Statistical Analysis Plan

Sponsor:	LMU Klinikum
Protocol No:	LMU-IMPH-BTZ-043-03
Protocol Title:	A SINGLE-CENTER, OPEN-LABEL STUDY TO INVESTIGATE THE MASS BALANCE, EXCRETION PATHWAYS AND METABOLITES AFTER A SINGLE ORAL DOSE OF 500 MG, 3.7 MBq, [^{14}C]BTZ-043 IN HEALTHY MALE VOLUNTEERS
ICON/PRA Project ID:	NVS543EC-185431
Version Date:	02-Dec-2021 (SAP)

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

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1.0 Table of Contents

2.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under LMU Klinikum Protocol LMU-IMPH-BTZ-043-03.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 01-Jul-2021 (including all amendments and notes-to-files up to this protocol date) and the final eCRF(s) dated 15-Sep-21 (Screening) and 11-Oct-2021 (during Study).

An approved and signed SAP is a requirement for database lock.

This SAP covers the results that will be processed by the ICON/PRA Early Development Services (EDS) Biostatistics Department, and the results that will be processed by Nuvisan GmbH. ICON/PRA EDS will perform and is responsible for the safety and tolerability evaluation as well as for the total radioactivity in all matrices, including mass balance evaluation. Nuvisan will perform and is responsible for the pharmacokinetic (PK) evaluation of parent drug and main metabolite data in plasma and urine.

ICON/PRA EDS will prepare the Tables, Figures and Listings (TFLs) for Total Radioactivity (TR), BTZ-043 (M0), and main metabolites M1, M2, $M4_{tot}$, and M10.

Metabolic profiling (and Fe(%) of metabolites) is not part of this SAP and will be provided in a separate document.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

3.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

4.0 Study Objectives

4.1 Primary

- To determine the rates and routes of excretion of [^{14}C]BTZ-043-related radioactivity, including mass balance of total drug-related radioactivity in urine and feces (and vomit, if applicable), following the oral administration of a single 500 mg dose of [^{14}C]BTZ-043 in healthy male volunteers.
- To determine the pharmacokinetics (PK) of total radioactivity in blood and in plasma.
- To characterize the plasma PK of BTZ-043 and main metabolites by liquid chromatography-mass spectrometry (LC-MS), if applicable.
- To characterize the urine concentrations of BTZ-043 and main metabolites by LC-MS, if applicable.

4.2 Secondary

- To assess the safety and tolerability of a single 500 mg oral dose of BTZ-043 administered to healthy male volunteers.

4.3 Exploratory

- To identify BTZ-043's metabolites in plasma, and to quantify metabolites not measured in the primary objectives by radiometry in order to elucidate key biotransformation pathways and clearance mechanisms of BTZ-043 in humans.

- To identify BTZ-043's metabolites in excreta (urine and feces) and to quantify metabolites not measured in the primary objectives by radiometry in order to elucidate key biotransformation pathways and clearance mechanisms of BTZ-043 in humans.

5.0 Study Design

This study is a Phase 1, single-center, open-label study to investigate the absorption, metabolism, and excretion of BTZ-043 after a single oral administration of 500 mg BTZ-043 containing 3.7 MBq of [^{14}C]BTZ-043 in 4 healthy adult male subjects.

A total of 4 evaluable subjects completing all procedures are required. Six (6) subjects will be enrolled in the cohort in order to have 4 evaluable subjects. If the cohort of 4 subjects administered with 500 mg BTZ-043 containing 3.7 MBq of [^{14}C]BTZ-043 leads to less than 4 evaluable subjects, the 2 back-up subjects can be dosed subsequently to ensure that 4 subjects have completed all study procedures and are evaluable. If any of the 4 subjects vomits within 4 hours after study drug administration (approximately 2 times the median T_{max} of BTZ-043), the subject will be replaced.

Subjects will be admitted to the clinical research center on Day -1, which is the day prior to Day 1, the day of drug administration.

Subjects will receive a single oral dose of 500 mg BTZ-043 containing 3.7 MBq of [^{14}C]BTZ-043 on Day 1. Subjects will be discharged from the clinical research center on Day 5 (approximately 96 hours after drug administration) upon satisfactory recovery of radioactivity. If the criteria for discharge are not met on Day 5, subjects will be required to remain confined for a maximum of 3 additional days (Days 6 to 8) until the criteria are met (daily check by quick counts or normal counts, as feasible). The in-house period should be prolonged up to the morning of Day 8 if at least 1 of the following applies:

- Total radioactivity in plasma is higher than 5% of radioactivity-C_{max} and/or PK parameters for determination of the total radioactivity-elimination phase cannot be determined reliably.
- The mass balance in urine and feces is not complete by Day 5 (i.e., <90%).
- The combined urinary and fecal excretion is not ≤1% of the administered dose per 24 hours for 2 consecutive days based on ^{14}C-radioactivity "quick counts" or normal counts, as feasible.

If the criteria for discharge are still not met on Day 8, subjects may be discharged from the clinical site upon discretion of the Investigator. To ensure that adequate consideration is given to the protection of the subject's interests, subjects with an incomplete mass balance on Day 8 will be asked to return to the clinical site for one or two 24-hour visits (Day 11-12 and Day 15-16).

The follow up assessments will be performed 30 days (±2 days) after the [^{14}C]BTZ-043 dose.

The schedule of assessments is shown in Appendix 2: Schedule of Assessments

5.1 Sample Size Considerations

Since the present study is a descriptive study aimed at assessing excretion routes of BTZ-043 by evaluating mass balance, a formal statistical sample size calculation was not performed. A sample size of 3 subjects is a minimum accepted number of subjects for AME studies and thus 4 subjects are considered sufficient to achieve the study objectives, even in case of one drop-out. Early termination subjects may be replaced if the total number of completers drops below 4, after mutual agreement between the Sponsor and ICON/PRA.

5.2 Randomization

This is an open label, non-randomized study.

