STATISTICAL ANALYSIS PLAN: INDV-2000-105

Protocol Title: A Phase I, Open Label Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of a Single dose of Oral [14C]-IDV184001AN in Healthy Adult Male Participants

Final Version: 15 May 2023

NCT: NCT05974046

Statistical Analysis Plan

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Protocol Number:	INDV-2000-105
Compound Number:	INDV-2000
Sponsor Name:	Indivior
Legal Registered Address:	10710 Midlothian Turnpike, Suite 125 North Chesterfield, VA 23235 USA
IND Number:	145881
Protocol Version:	Original
Date:	15 May 2023

Statistical Analysis Plan Approval

Submitted by: [redacted]

Approved by: [redacted]

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1. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study INDV-2000-105 and is based on the original protocol dated 15May2023. This SAP supersedes the statistical considerations stated in the protocol; any differences are identified in Section 6.2 (Appendix 2) of this document. However, major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Post hoc or unplanned analyses not specified in the SAP will be documented in the clinical study report (CSR).

Note: INDV-2000 is the current name for the IDV184001 drug compound, and IDV184001 is the active moiety of IDV184001AN.

VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	SAP Finalization Date	Associated Protocol Version	Protocol Approval Date	Change	Rationale
1.0	15Nov2023	Original	15May2023	Not Applicable	Original version

1.1. Objectives and Endpoints

Each study objective is presented in Table 2 with associated estimands. Intercurrent events occur after treatment starts and either preclude the observation of an endpoint or affect its interpretation. For the intercurrent event of study discontinuation, the principal stratum strategy will be used for pharmacokinetic (PK) and mass balance endpoints in that only subjects with an adequate amount of PK and mass balance data will be included in the PK Analysis Set (Table 3); for all other endpoints, the treatment policy strategy will be used and all available data will be summarized. Other potential intercurrent events in this study are prohibited medications and lifestyle restrictions detailed in protocol sections 6.9 and 5.3, respectively. Possible strategies for these intercurrent events are treatment policy (intercurrent event is ignored), while on treatment (data collected after the event would be ignored), and principal stratum for PK and mass balance endpoints (subject would be excluded from the PK Analysis Set), to be decided by the sponsor on a case-by-case basis.

Table 2 Study Objectives and Estimands

		Estimand		
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Pop-ulation**	**Population-Level Summary**
Primary Objectives • To investigate the route(s) of elimination and the overall mass balance of IDV184001, following a single oral dose of [^{14}C]-IDV184001AN in healthy adult male participants. • To quantitate total radioactivity (TRA) in whole blood, plasma, urine, and feces following a single oral dose of [^{14}C]-IDV184001AN in healthy adult male participants. • To characterise the PK profile of unlabeled IDV184001 and M12 in plasma following a single oral dose of [^{14}C]- IDV184001AN in healthy adult male participants. • To perform metabolite identification, profiling and quantitation for IDV184001 in plasma, urine, and feces following a single oral dose of [^{14}C]-IDV184001AN in healthy adult male participants. • To determine the ratio of TRA concentration equivalents in whole blood versus plasma following a single oral dose of [^{14}C]-IDV184001AN in healthy adult male participants.				
PK	Primary	TRA recovery and the percent of the radioactive dose excreted in the urine, feces, and urine+feces: % Dose, Cum%Dose [Time Frame: Pre-dose to 168 hours post-dose, collection time can be extended].	PK	Numeric descriptive
		TRA PK parameters in plasma and whole blood: AUC_{last}, $AUC_{0-\infty}$, $AUC_{extrap(\%)}$, C_{max}, T_{max}, λ_z, and $T_{1/2}$ as data permit [Time Frame: Pre-dose to 168 hours post-dose, collection time can be extended].	PK	Numeric descriptive (median and range only for T_{max})
		TRA PK parameters in urine, feces, and urine+feces: Ae_{t1-t2}, CumAe, and CL_r (urine only) [Time Frame: Pre-dose to 168 hours post-dose, collection time can be extended].	PK	Numeric descriptive
		Unlabeled IDV184001 and M12 PK parameters in plasma: AUC_{last}, $AUC_{0-\infty}$, $AUC_{extrap(\%)}$, C_{max}, T_{max}, λ_z, $T_{1/2}$, as data permits [Time Frame: Pre-dose to 168 hours post-dose].	PK	Numeric descriptive (median and range only for T_{max})
		Ratio of unlabeled IDV184001 and M12 in plasma to plasma TRA for AUC_{last} and C_{max}, where appropriate [Time Frame: Pre-dose to 168 hours post-dose].	PK	Numeric descriptive

