1, 4 mg/day for Cohort 2);
- Period 2 – Combination of dotinurad (2 mg/day for Cohort 1, 4 mg/day for Cohort 2) and allopurinol (300 mg/day);
- Period 3 – Allopurinol monotherapy (300 mg/day).

Additional details are provided in Table 1.

Colchicine Treatment

Subjects will initiate an open-label colchicine 0.6 mg QD (once daily each morning) at least 2 weeks (14 days) prior to check-in to the CRU. Treatment with colchicine will continue through the course of the 3 treatment periods until the end of follow-up period. Additional details are provided in Table 1.

Baseline Value

The baseline value of any parameter will be defined as the last non-missing measurement prior to the time of the first dose of study treatment, including both scheduled and unscheduled assessments.

Post-baseline Values

Post-baseline values of any parameter will be defined as all measurements on or after the first dose of the study treatment, including both scheduled and unscheduled assessments.

Change from the Baseline

The change from the baseline value of a parameter is defined as the post-baseline value minus the baseline value.

Study Day

Study day will be calculated as (date – date of the first administration of study treatment) + 1 if the date was on or after the first study treatment administration. If the date was before the first study treatment administration, study day is calculated as (date – date of the first administration of study treatment).

Analysis Treatment Period

There will be 3 analysis periods defined for this study based on administrations of study treatments:

Period Name	Expected Study Days	Start Date and Time	End Date and Time
Period 1	Days 1-7	Date and time of the first dosing of dotinurad monotherapy	Date and time of the first dosing of combination of dotinurad and allopurinol
Period 2	Days 8-14	Date and time of the first dosing of combination of dotinurad and allopurinol	Date and time of the first dosing of allopurinol monotherapy
Period 3	Days 14-28	Date and time of the first dosing of allopurinol monotherapy	Date of the end of study follow-up

In the case of the subject discontinuing early prior to receiving all planned doses, the End Date of the last period will be defined as date of the study discontinuation. In cases where one of the planned periods was not started (for example, due to early discontinuation) then corresponding analysis treatment period will not be defined.

Specified analysis periods will be used for analysis of adverse events (AE), concomitant medications, and protocol deviations. For each AE/concomitant medication treatment period will be identified based on the start date and time satisfying (Period Start Date/Time ≤ Start Date/Time < Period End Date/Time) for any treatment period except the last one and (Period Start Date/Time ≤ Start Date/Time ≤ Period End Date/Time) for the last treatment period. In case of a partially missing date, rules from Section 3.2.1 will be applied. In case of Time part is missing (e.q., the End date of the last period based on the end of study follow-up), then only the date portion will be compared with the corresponding period boundary. The same will be applied for each protocol deviation based on the protocol deviation date to identify the corresponding treatment period.

Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) will be defined as any AE starting on or after the date and time of the first dose of study treatment or any AE whose severity increases any time after the first dose of study treatment. TEAE is assigned to the specific treatment period based on the start date and time of the corresponding AE as per the definition of analysis periods. AEs reported after signing the informed consent but before the first administration of study treatment will be considered non-treatment emergent.

Duration of AE

The duration of an AE will be computed in days for AEs lasting longer than 24 hours, and as hours for AEs lasting less than 24 hours. Duration in hours will be calculated as the end date/time of the event minus the start date/time. Duration in days will be calculated as the end date of the event minus the start date + 1.

Prior and Concomitant Medications

Prior medications will be defined as all medications taken prior to the first administration of study treatment. Concomitant medications will be defined as all medications taken at or after the first dose of study treatment. Concomitant medication is assigned to the specific treatment period based on the start date and time of the corresponding medication administration as per the definition of analysis periods.

5 ANALYSIS POPULATION AND TREATMENT GROUPS

5.1 Analysis Population

The following analysis populations will be defined:

5.1.1 Screened Population

Screened Population will be defined as all subjects signing informed consent.

5.1.2 Safety Population

Safety Population will be defined as all subjects treated with at least one dose of dotinurad.

5.1.3 Pharmacokinetic and Pharmacodynamic Populations

5.1.3.1 PK and PD Populations

The PK and PD Populations will be defined as all subjects with at least 80% compliance with dosing during the required periods with sufficient concentration results to estimate at least one area or Cmax for the PK population and area or Emax for the PD population.