5.3 Method of Assigning Subjects to Treatment Groups

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. Subjects who meet all eligibility criteria receive a subject number upon inclusion in the study (Subject numbers 001-004). They receive the subject number just prior to dosing. The subject number ensures identification throughout the study. Replacement subjects will receive the number of the subject to be replaced, increased by 100 (eg, 101 replacement number for Subject Number 001), and will be administered the same treatment.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully, are considered “screening failures“. Such subjects do not receive a subject number, and data will not be entered in the eCRFs.

6.0 Overview of Planned Analysis

6.1 Changes from Protocol

The protocol mentions a separate PK SAP. It has been decided to provide one integrated SAP, covering PK, safety and tolerability.

The protocol states in section 3.2 that four subjects are the minimum number of subject for AME studies. Although 4-6 subjects are preferred, AME data of three subjects are considered to be sufficient to achieve the study objectives.

6.2 Interim Analysis and Key

Interim analysis or TFLs before Database freeze (softlock) are not planned.

6.3 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the first draft CSR.

7.0 Data Review

7.1 Data Management

Data handling and transfer will take place under the ICON/PRA Data Management Plan for the study.

7.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC’d) after database lock. Only quality assured (QA’d) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer, Statistician (ICON/PRA EDS) or PK Analyst (Nuvisan) who identified the issue will follow it to resolution.

8.0 Definitions and General Analysis Methods

8.1 Analysis Data Presentation

8.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

Baseline, safety and tolerability data:

For all summaries, all descriptive statistics will be presented with the same precision (number of decimals) as the data they are calculated from. Percentages will be presented with one decimal.

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics.

PK concentration, parameters and total radioactivity data:

Derived PK parameters, except t_{max}, will be reported with a precision of 3 significant digits or as integers when the value is ≥1000. The t_{max} will be reported with 2 decimals.

Any ratio will be rounded to one place beyond the decimal, no matter the value of the ratio.

Additional derived data will be rounded in the derived dataset as determined by the statistician.

8.1.2 Imputation

The following imputation will be performed:

• PK concentrations below the lower limit of quantification (LLOQ) (see 16.2.1)

• If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameters (see 16.2.2)

• Last observation carried forward (LOCF) for mass balance/ urine will be applied (see 16.2.3)

• missing period start or end date/times in Subject-level analysis dataset (ADSL), as appropriate.

• missing start or end date/times of adverse events (AEs) for the calculation of onset and duration (see 18.1.1)

• missing AE severity, relationship and seriousness of AEs (see 17.1.1)

• Laboratory data that are <x or >x (e.g. “<1.03”, “>1000”) will be imputed to x (respectively to 1.02 and 1001 in the example, see section 17.1.2).

Imputations / substitutions will be used in calculations and summaries only. Original data will be listed. If imputations / substitutions are listed, they will be listed along with the original data.

8.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), coefficient of variation (%CV, only for PK data), minimum (min) value, median, and maximum (max) value.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the database.

8.1.4 Pooling

Not applicable for this SAP.

8.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis. In case an unscheduled measurement was performed immediately after the scheduled measurement because of a previous measurement error (e.g. equipment failure), this repeated measurement will be used, and the original erroneous measurement will be excluded from the analysis.

8.2 Analysis Data Definitions

8.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement. If a pre-treatment observation is missing in a given period, then the screening value may be used.

8.2.2 Treatment/Subject Grouping

Label	Grouping
Study Drug	[^{14}C]-labeled BTZ-043
Treatment	500 mg BTZ-043 containing 3.7 MBq of [^{14}C]BTZ-043
Dose Level	500 mg

8.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation
Change from Baseline	All	Post-dose Observation minus Baseline Observation
Analysis Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1
Relative Actual time from	Dosing	Actual time calculated as the sampling date/time minus IMP start of dosing date/time

8.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the general ICON/PRA EDS QC plan.

8.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. Subject level, pharmacokinetic, and adverse events (ADSL, ADPC, ADPP, and ADAE) are considered as critical datasets. These datasets will be double programmed per the QC Plan.

8.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1, and CDISC ADaM Implementation Guide 1.2. The following ADaM datasets will be prepared:

Table 1 ADaM Datasets

ADaM Dataset Name	Description	Double Programmed?
ADSL	Subject-Level Analysis Dataset	Yes
ADAE	Adverse Events Analysis Dataset	No
ADEG	ECG Analysis Dataset	No
ADLB	Laboratory Test Results Analysis Dataset	No
ADPC	Pharmacokinetic Concentrations Analysis Dataset	Yes
ADPP	Pharmacokinetic Parameters Analysis Dataset	Yes
ADVS	Vital Signs Analysis Dataset	No

A define.xml file version 2 with the corresponding metadata and Analysis Data reviewers guide (ADRG) will be included. Analysis results (analysis displays or program details) metadata are excluded from the define.xml.

8.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® (WNL) Version 7.0 or higher (Certara USA Inc.). For TR in plasma and blood, version 8.1 will be used. Additional PK computations may be performed in SAS®.

8.4 Statistical Methods

8.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

8.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

8.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

8.5 TFL Layout

Report layout will be according to the ICON/PRA EDS – ICH E3 compliant – CSR Template. The layout of Tables, Figures and Listings (TFLs) will be according to the ICON/PRA EDS standards.

No table shells will be provided. The TFLs will be provided in Adobe PDF format.

Format:

- Page size: A4
- Data in listings will be sorted by subject number and time point.

- Data in tables will be sorted by treatment and time point (where applicable).
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The following treatment label will be used in the TFLs: [14C]BTZ-043
  PK and mass balance TFLs will be presented with a subtitle for the analyte and specimen type, using BTZ-043, M1, M2, M4tot, M10 and Σ(BTZ-043, M1, M2, M4tot, M10) in plasma and urine, total radioactivity in plasma and blood, and total radioactivity excretion in urine/feces/vomitus/sum of excreta.
  Σ(BTZ-043, M1, M2, M4tot, M10) will be reported as Sum (BTZ-043, M1, M2, M4tot, M10).

9.0 Analysis Sets

Analyses	Safety Set	Pharmacokinetic Set
Disposition Summaries		
Safety Assessments	✓	
Baseline Characteristics	✓	
Primary Analysis		✓
PK Concentrations		✓
PK Parameters		✓

9.1 Safety Set

The safety set will consist of subjects who receive one dose of [^{14}C]BTZ-043. This set will be used for the safety data summaries, baseline characteristic summaries, and disposition summaries.

9.2 Pharmacokinetic Set

The PK set will consist of all subjects who receive the complete dose of [^{14}C]BTZ-043 and have sufficient concentration-time data to calculate a valid C_{max} and AUC_{last}. Summaries of PK concentrations and summaries of PK parameters will be based on the PK set.

10.0 Subject Disposition

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

11.0 Protocol Deviations

Protocol deviations will be listed by subject.

12.0 Demographic and Baseline Characteristics

12.1 Demographics

All demographic data as collected during the screenings visit will be listed by subject.

Subject demographics will be summarized descriptively for all subjects by treatment. The summary will include the subjects' age (in years), gender, race, ethnicity, weight at screening (in kg), height (in cm), and BMI at screening (in kg/m2). Demographics will be summarized for the safety set (and PK set if different from safety set).

12.2 Medical History

Medical history will be listed. Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA), version 24.1.

12.3 Other Baseline Characteristics

The results of drug and alcohol screen at screening will be listed.

The results of serology at screening will be listed.

The results of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) tests will be listed.

Non-compliance to in- or exclusion criteria (if any) will be listed.

13.0 Concomitant Medications

Concomitant medications will be listed uncoded by subject. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

14.0 Treatment Compliance and Exposure

Exposure data will be listed by subject.

15.0 Pharmacokinetic Analyses

Due to the known instability of some BTZ-043 metabolites in native matrices, not every metabolite will be quantified by radio-profiling during this hAME study (stabilization measures are not compatible with radio-analysis sample processing). Instead, BTZ-043 and its main metabolites will be measured in plasma and urine samples by validated / qualified LC-MS methods applying appropriate stabilization measures, and all 'other metabolites' will be quantified by radio-profiling. For feces, such stabilization measures are not feasible, but labile metabolites are also expected to be of low priority/amounts, as anticipated from rat data. Therefore, quantitative PK feces data of BTZ-043 and its metabolites will come from radio-profiling solely.

Total radioactivity data and its PK evaluation will be generated as a separate report by ICON/PRA. An integrated PK evaluation will combine the metabolite quantification data from LC-MS measurements and radio-profiling for an overall evaluation of the drug's metabolic fate and excretion pathways, and compare these data with the total radioactivity data.

Note: The term 'other metabolites' in the following means all BTZ-043 metabolites, except the main metabolites M1, M2, $M4_{total}$ and M10.

15.1 Pharmacokinetic Variables

PK concentrations will be collected in plasma, urine, and feces. If applicable - TR concentrations will be measured in vomitus.

15.1.1 Plasma Variables

15.1.1.1 Concentrations

- Individual plasma concentrations per time point for TR (reported in ICON/PRA TFLs + CSR).
- Individual plasma concentrations per time point for BTZ-043 (as measured by LC-MS, reported in ICON/PRA TFLs + CSR)
- Individual plasma concentrations per time point for metabolites M1, M2, $M4_{tot}$ and M10 (as measured by LC-MS, reported in ICON/PRA TFLs + CSR)
- Sum of plasma concentrations per time point for BTZ-043 and its metabolites M1, M2, $M4_{tot}$ and M10 (reported in ICON/PRA TFLs + CSR)
- Individual plasma concentrations per Hamilton AUC-pool for individual 'other metabolites' (as measured by radio-profiling– not a part of this SAP (reported in integrated PK report)

15.1.1.2 Parameters

- PK parameters for TR, BTZ-043 (M0), M1, M2, $M4_{total}$, M10 (reported in ICON/PRA TFLs +CSR), defined in table 1
- PK parameters Σ(M0, M1, M2, $M4_{total}$, M10) [reported in ICON/PRA TFLs +CSR]
- PK parameters for 'other metabolites', Σ(parent and all metabolites) as applicable, and defined in table 1 (reported in integrated PK report)

Table 1: Plasma Parameters

Parameter	Description	Analyte	SAS Programming Notes
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	TR, M0, M1, M2, $M4_{total}$, and M10	Cmax from WNL
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	TR, M0, M1, M2, $M4_{total}$, and M10	Tmax from WNL
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	TR, M0, M1, M2, $M4_{total}$, and M10, Σ(M0, M1, M2, $M4_{total}$, M10)	AUClast from WNL
AUCall	Area under the curve from the time of dosing to the time of the last observation. If the last concentration is positive $AUC_{0\text{-}tlast} = AUC_{all}$. Otherwise, AUC_{all} will not be equal to $AUC_{0\text{-}tlast}$ as it includes the additional area from the last measurable concentration down to zero or negative observations	TR, M0, M1, M2, $M4_{total}$, and M10, Σ(M0, M1, M2, $M4_{total}$, M10)	AUCall from WNL
AUCinf	Area under the blood concentration-time curve (time 0 to infinity), calculated as: $AUC_{inf}=AUC_{0\text{-}t}+C_{last}/k_{el}$, where Clast is the last measurable blood concentration.	TR, M0, M1, M2, $M4_{total}$, and M10, Σ(M0, M1, M2, $M4_{total}$, M10)	AUCINF_obs from WNL
Λz (Kel)	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve.	TR, M0, M1, M2, $M4_{total}$, and M10	Lambda_z from WNL

Parameter	Description	Analyte	SAS Programming Notes
$t_{1/2}$	Terminal phase half-life expressed in time units.	TR, M0, M1, M2, $M4_{total}$, and M10	HL_Lambda_z from WNL
AUC0-t	Area under the blood concentration-time curve from time 0 to t hours post-dose.	TR, M0, M1, M2, $M4_{total}$, M10 and individual 'other metabolites', Σ(M0, M1, M2, $M4_{total}$, M10), Σ(M0 and all metabolites)	n.a. Part of the integrated PK report.
CL/F	Apparent oral clearance, calculated as dose/AUCinf	M0	CL/F from WNL
Vz/F	Apparent volume of distribution at terminal phase	M0	Vz/F from WNL

Note: AUCs will be calculated using linear up / log down, expressed in units of concentration (ng eq/mL) x time (h).