5.1.3.2 PK and PD Dotinurad Populations (Dotinurad Dose-Proportionality)

The PK and the PD Dotinurad Populations will be defined as all subjects who meet the criteria in Period 1.

5.1.3.3 DDI PK(PD) Dotinurad Population

The DDI PK and PD Dotinurad Populations will be defined as all subjects who meet the criteria in both Period 1 and Period 2.

5.1.3.4 DDI PK and PD Allopurinol Populations

The DDI PK and PD Allopurinol Populations will be defined as all subjects who meet the criteria in both Period 2 and Period 3.

5.2 Dose Groups

The following dose groups will be considered for the study:

- Dotinurad 2 mg - Cohort 1 with Dotinurad 2 mg/day;
- Dotinurad 4 mg - Cohort 2 with Dotinurad 4 mg/day.

Unless otherwise specified all summaries will be stratified by dose group.

6 ANALYSES METHODS AND REPORTING DESCRIPTIONS

6.1 Subject Disposition

Disposition will be summarized descriptively using counts and percentages for the Screened population by dose group and overall. The number and percentage of subjects screened, screen failures, subjects who received any amount of study treatment, and subjects who withdrew early from the study (stratified by the day of discontinuation) and the reason for withdrawal will be summarized in the subject disposition summary table.

A listing of subjects' disposition status will be provided. The number of subjects in each analysis population will be summarized descriptively with counts and percentages. All subjects and the populations for which they qualify for inclusion will be listed. All subjects who are screened and who fail screening or withdraw consent prior to treatment will be listed.

6.2 Demography and Baseline Characteristics

Demographic data and baseline characteristics will include:

- Age (years);
- Sex;
- Race;
- Ethnicity;
- Height (cm);
- Weight (kg);
- BMI (kg/m^2).

Demographics and baseline characteristics will be summarized descriptively by dose group and overall. Summary statistics including number of subjects, mean and standard deviation, median, minimum, and maximum will be generated for all continuous variables such as age, height, weight, and BMI. The number and percentage of subjects within each category will be presented for all categorical variables such as sex, race, and ethnicity. The summary results will be reported on the Safety population and for any populations that differ from the Safety population (with exception of Screened population).

Demographic data and baseline characteristics will be listed for the Safety population.

6.3 Medical History

All medical history conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 26.0 or later). Medical history data will be summarized by dose group and overall, by MedDRA preferred term (PT) and system organ class (SOC) for the Safety population. Subjects will be counted only once at the PT, only once at the SOC, and only once at subject level for the counting of total number of subjects with a medical history term. Counts will be presented in

descending frequency unless otherwise specified. The data will be listed by subject, including medical history presented by SOC, PT, reported term, start date, end date, and whether the condition is ongoing.

Listings of medical history conditions for subjects in the Safety population will be provided.

6.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODRUG; Global Version Mar2023 or later) and categorized by PT and Anatomical Therapeutic Chemical (ATC) class. ATC class level 3 will be used when displaying drug class in data listings and summaries. In case ATC class level 3 is not available then latest available level was used.

The number and percentage of subjects who take prior medications will be summarized by PT and ATC class by dose group and overall, for the Safety population. The number and percentage of subjects who take concomitant medications will be summarized by PT and ATC class by dose group and overall and by period of occurrence, for the Safety population. Subjects may have more than one medication per ATC category and PT. At each level of subject summarization, a subject will be counted only once.

All prior and concomitant medications will be presented in the by-subject listing for the Safety population.

6.5 Protocol Deviation

The number and percentage of subjects with any protocol deviation will be summarized by deviation type and classification by dose group and overall and by period of occurrence, for the Safety population.

A listing of protocol deviations will be presented by subject using the Screened population.

6.6 Study Treatment Exposure and Compliance

The study treatment compliance will be defined overall per period according to the number of protocol-compliant study treatment administrations (Dotinurad Monotherapy, Combination of Dotinurad and Allopurinol, Allopurinol Monotherapy) out of 7 planned per each period (Period 1, Period 2, Period 3). Study treatment administration will be considered as protocol-compliant if it was conducted according to protocol-defined schedule and the dosage of study treatment administered was the one defined per the protocol for the corresponding period and dose group (Table 1). The study treatment compliance for specific study treatment/period will be that calculated as:

$$\text{Dotinurad Monotherapy (Period 1) Compliance (\%)} = \frac{\text{Actual number of protocol compliant administrations of Dotinurad Monotherapy}}{7} \times 100\%;$$

$$\text{Combination of Dotinurad AND Allopurinol (Period 2) Compliance (\%)} = \frac{\text{Actual number of protocol compliant administrations of Combination of Dotinurad AND Allopurinol}}{7} \times 100\%;$$

$$\text{Allopurinol Monotherapy (Period 3) Compliance (\%)} = \frac{\text{Actual number of protocol compliant of administrations Allopurinol Monotherapy}}{7} \times 100\%.$$

Additionally, washout treatment compliance of colchicine will be calculated as the total number of days with washout treatment administrations divided by 42 (at least 14 days prior to starting treatment, 21 days of treatment and 7 days of follow-up) as follows:

$$\text{Washout Treatment (colchicine 0.6 mg) Compliance (\%)} = \frac{\text{Actual total number of days with washout treatment (colchicine 0.6 mg) administrations}}{42} \times 100\%.$$

The exposure to study treatment and study treatment compliance will be summarized descriptively by period and dose group along with total duration of treatment for Safety population. The exposure to washout treatment (colchicine 0.6 mg) and compliance will be summarized descriptively by dose group along with the total duration of washout treatment for the Safety population.

The total study treatment duration will be analyzed by subject with swimmer plots based on the last day of study treatment administration by dose group for Safety population.

All study treatment exposure data will be provided in the by-subject listing for Safety population.

6.7 Safety Analysis

Safety data will be summarized descriptively by dose group and overall, unless otherwise specified. No inferential analysis will be conducted. Analyses of safety data will comprise summaries of AEs, vital signs, 12-lead ECG, clinical laboratory values, and physical examinations. Vital signs, 12-lead ECG, and clinical laboratory values will be summarized by timepoint as applicable, in addition to change from baseline.

Safety data will be summarized and listed using the Safety population.

6.7.1 Adverse Events

All AEs will be coded using MedDRA (Version 26.0 or later). Definitely, Probably, and Possibly related AE collected in CRF will be summarized as Related. Remote and Definitely Not related AE collected in CRF will be summarized as Not Related.

The following AE summaries will be provided:

- A summary of the number and percentage of subjects reporting any AE, any TEAE, any severe TEAE, any serious TEAE, any TEAE related to study treatment, any TEAE leading to treatment withdrawn, any TEAE leading to study discontinuation, any TEAE leading to death by dose group and overall and by period of occurrence.
- A summary of the number and percentage of subjects reporting a TEAE by dose group and overall, period of occurrence, SOC, and PT.
- A summary of the number and percentage of subjects reporting a TEAE by dose group and overall, period of occurrence, SOC, PT, and maximum severity.
- A summary of the number and percentage of subjects reporting a TEAE by dose group and overall, period of occurrence, SOC, PT, and strongest relationship to study treatment.
- A summary of the number and percentage of subjects reporting a serious TEAE by dose group and overall, period of occurrence, SOC, and PT.
- A summary of the number and percentage of subjects reporting a TEAE leading to treatment withdrawn by dose group and overall, period of occurrence, SOC, and PT.
- A summary of the number and percentage of subjects reporting a TEAE leading to death by dose group and overall, period of occurrence, SOC, and PT.

Subjects will be counted only once at the PT and only once at the SOC level at the greatest severity, and only once at subject level for at the maximum severity and strongest relationship to study treatment. Counts will be presented in descending incidence unless otherwise specified.

A by-subject listing of AEs will be provided, including verbatim term, PT, SOC, start date, end date, severity, CTCAE toxicity grade (Version 4.03 or higher), outcome, action taken and relationship. Additionally, serious AE, AEs leading to study discontinuation and AEs leading to death will be provided in a by-subject listing.