15.1.2 Blood Variables

15.1.2.1 Concentrations

- Individual blood concentrations per time point for TR. Reported in ICON/PRA TFLs + CSR.

15.1.2.2 Parameters

- Individual PK parameters for TR, as defined in table 2

Table 2: Blood Parameters

Parameter	Description	Analyte	SAS Programming Notes
Cmax	Maximum blood concentration of total radioactivity. Observed peak analyte concentration obtained directly from the experimental data	TR	Cmax from WNL

Parameter	Description	Analyte	SAS Programming Notes
	without interpolation, expressed in concentration units		
Tmax	Time to maximum blood total radioactivity concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	TR	Tmax from WNL
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	TR	AUClast from WNL
AUCinf	Area under the blood concentration-time curve (time 0 to infinity), calculated as: $AUC_{inf}=AUC_{0-t}+C_{last}/k_{el}$, where Clast is the last measurable blood concentration	TR	AUCINF_obs from WNL
Λz (Kel)	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve	TR	Lambda_z from WNL
$t_{1/2}$	Terminal phase half-life expressed in time units.	TR	HL_Lambda_z from WNL
AUC0-t	Area under the blood concentration-time curve from time 0 to t hours post-dose.	TR	n.a. Part of the integrated PK report.

15.1.3 Urine Variables

15.1.3.1 Amounts Excreted

- Individual cumulative amount of TR excreted in urine (Ae,urine). Reported in ICON/PRA TFLs + CSR.
  - Calculated as the urine volume times the urine concentration for each day pool and added up per subject.
- Individual cumulative amount of BTZ-043 (M0) excreted in urine (Ae,urine), as measured by LC-MS. Reported in ICON/PRA TFLs + CSR.
  - Calculated as the urine volume times the urine concentration for each day pool and added up per subject.
- Individual cumulative amount of M1, M2, $M4_{tot}$ and M10, excreted in urine (Ae,urine), as measured by LC-MS. Reported in ICON/PRA TFLs + CSR.
  - Calculated as the urine volume times the urine concentration for each day pool and added up per subject.
- Individual cumulative amount of Σ(M0, M1, M2, $M4_{total}$, M10), excreted in urine (Ae,urine). Reported in ICON/PRA TFLs + CSR.
  - Calculated as the urine volume times the urine concentration for each day pool and added up per subject.
- Inter-subject average cumulative amounts of individual 'other metabolites' in urine (Ae,urine), as measured by radio-profiling (see study protocol G-A-MET-21-002). Reported in integrated PK report.

15.1.3.2 Parameters

- PK parameters for TR, BTZ-043 (M0), M1, M2, $M4_{total}$, M10, and Σ(M0, M1, M2, $M4_{total}$, M10) as applicable, as defined in table 3. Reported in ICON/PRA TFLs + CSR
- PK parameters for 'other metabolites' and Σ(M0 and all metabolites), as applicable, as defined in table 3. Reported in integrated PK report.

Table 3: Urine Parameters

Parameter	Description	<Analyte	SAS Programming Notes
Aet (urine)	Total amount of drug/metabolites excreted into urine to time t, obtained by adding the amounts excreted over each collection interval per subject.	TR, M0, M1, M2, $M4_{total}$, M10 and Σ(M0, M1, M2, $M4_{total}$, M10)	Summation t1-tn(Concentration (ng eq/mL)ti-t2*volume(mL)t1-t2)
Aet (urine)	Total amount of drug/metabolites excreted to time t, as obtained from one pool sample across all subjects covering ≥ 90% of TR in urine.	Individual 'other metabolites', Σ(M0 and all metabolites)	n.a.
Fe (urine)	Fraction (%) of the administered dose excreted into urine Fe = (Aet (urine) / Dose) * 100 per subject.	TR, M0, M1, M2, $M4_{total}$, M10, Σ(M0, M1, M2, $M4_{total}$, M10	Aet/500 mg*100

Parameter	Description	<Analyte	SAS Programming Notes
Fe (urine)	Fraction (%) of the administered dose excreted into urine Fe = (Aet (urine) / Dose) * 100, across all subjects.	Individual 'other metabolites', Σ(M0 and all metabolites)	n.a.
CL_R	Renal clearance of parent drug calculated as Ae/AUCinf	M0	Ae/AUCinf

15.1.4 Feces Variables

15.1.4.1 Amounts Excreted

- Individual cumulative amount of TR excreted in feces (Ae,feces). Reported in ICON/PRA TFLs + CSR.
  - Calculated as the feces homogenate weight times the feces homogenate concentration for each day pool and added up per subject.
- Inter-subject average cumulative amount of BTZ-043 (M0) in feces (Ae,feces), as measured by radio-profiling (see study protocol G-A-MET-21-002). Reported in integrated PK report.
- Inter-subject average cumulative amounts of M1, M2, $M4_{total}$, M10 and individual 'other metabolites' in feces (Ae,feces, as applicable), as measured by radio-profiling (see study protocol G-A-MET-21-002). Reported in integrated PK report.

15.1.4.2 Parameters

- PK parameters for TR, as applicable, as defined in table 4
- PK parameters for BTZ-043 (M0), and individual metabolites, as applicable, as defined in table 4

Table 4: Feces Parameters

Parameter	Description	<Analyte>	SAS Programming Notes
Aet (feces)	Total amount of radioactivity excreted into feces to time t, obtained by adding the amounts excreted over each collection interval per subject.	TR	Summation t1-tn(Concentration (ng eq/mg)ti-t2*weight(mg)t1-t2)
Aet (feces)	Total amount of drug/metabolites excreted to time t, as obtained from one pool sample across all subjects covering ≥ 90% of TR in feces.	M0, and individual metabolites, Σ(M0 and all metabolites)	n.a.
Fe (feces)	Fraction (%) of the administered dose excreted into feces Fe = (Aet (feces) / Dose) * 100.	TR	Aet/500mg*100

Parameter	Description	<Analyte>	SAS Programming Notes
Fe (feces)	Fraction (%) of the administered dose excreted unchanged / as individual metabolites into feces Fe = (Aet (feces) / Dose) * 100 across all subjects and days.	M0 and individual metabolites, Σ(M0 and all metabolites)	n.a.