6.7.2 Clinical Laboratory Test Results

Laboratory samples will be collected per the schedule of events (Table 2), with the following analytes and tests assessed:

- *Hematology: Red blood cells (RBC), White blood cells (WBC) (absolute counts and differential), Hemoglobin, Hematocrit, Platelets.*
- *Serum Chemistry: ALT, Albumin, Alkaline phosphatase, AST, Bilirubin (total and direct), Total protein, Creatinine, Uric acid, Blood urea nitrogen, Creatine kinase, gamma-Glutamyl*

transferase, Potassium, Sodium, Glucose, Chloride, Bicarbonate, Calcium. eGFR will be provided as part of the serum chemistry.

- *Urinalysis: pH, Specific gravity, Protein, Glucose, Blood, Nitrite, Leukocyte esterase, Ketones, Bilirubin, Urobilinogen.*
- *Coagulation: PT/INR, aPTT.*
- *Serology diagnostic screening: HIV test, Hepatitis panel, including HBsAg and anti-HCV*
- *Female patients: serum hCG and or FSH, urine hCG.*
- *Drug screen: amphetamines, barbituric acids, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine.*
- *Breath alcohol test.*
- *Covid-19 testing (prior to admission into CRU each Period).*

The continuous hematology, chemistry, urinalysis, and coagulation parameters will be summarized descriptively (n, mean, SD, median, min, and max) for actual values and changes from baseline by timepoint and dose group. Values reported as "< xx" or "> xx" (where xx is a number) will be treated as xx for the purposes of these summaries.

The categorical urinalysis parameters will be summarized descriptively with frequency counts and percentages by timepoint and dose group.

Laboratory test results will be classified with CTCAE toxicity grades (Version 4.03 or higher). Hematology, chemistry, urinalysis, and coagulation data will be summarized by displaying shifts from baseline CTCAE toxicity grades to the worst post-baseline CTCAE toxicity grades by dose group.

The continuous hematology, chemistry, and urinalysis parameters collected starting from Day 1 will be presented graphically for mean results (+/- SD) by timepoint for each parameter.

All laboratory assessments will be provided in by-subject listings by panel with the corresponding normal ranges for each parameter.

6.7.3 12-Lead ECG

All scheduled ECGs will be performed after the subject has rested supine for approximately 5 minutes. ECG results will be evaluated categorically based on the assessment by the investigator (Normal, Abnormal CS, Anormal NCS, Not Evaluable) and summarized by displaying shifts from baseline to the post-baseline evaluation for each scheduled post-baseline timepoint by dose group. Additionally, ECG parameters (RR, PR, QRS, QT, and QTc intervals) will be summarized descriptively for actual values and changes from baseline at each time point by dose group and overall.

ECG parameters collected starting from Day 1 will be presented graphically for mean results (+/- SD) by timepoint for each parameter.

All 12-Lead ECG results will be provided in the by-subject listing.

6.7.4 Vital Signs

Vital sign parameters will include blood pressure (mmHg), pulse (bpm), oxygen saturation (SpO2%), temperature (˚C) and respiratory rate (breaths/min) that are taken in the seated position after 2 minutes rest. Vital signs parameters will be summarized descriptively for actual values and changes from baseline at each time point by dose group and overall.

Vital signs parameters collected starting from Day 1 will be presented graphically for mean results (+/- SD) by timepoint for each parameter.

All vital sign results will be provided in the by-subject listing.

6.7.5 Physical Examination

A physical examination will be conducted and abnormalities will be described. At times indicated in the schedule of events, only symptom-driven examinations will be performed. Physical examination results will be summarized by displaying shifts from baseline on the assessment by the investigator (Normal, Abnormal CS, Anormal NCS, Not Done) to the post-baseline examination for each scheduled post-baseline timepoint by dose group and body system.

All physical examination findings will be provided in the by-subject listing.

6.8 PK/PD Analysis

6.8.1 Pharmacokinetics

The following PK parameters (Table 4) will be determined where possible from the plasma and urine concentrations of dotinurad, as well as for allopurinol and oxypurinol using noncompartmental methods using Phoenix® WinNonlin® version 8.2 or higher.

Table 4: PK Profile: Period 1 Day 1 and Day 4 and Day 7, Period 2 Day 14, and Period 3 Day 21

Parameter	Units[a]	Definition
$AUC_{0\text{-last}}$	h*ng/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration, calculated using linear-up log-down trapezoidal summation
$AUC_{0\text{-}\tau}$	h*ng/mL	inter-dose interval area under the concentration- time curve from time 0 to the time of next dose, calculated using linear-up log-down trapezoidal summation
$AUC_{0\text{-inf}}$	h*ng/mL	area under the concentration-time curve from time 0 to infinity[b] (profile day 1 only)

$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity (profile day 1 only)
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time to maximum observed concentration
t_{last}	h	time of the last quantifiable concentration
k_e	1/h	apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration versus time curve
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
Vz/F	L	apparent volume of distribution during the terminal phase
$R_{AUC0-\tau}$		accumulation ratio based on $AUC_{0-\tau}$
R_{Cmax}		accumulation ratio based on C_{max} during the dosing interval
$DAUC_{0-last}$	h*ng/mL/mg	dose normalized area under the concentration-time curve from time 0 to the time of the last quantifiable concentration, calculated using linear-up log-down trapezoidal summation[c]
$DAUC_{0-\tau}$	h*ng/mL/mg	dose normalized inter-dose interval area under the concentration- time curve from time 0 to the time of next dose, calculated using linear-up log-down trapezoidal summation[c]
$DAUC_{0-inf}$	h*ng/mL/mg	dose normalized area under the concentration-time curve from time 0 to infinity[bc] (profile day 1 only)
DC_{max}	ng/mL/mg	dose normalized maximum observed concentration[c]
Ae_{t1-t2}	mg	amount of the dose administered recovered in urine over the collection time interval t1 to t2 (i.e. 0-2, 2-4, 4-6, 6-12, and 12 -24)
fe_{t1-t2}	%	percentage of the dose administered recovered in urine over the collection time interval t1 to t2 (i.e. 0-2, 2-4, 4-6, 6-12, and 12 -24)
Ae_{0-x}	mg	amount of the dose administered recovered in urine over the time interval 0 to x, where x = 6, 12 and 24
fe_{0-24}	%	percentage of the dose administered recovered in urine over the time interval 0 to 24
CL_R	L/h	renal clearance

The dosing interval τ is 24 hours.

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.

[b] Based on the last observed quantifiable concentration.

[c] Calculated by dividing the parameter by the dose administered (mg).

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If a sampling time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

The accumulation ratio(s) ($R_{AUC0-\tau}$ and R_{Cmax}) will be calculated as follows:

- $R_{AUC0-\tau}$ = $AUC_{0-\tau}$ Profile Day 7 / $AUC_{0-\tau}$ Profile Day 1;
- R_{Cmax} = C_{max} Profile Day 7 / C_{max} Profile Day 1.

The PK parameters (Areas, C_{max}, and Ae_{0-24}, as-calculated and dose-normalized) will be log-transformed and separately analyzed using Proc Mixed in SAS. Analysis of variance (ANOVA), considering treatment, dose group and treatment-by-dose group as fixed effects and subject nested within dose group as a random effect in the model, will be performed to evaluate the drug-drug interaction between Dotinurad and Allopurinol. If the treatment-by-dose group interaction is not significant at the 10% level, then it will be dropped from the model. If the interaction term is significant ($p<0.10$), additional analyses may be conducted to determine the cause. Point estimates and their associated 90% confidence intervals will be constructed for the differences in the log-scale, Day 7, PK parameter values between the combination treatment (Period 2) and each of the monotherapy treatments, Dotinurad (Period 1) and Allopurinol (Period 3), separately. The least squares means together with their 95% CIs by treatment will also be estimated. The point estimates of the differences and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of PK parameters between the treatments. The parameters $t_{1/2}$, CL/F, Vz/F, fe_{0-24}, and CL_R will be evaluated by Proc Mixed without transformation. T_{max} will be evaluated using the Wilcoxon signed-rank test.

For the assessment of DDI, the geometric mean ratios of key PK parameters (C_{max}, AUC, Ae_{0-24}) will be evaluated to determine the differences (if any) between combination therapy vs monotherapy of each drug, with tests of bioequivalence (BE) performed based on the 90% confidence interval being contained within the bioequivalence interval (80%, 125%).