15.1.5 Vomitus Variables

15.1.5.1 Amounts Recovered

- Individual cumulative amount of TR recovered from vomitus (Ae,vomitus), if applicable. Reported in ICON/PRA TFls + CSR.
  - Calculated as the vomitus homogenate volume times the vomitus homogenate concentration for day 1 of each subject.

15.1.5.2 Parameters

- PK parameters for TR as defined in table 5, if applicable. Reported in ICON/PRA TFls + CSR.

Table 5: Vomitus Parameters

Parameter	Description	<Analyte>	SAS Programming Notes
Aet (vomitus)	Total amount of radioactivity recovered in vomitus to time t on Day 1.	TR	Summation t1-tn(Concentration (ng eq/mg)ti-t2*weight(mg)t1-t2) on Day 1 only
Fe (vomitus)	Fraction (%) of the administered dose recovered from vomitus Fe = (Aet (vomitus) / Dose) * 100, on Day 1.	TR	Aet/500mg*100

15.1.6 Total Excretion Variables

15.1.6.1 Amounts Recovered

- Individual cumulative amount of TR recovered from urine, feces and vomitus (Ae,total). Reported in ICON/PRA TFLs + CSR.
  - Calculated as the sum of Ae_{urine}, Ae_{feces} and $Ae_{vomitus}$.

15.1.6.2 Parameters

- PK parameters for TR as defined in table 6, if applicable. Reported in ICON/PRA TFLs + CSR.

Table 6: Total Excretion Parameters

Parameter	Description	<Analyte>	SAS Programming Notes
Aet (total)	Total amount of radioactivity excreted in / recovered from urine, feces and vomitus	TR	Aet (total) = Aet (urine) + Aet (feces) + Aet (vomitus)
Fe (total)	Fraction (%) of the administered dose excreted in / recovered from urine, feces and vomitus Fe = (Aet (total) / Dose) * 100.	TR	Aet (total)/500mg*100

15.2 Pharmacokinetic Summaries

15.2.1 Pharmacokinetic Concentrations

Measured concentrations will be listed and summarized for each sampling time point, analyte and matrix with calculation of arithmetic means, standard deviation and coefficients of variation, as applicable. For inter-subject pooled samples, descriptive statistics will not be provided. Any results below the limit of quantification will be reported as "BLOQ" and samples where no results were obtained will be reported as "NR".

When calculating means for purpose of descriptive statistics and plots, the following rules apply:

- Numeric values > sum of BLOQ & NR → mean will be reported
- Numeric values ≤ sum of BLOQ & NR and NR ≥ BLOQ → NR will be reported
- Numeric values ≤ sum of BLOQ & NR and BLOQ > NR → BLOQ will be reported

Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation) will be used to summarize the plasma concentrations across the 4 subjects at each scheduled time point.

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided per subject for:

- M0, M1, M2, $M4_{total}$, and M10 (combined in one plot)
- TR in plasma and whole blood (combined in one plot)
- TR, and Σ(M0, M1, M2, $M4_{total}$, M10) (combined in one plot)

In addition, across subject data (arithmetic mean) will be provided for:

- M0, M1, M2, $M4_{total}$, M10 (combined in one plot)
- TR in plasma and whole blood (combined in one plot)
- TR, and Σ(M0, M1, M2, $M4_{total}$, M10) (combined in one plot)

These plots will show time in hours. Individual plots will use the BLOQ handling procedure described above.

Individual plasma concentration data will be presented together with descriptive statistics.

A separate listing with time deviations and comments will be provided.

<u>For MetID and the integrated PK report:</u>

Concentrations of M0 and metabolites derived from metabolite profiling in Hamilton pool samples of individual subjects will be listed in the MetID and in the integrated PK report for the pooling interval. Plasma exposure of M0 and all metabolites (AUC_{0-t}) and $\%AUC_{0-t}$ of TR, M0 and metabolites will be calculated. Descriptive statistics (number of subjects, arithmetic mean, standard deviation) may be used to summarize the plasma concentrations and exposures across the 4 subjects for the pooling interval (if appropriate). The Σ(M0, M1, M2, M3, M4, M10) as well as Σ(individual 'other metabolites') may be listed (if appropriate).

15.2.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated using the software Phoenix WinNonlin 7.0 or higher. TR in plasma and blood will be calculated in version 8.1.

Actual times will be used for the calculation of the parameters. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameters.

The AUC calculation method will be Linear Up Log Down. Pharmacokinetic plasma parameters will be calculated on individual data with group means and relative standard deviation, on pool concentration data or on sum concentration data, as applicable. All parameters will be rounded to three significant figures

before presentation. Plasma concentrations below the limit of quantification (BLOQ) will be handled according to the following rules:

- BLOQ values before the first numeric value will be set to zero.
- BLOQ values after the first numeric value and before t_{max} will be set to missing (i.e. value will be ignored by Phoenix and a linear interpolation will be performed)
- BLOQ values after t_{max} and before the last numeric value will be set to zero (Phoenix will switch from log interpolation to linear interpolation in this case).
- BLOQ values after the last numeric value will be set to zero.

Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation) will be used to summarize the calculated PK parameters. For t_{max} (and t_{last} if applicable), only median will be presented.

According to the Nuvisan SOP BAS_PKM_03, the elimination half-life (t1/2) will be calculated using the automatic detection method for profiles with at least 3 numeric data points and a coefficient of determination $r^2 \geq 0.9025$. Where these criteria are not fulfilled, the results will be reported as NC in the result tables.

Parameters based on $\%AUC_{extra}$ above 20% will be flagged but not excluded from descriptive statistics.

15.2.3 Pharmacokinetic Amounts Excreted

Urinary and fecal TR PK parameters will be calculated using SAS. Excretions in mg equivalent (mg eq) and % of dose for each interval (Ae_{t1-t2}) will be derived from the urinary and fecal concentrations and the sample collection interval volumes or weights respectively, by multiplying the concentration in the interval (C) and the volume or weight (V):

$$Ae_{t1-t2} = C \times V$$

If the concentration is <LLOQ the excretion will be assumed to be zero. For intervals in which no sample was collected (e.g., no defecation), the excretion will be assumed to be zero. If needed, for cumulative excretions, the last observation carried forward (LOCF) method will be used up to the last time point.

Cumulative excretions for each continuously sampled interval will be calculated by summarizing the excretions in the current and all previous collection intervals:

$$Ae_{0-t} = \sum_{i=1}^{n} (Ae_{t_{start}-t_{end}})_i$$

For subjects with an incomplete mass balance on Day 8, the cumulative excretion up to each interval (Day 12 and Day 16) will be supplemented by estimating the area under the excretion rate versus time curve (AURC) for intervals between the in house period and ambulant visits.

The excretion rate ($\Delta Ae/\Delta t$) will be calculated by dividing the excretion in each interval by the time difference in hours between the end and the start of the collection interval:

$$\Delta Ae/\Delta t = \frac{Ae}{t_{end} - t_{start}}$$

Ae_{urine} and Fe_{urine}: Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation) will be used to summarize the urine amounts excreted as TR, BTZ-043 (M0), M1, M2, $M4_{total}$, M10, and Σ(M0, M1, M2, $M4_{total}$, M10) by the 4 subjects for each day pool, as well as for the total collection periods. No statistics will be available for the urine amounts excreted as individual 'other metabolites' due to the pooled analysis of the radio-profile. The same holds true for the overall sum of excreted amounts of metabolites in urine.

Ae_{feces} and Fe_{feces}: Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation) will be used to summarize the feces amounts excreted as TR by the 4 subjects for

each day pool, as well as for the total collection periods. No statistics will be available for the feces amounts excreted as BTZ-043 (M0), M1, M2, $M4_{total}$, M10 and individual 'other metabolites' due to the pooled analysis of the radio-profile. The same holds true for the sum of excreted amounts of metabolites.

Ae_{total} and Fe_{total}: Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation) will be used to summarize the overall excreted amounts of TR by urine, feces (and vomitus, if applicable) of the 4 subjects over the total collection period. No statistics will be available for the overall excreted amounts of BTZ-043 (M0), M1, M2, $M4_{total}$, M10, individual 'other metabolites' and overall sum of metabolites.

Linear plots of the cumulative TR (Fe) in urine, feces and total amounts excreted per day pool will be provided by subject and as mean over 4 subjects. These plots will show time in hours.

Individual total radioactivity excretion data (concentrations, volumes, weights, amount excreted and excretion rate [if applicable]) will be listed per collection interval.

16.0 Safety Analyses

16.1 Safety Variables

The following safety variables will be summarized:

- Adverse Events (AEs)
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure (SBP)
    - Diastolic Blood Pressure (DBP)
  - Pulse rate
  - Temporal temperature
  - Respiratory rate
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Fridericia's) Interval
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis
- Physical Examination

16.1.1 Adverse Events

All AE summaries will include only treatment emergent adverse events. Treatment-emergent adverse events (TEAE) are those which occur after the first dose of study drug.

A summary of the number of events, and the number and percentage of subjects reporting each TEAE, categorized by system organ class (SOC) and preferred term coded according to the MedDRA (Version 24.1) will be presented by treatment. Subjects will only be counted once within each SOC or preferred term. This summary will be provided for all TEAEs and for related TEAEs.

Summary tables will present the counts in descending order by SOC and preferred term (within a SOC) based on the number of subjects experiencing the event.

A summary of the number of events, and number and percentage of subjects reporting each TEAE, categorized by relationship to study drug as recorded on the eCRF, will be provided.

A summary of the number of events, and number and percentage of subjects reporting each TEAE, categorized by severity as recorded on eCRF, will also be provided.

A listing of adverse events leading to study discontinuation will be provided.

All adverse events (including non-treatment-emergent events) recorded on the eCRF will be listed.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times. If the missing AE start time occurs at day of dosing, it will be set to one minute after dosing
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start date will be assumed to be after treatment for the determination of TEAE
- Missing AE severity or relationship will be assumed to be severe or related, respectively

16.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

16.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

All laboratory data and comments will be listed, including laboratory variables not listed in the protocol (ad hoc measurements). A separate listing, including out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology and coagulation (observed and derived changes from baseline) by treatment and scheduled time will be provided.

Laboratory data that are <x or >x (e.g. “<1.03”, “>1000”): the analysis value or normal limit value will be the value of the detection limit itself plus or minus one precision unit for the parameter concerned (respectively 1.02 and 1001 in the example). The values before imputation (“<1.03”, “>1000”) will only be shown in listings.

16.1.4 Vital Signs

Descriptive statistics will be provided to summarize vital signs (observed values and changes from baseline) by treatment and scheduled time.

All vital signs measurements will be listed.

16.1.5 Electrocardiograms

All ECG parameters and the corresponding abnormalities and physician’s conclusions will be listed by subject.

Descriptive statistics will be provided to summarize ECG parameters (observed values and changes from baseline) by treatment and scheduled time.

16.1.6 Other Observations Related to Safety

Findings at screening and changes from screening for the physical examination will be listed.

17.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A SINGLE-CENTER, OPEN-LABEL STUDY TO INVESTIGATE THE MASS BALANCE, EXCRETION PATHWAYS AND METABOLITES AFTER A SINGLE ORAL DOSE OF 500 MG, 3.7 MBq, [^{14}C]BTZ-043 IN HEALTHY MALE VOLUNTEERS. Version 2.0, Final, 01-Jul-2021.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
ADRG	Analysis data reviewer's guide
AME	Absorption, metabolism, and excretion
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
n	Number of observations
PCR	Polymerase chain reaction
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study data tabulation model

SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WHO	World Health Organization
WNL	WinNonlin
For PK parameters please refer to Section 16	