The dose-proportionality for Dotinurad will be evaluated for dose-normalized Areas, C_{max}, and Ae_{0-24} from Period 1 using Proc Mixed with an Analysis of Variance model with dose group, Day, and dose group-by-Day as fixed effects and Subject nested within dose group as a random effect. The dose group-by-Day interaction will be dropped from the model if it is not significant at the 5% level. The point estimate and the 90% confidence interval for the geometric mean ratio of the two dose groups (Dotinurad 4 mg/ Dotinurad 2 mg) will be evaluated to see if they support dose proportionality.

Dose-normalized dotinurad trough concentrations from Days 3-8 will be evaluated to demonstrate attainment of steady. The determination of steady state will be performed by applying Helmert contrasts to the period 1 trough (i.e. morning pre-dose) dotinurad dose-adjusted concentrations on Days 3, 4, 5, 6, 7, and 8 within a mixed-model repeated measures ANOVA. The Proc Mixed model will include C_{trough} as the outcome variable, day and dose group as independent class variables and

subject nested within dose group as a repeated measures effect to account for within-subject correlations between trough concentrations.

Each Helmert contrast will compare the mean at a given time point to the pooled mean over all subsequent time points. The earliest time point for which the Helmert contrast is not statistically significant will be considered to correspond to the dosing interval at which steady state is attained. Within Helmert contrasts, the first contrast tested compares the mean trough concentration at the first time point (Day 3) to the pooled mean over all remaining time points (Days 4 to 8). The second contrast compares the mean at the second time point (Day 4) to the pooled mean over all remaining time points (Days 5 to 8). Testing continues until the contrast is not statistically significant at the 5% significance level ($p<0.05$). The first time point included in this non-significant contrast is concluded to be the start of the dosing interval where steady state has been attained. There are 6 time points between Day 3 and Day 8 inclusive that will be included in the steady-state ANOVA evaluation. The coefficients for the five contrasts involved are shown in the following table.

Coefficients for Linear Contrasts in Helmert Approach

Contrast	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1	-1	1/5	1/5	1/5	1/5	1/5
2		-1	1/4	1/4	1/4	1/4
3			-1	1/3	1/3	1/3
4				-1	1/2	1/2
5					-1	1

The individual and mean plasma drug concentration data will be plotted (using linear and semi-logarithmic plots). The individual bar charts of drug amounts excreted in urine data will be plotted over the 0-2, 2-4, 4-6 6-12, and 12-24 hour intervals. Descriptive statistics for plasma drug concentrations, drug amounts excreted in urine and calculated PK parameters will include: n (number of non-missing observations), arithmetic mean, SD, arithmetic CV, median, minimum, maximum, geometric mean, and geometric CV%, where GCV%=SQRT(e^{s^2}-1)*100 and s is the standard deviation of the log transformed values. For Tmax, only median, minimum, and maximum values will be presented. Bar charts comparing the results for the treatments will be constructed for Ae over the 0-6, 6-12, 0-12 12-24, and 0-24 hour intervals.

The compound symmetry (CS) covariance structure will be used to model the within-subject errors for treatment comparison and the autoregressive (1) covariance structure (AR(1)) will be used to model the within-subject errors for the Period 1 trough sample analyses.

6.8.2 Pharmacodynamics

The following pharmacodynamic (PD) parameters will be determined where possible from the serum and urine concentrations of absolute uric acid and baseline-adjusted uric acid using noncompartmental methods in Phoenix® WinNonlin® version 8.2 or higher.

Table 5: Pharmacodynamic Profile Screening Day -1 (Urine Only) and Period Days 1, 4, and 7, Period 2 Day 14, and Period 3 Day 21 (Serum and Urine)

Parameter	Units	Definition
$AUEC_{0-24}$	h*mg/dL	area under the effect-time curve from time 0 to 24 hours postdose
E_{max}	mg/dL	maximum observed response
TE_{max}	h	time of maximum observed response
Ae_{t1-t2}	mg	amount excreted in urine over the collection time interval t1 to t2 (i.e. 0-2, 2-4, 4-6, 6-12, and 12 -24). This will also be calculated for the intervals 0-6, 0-12, and 0-24.
fe_{t1-t2}	%	fractional excretion in urine, relative to Day 1, over the time interval t1 to t2, (i.e. 0-2, 2-4, 4-6, 6-12, and 12 -24), This will also be calculated for the intervals 0-6, 0-12, and 0-24.
CL_R	mL/min	renal clearance

Comparison of the PD parameters between coadministration and monotherapy will be performed.