Appendix 2: Schedule of Assessments

Table 2 Schedule of Assessments

Visit	Screening	Treatment Period[a]									24-hour Visits[a]				Follow-up
Study Day	Days -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6[m]	Day 7[m]	Day 8[m]	Day 11[m]	Day 12[m]	Day 15[m]	Day 16[m]	Day 31 (±2 days)
Confinement[a]		X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Ambulatory	X														X
Admission		X									(X)		(X)		
Discharge[b]							X	(X)	(X)	(X)		(X)		(X)	
Informed Consent	X														
Medical History	X														
Demographics	X														
Physical Examination[c]	X	X													X
Body Weight	X	X													
Height and BMI Calculation	X														
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X														
SARS-CoV-2 PCR[d]		X		X							(X)		(X)		
Drug and Alcohol Screen	X	X													
Clinical Laboratory[e]	X	X		X		X									X
Urinalysis	X	X		X		X									X
12-lead ECG[f]	X	X	X	X			X	(X)	(X)	(X)		(X)		(X)	X
Vital Signs[g]	X	X	X	X			X	(X)	(X)	(X)		(X)		(X)	X
Eligibility Check	X	X	X												
Study Drug Administration			X												
Plasma Sampling for BTZ-043 and Main Metabolites[h]			X	X	X										
Whole Blood Sampling for Radioactivity[i]			X	X	X	X	X	(X)	(X)	(X)	(X)		(X)		

Visit	Screening	Treatment Period[a]								24-hour Visits[a]				Follow-up
Study Day	Days -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6[m]	Day 7[m]	Day 8[m]	Day 11[m]	Day 12[m]	Day 15[m]	Day 16[m]	Day 31 (±2 days)
Plasma Sampling for Total Radioactivity and Metabolite Profiling[i]			X	X	X	X	X	(X)	(X)	(X)	(X)		(X)		
Urine Collection and Pooling for BTZ-043 and Main Metabolites, Total Radioactivity, and Metabolite Profiling[j]		X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Feces Collection for Total Radioactivity and Metabolite Profiling[k]	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Vomit Collection for Total Radioactivity, if available[l]			X												
Previous and Concomitant Medication	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
AE Monitoring		X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus;PCR=polymerase chain reaction; PK=pharmacokinetic(s)

a Subjects will be in the clinic from Day -1 (predose) until Day 5 with possible extension (Day 6 to Day 8) as well as possible 24-hour visits (Day 11-12, Day 15-16). The 2 back-up subjects will stay in the clinic until the morning of Day 2.
b Subjects will be released from the clinic 96 hours after dose administration and upon satisfactory recovery of radioactivity.
c Complete physical examinations will be conducted at screening, Day -1, and follow-up/early termination. Symptom driven physical examinations may be conducted at any time, per the Investigator's discretion.
d Sampling of nasal and throat mucosal cells. If deemed necessary, additional tests may be conducted during the study. The nonclinical project manager will be informed immediately upon availability
of Day 11 results, as this will qualify the feces samples for metabolite profiling with regard to potential COVID-19 infectivity.
e Clinical laboratory tests (including clinical chemistry, hematology, and urinalysis): at screening; on Day -1 (admission), Day 2, and Day 4; and at follow-up.
f 12-lead ECG: at screening; Day -1, and 1 hour, 4 hours, and 24 hours postdose; at discharge; and at follow-up.
g Vital signs (supine systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate): at screening; at admission; at predose and at 1 hour, 4 hours, and 24 hours postdose; at discharge; and at follow-up.
h Plasma sampling for PK of BTZ-043 and main metabolites in plasma: at predose and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, and 48 hours postdose.
i Total radioactivity in whole blood and plasma: at predose and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, 72, and 96 hours postdose (in case total radioactivity recovered is still <90%: in addition 120, 144, and 168 hours postdose and at further 24-hour visits [264 and 360 hours postdose] until study completion). Metabolite profiling in plasma: at predose and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, 72, and 96 hours postdose (in case total radioactivity recovered is still <90%: in addition 120, 144, and 168 hours postdose. Metabolite profiling in plasma: at predose and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, 72, and 96 hours postdose (in case total radioactivity recovered is still <90%: in addition 120, 144, and 168 hours postdose.
j Urine collection and pooling for BTZ-043 and main metabolites, total radioactivity, and metabolite profiling: at predose (within 12 hours prior to dosing) and over 0-24, 24-48, 48-72, and 72-96 hours postdose collection intervals (in case total radioactivity recovered is still <90%, in addition 96-120, 120-144, and 144-168 hours postdose and at further 24-hour intervals [Day 11-12 and Day 15-16] until study completion).
k Feces collection for total radioactivity and metabolite profiling; predose feces collection to be collected at any time within 48 hours prior to study drug administration (at home or in the clinic). After administration of BTZ-043, feces will be collected in 24 hour collection intervals up to 96 hours postdose (in case total radioactivity recovered is still <90%: in addition 120, 144, and 168 hours postdose and at further 24-hour intervals [Day 11-12 and Day 15-16] until study completion).
l If produced, vomit will be collected up to 8 hours after the administration of the study drug for total radioactivity determination.
m Day 6-8 procedures will only be conducted in case that the recovery of radioactivity was not satisfactory until Day 5. 24-hour visits procedures will only be conducted in case that the recovery of radioactivity was not satisfactory until Day 8. For the 24-hour visits (if applicable): feces collection to be collected at home within 48 hours prior to admission.

Appendix 3: List of In-Text Outputs

For PK, TFLs and CSR are restricted to TR, BTZ-043 (M0), M1, M2, $M4_{tot}$, M10, and Σ(M0, M1, M2, $M4_{total}$, M10).

List of In Text Tables and Figures:		
Output	**Title**	**Population Set**
Table	Subject Disposition	Safety
Table	Demographic Parameters	Safety, PK
Table	PK parameters of BTZ-043 and Main Metabolites in Plasma	PK
Figure	Arithmetic Mean Plasma Concentrations Versus Time Profiles of BTZ-043 and Main Metabolites (Linear and Semi-Logarithmic Scale)	PK
Table	PK parameters and Total Radioactivity in Plasma and Whole Blood	PK
Figure	Arithmetic Mean Plasma and Whole Blood Concentrations Versus Time Profiles of Total Radioactivity (Linear and Semi-Logarithmic Scale)	PK
Table	Excretion Parameters of Total Radioactivity in Urine, Feces and Sum of Excreta	PK
Figure	Mean Cumulative Excretion vs Time Profiles of Total Radioactivity in Urine, Feces and Sum of Excreta	PK
Table	Urine PK parameters	PK
Table	Treatment Emergent Adverse Events by SOC and Preferred Term	Safety
Table	Treatment Emergent Adverse Events by Relationship and Severity	Safety

Appendix 4: List of End of Text Outputs

For PK, TFLs and CSR are restricted to TR, BTZ-043 (M0), M1, M2, $M4_{tot}$, M10, and Σ(M0, M1, M2, $M4_{total}$, M10).

List of End of Text Tables and Figures:		
Output	**Title**	**Population Set**
Section 15.1 – Disposition and Demographic Data		
Table 15.1.1	Summary of Subject Disposition	Safety
Table 15.1.2.1	Summary of Demographics	Safety
Table 15.1.2.2	Summary of Demographics	PK
Section 15.2 – Pharmacokinetic Data		
Section 15.2.1 Plasma and Whole Blood		

Table 15.2.1.1	Individual Values and Descriptive Statistics of BTZ-043, Main Metabolites and Sum of Analytes Plasma Concentrations	PK
Table 15.2.1.2	Individual Values and Descriptive Statistics of Total Radioactivity Plasma and Whole Blood Concentrations	PK
Figure 15.2.1.3	Arithmetic Mean Plasma Concentrations Versus Time Profiles of BTZ-043 and Main Metabolites (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.1.4	Arithmetic Mean Plasma and Whole Blood Concentrations Versus Time Profiles of Total Radioactivity (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.1.5	Arithmetic Mean Plasma Concentrations Versus Time Profiles of Total Radioactivity, BTZ-043 (M0) and Sum of Analytes (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.1.6	Individual Plasma Concentrations Versus Time Profiles of BTZ-043 and Main Metabolites (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.1.7	Individual Total Radioactivity Plasma and Whole Blood Concentrations Versus Time Profiles (Linear and Semi-Logarithmic Scale)	PK
Figure 15.2.1.8	Individual Plasma Concentrations Versus Time Profiles of Total Radioactivity, BTZ-043 (M0) and Sum of Analytes (Linear and Semi-Logarithmic Scale)	PK
Table 15.2.1.9	Individual Values and Descriptive Statistics of BTZ-043, Metabolites and Sum of Analytes PK Plasma Parameters	PK
Table 15.2.1.10	Individual Values and Descriptive Statistics of Total Radioactivity Plasma and Whole Blood PK Parameters	PK
Section 15.2.2 Mass balance and Amounts Excreted in Urine		
Table 15.2.2.1	Individual Values and Descriptive Statistics of BTZ-043 and Metabolite Excretion in Urine by Collection Interval	PK
Table 15.2.2.2	Individual Values and Descriptive Statistics of Total Radioactivity Excretion in Urine, Feces and Sum of Excreta by Collection Interval	PK
Table 15.2.2.3	Individual Values and Descriptive Statistics of Urine PK Parameters	PK
Table 15.2.2.4	Individual Values and Descriptive Statistics of Total Radioactivity Excretion Parameters in Urine, Feces and Sum of Excreta	PK
Figure 15.2.2.5	Arithmetic Mean Profiles of Cumulative Radioactivity Excretion in Urine, Feces and Sum of Excreta (Linear Scale)	PK
Figure 15.2.2.6	Individual Profiles of Cumulative Radioactivity Excretion in Urine, Feces and Sum of Excreta (Linear Scale)	PK
Section 15.3 – Safety Data		
15.3.1 Adverse Events		
Table 15.3.1.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 15.3.1.2	Summary of Treatment Emergent Adverse Events by SOC and Preferred Term	Safety
Table 15.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug	Safety
Table 15.3.1.4	Summary of Treatment Emergent Adverse Events by Severity	Safety

15.3.2 Lists of Deaths, Other Serious and Significant Adverse Events		
Table 15.3.2.1	Listing of Deaths and Other Serious Adverse Events	All Subjects
Table 15.3.2.2	Not part of TFL – Reserved for Narratives in CSR	
Section 15.3.3 –Laboratory Data		
Table 15.3.3.1	Listing of Abnormal Laboratory Values	Safety
Table 15.3.3.2	Descriptive Statistics of Laboratory Results - Clinical Chemistry	Safety
Table 15.3.3.3	Descriptive Statistics of Laboratory Results - Hematology	Safety
Table 15.3.3.4	Descriptive Statistics of Laboratory Results - Urinalysis	Safety
Section 15.3.4 Other Safety Parameters		
Table 15.3.4.1	Descriptive Statistics of Vital Signs	Safety
Table 15.3.4.2	Descriptive Statistics of 12-Lead Electrocardiogram	Safety

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1	Subject Disposition
Listing 16.2.2	Protocol deviations
Section 16.2.3 – Excluded Subjects/ Analysis Sets	
Listing 16.2.3	Analysis Sets
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Listing 16.2.4.4	Drug and Alcohol Screen
Listing 16.2.4.5	Serology
Listing 16.2.4.6	SARS-CoV-2 PCR Test Results
Section 16.2.5 - Compliance	
Listing 16.2.5	Study Drug Administration
Section 16.2.6 – Response Data	
Listing 16.2.6.1	Individual PK Plasma and Total Radioactivity Plasma and Whole Blood Sampling Time Deviations and Comments
Listing 16.2.6.2	Individual Total Radioactivity Excretion Data in Urine and Feces, Including Volumes, Weights and Amount Excreted by Collection Interval
Listing 16.2.6.3	Individual BTZ-043 and Metabolites Excretion Data in Urine Including Volumes, and Amount Excreted by Collection Interval

Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Withdrawal
Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Hematology
Listing 16.2.8.2	Clinical Laboratory Results – Chemistry
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Comments
Section 16.2.9 – Other Safety Data	
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	12-Lead Electrocardiogram Results
Listing 16.2.9.3	Physical Examination – Findings and Changes

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2	Statistical Appendices (if applicable)

18.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
08-Apr-2021	JWi	Set up from template, up to section 10. Section 16 will be for Nuvisan
13-Jul-2021	Nuvisan input	PK sections provided by Nuvisan
28-Sep-2021	JWi	Version for internal review
30-Sep-2021	JWi	First draft
28-Oct-2021	JWi	2nd draft
23-Nov-2021	JWi	Final