Response thresholds of serum uric acid levels will be determined using pre-dose concentrations on Days 7, 14, and 21, using <6 mg/dL, <5 mg/dL, and <4 mg/dL as prospectively defined response definitions. The number (%) of patients responding on serum uric acid by various response definitions will be compared between the two dotinurad dose levels.

Dose proportionality on Day 7 between the two dotinurad dose levels will be evaluated with statistical assessments identically to that used for the PK parameters results.

The absolute values and change from baseline values will be calculated for the PD parameters ($AUEC_{0-24}$, E_{max}, and Ae_{0-24}). These values will be log_e-transformed and separately analyzed using Proc Mixed in SAS. The parameters CL_R and fe_{0-24}, will be evaluated without transformation. The least squares means, ratios of least squares means and confidence intervals on the least squares means and ratios for the log_e-transformed parameters will be back transformed to obtain geometric least squares means, ratios of geometric least squares means and confidence intervals for those geometric least squares mean and ratios. The statistical assessment for DDI will be conducted identically to that used for the PK parameter results. TE_{max} will be evaluated using the Wilcoxon signed-rank test.

6.8.3 Pharmacokinetics combined with Pharmacodynamics

Association between PK and PD measurements (Cmax compared to Emax; AUC_{0-t} compared to $AUEC_{0-24}$) will be explored graphically.

Associated trends will be explored using the subject and mean level plots of PK and PD concentrations over time on X-axis with different scaling for each measurement on the Y-axis.

Associated treatment differences will be explored with PK parameter on the X-axis, and PD parameter on the Y-axis. Trend lines will be estimated by treatment and dose level.

6.9 Pooled Analyses

No pooled analyses will be conducted in this trial.

6.10 Subgroup Analyses

No Subgroup analyses will be conducted in this trial.

6.11 Interim Analysis

No Interim analyses will be conducted in this trial.

6.12 Changes to Analyses Specified in Protocol

The following changes from the protocol-specified analysis were implemented:

- The protocol defined DDI analysis populations required treatment compliance for all 3 periods. Considering that Allopurinol monotherapy compliance is not required for the DDI analysis of Dotinurad monotherapy and Combination therapy and that Dotinurad monotherapy compliance is not required for the DDI analysis of Allopurinol monotherapy and Combination therapy, the protocol defined DDI analysis population was split into independent DDI Dotinurad and DDI Allopurinol populations.

7 REFERENCE

1. US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, No. 138, July 17, 1996, page 37320.
2. US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.
3. US Federal Register. (2020) Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions and In Vitro Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions; Guidance for Industry. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 85, No. 15, January 23, 2020, page 3932.

8 APPENDIX

Appendix A: List of Tables, Listings and Figures

8.1.1 Tables

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14.2.2.2.2.1	Drug-Drug Interaction Bioequivalence Analysis of Urine Pharmacokinetic Parameter Estimates for Combination of Dotinurad and Allopurinol vs. Dotinurad Monotherapy, DDI PK Dotinurad Population
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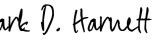
Mark D. Harnett markharnett@comcast.net Study Biostatistician Avenue Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 0D9F4DA5-2C0A-4BDD-8A63-BE5F1FE45B64 Using IP Address: 73.253.104.57 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/12/2023 7:40:31 AM Viewed: 9/12/2023 8:06:26 AM Signed: 9/12/2023 8:06:49 AM
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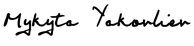
Mykyta Yakovliev mykyta.yakovliev@veranex.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: DC921558-5A7B-4FE7-9FBE-3613817FC356 Using IP Address: 195.39.243.10 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Я — автор цього документа	Sent: 9/12/2023 7:40:30 AM Viewed: 9/12/2023 7:42:18 AM Signed: 9/12/2023 7:52:18 AM
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