Objective Clinical Category	Statistical Category	Variable/Endpoint	Pop-ulation	Population-Level Summary
PK (continued)	Primary (continued)	Identification of parent and metabolites in plasma, urine, and feces.		Descriptive
		% of AUC of each metabolite in plasma, % of dose of each metabolite in urine, % of dose of each metabolite in feces [Time Frame: Pre-dose to 168 hours post-dose, collection time can be extended]	PK	Numeric descriptive
		The ratio of TRA concentration equivalents in whole blood relative to plasma at each time matched determination of TRA in whole blood and plasma [Time Frame: Pre-dose to 168 hours post-dose, collection time can be extended].	PK	Numeric descriptive
Secondary Objective • To assess the safety and tolerability of a single oral dose of [^{14}C]-IDV184001AN as determined by adverse event (AE) reporting.				
Safety	Secondary	Incidence, seriousness, severity, and relatedness of treatment-emergent AEs (TEAEs).	Safety	Categorical descriptive
Tertiary/Exploratory Objective				

[redacted]

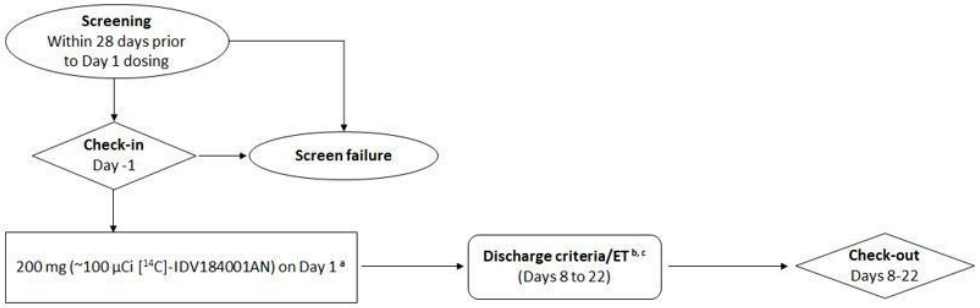
		Estimand		
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Pop-ulation**	**Population-Level Summary**
[redacted]				

1.2. Study Design

This is a Phase I open-label, single-center, single-dose study in healthy adult male participants to characterize the absorption, metabolism, excretion, and mass balance of [^{14}C]-IDV184001.

The study schematic is depicted in Figure 1.

Figure 1. Study Schematic



a. Day 1 to 8 : Blood sample collection for TRA (whole blood and plasma), unlabeled INDV-2000 and M12 PK (plasma), and metabolite profiling (plasma) ; urine and fecal sample collection for TRA and metabolite profiling.

b. Participants may be discharged from the study site following the 168-hour post-dose blood draw and/or study procedures on Day 8, if at least one discharge criterion is met . If neither discharge criteria is met by 168 hours post-dose (i.e., Day 8), participants will remain confined at the CRU until at least one discharge criterion is met or a maximum stay of 21 days post-dose is reached (i.e., Day 22).

c. Participants who terminate the study early will be asked to return to the study site 7±2 days after the last dose for follow-up procedures, and to determine if any AE has occurred since the last study visit.

Abbreviations: AE=adverse events; ET= Early termination; PK=pharmacokinetics; TRA= total radioactivity.

Key features of the study design are described below.

- Approximately 7 healthy adult males will be enrolled to ensure at least 6 participants complete the study.

- On Day 1, participants will receive a single oral dose of 200 mg (~100 µCi) [^{14}C]-IDV184001AN.

- Blood (for plasma and whole blood), urine, and fecal samples will be collected pre-dose and for at least 168 hours post-dose (ie, Day 8) to measure TRA (all sample matrices), and for metabolite identification, profiling and quantitation (plasma, urine, and feces), as appropriate. Blood samples for plasma concentrations of unlabeled IDV184001 and M12 will also be collected for at least 168 hours post-dose.

- Participants may be discharged from the study site following the 168-hour post-dose blood draw and/or study procedures on Day 8, if at least one discharge criterion is met (refer to Protocol Section 4.1.1[redacted] If neither discharge criterion is met by 168 hours post-dose (ie, Day 8), participants will remain confined at the study site until at least one discharge criterion is met or a maximum stay of 21 days post-dose is reached (ie, Day 22), whichever is first.

- For participants who remain confined past Day 8, collection of urine and fecal samples for TRA determination and metabolite identification, profiling and quantitation will continue in 24-hour intervals and collection of blood for TRA determination (whole blood and plasma) and metabolite identification, profiling and quantitation (plasma) will continue in 72-hour intervals.

- The total planned study duration for each participant will be up to 7 weeks. This includes a screening period of up to 4 weeks and a treatment period of at least 1 week (Days 1 to 8) up to a maximum of 3 weeks (Days 1 to 22) until at least one discharge criterion is met.

2. STATISTICAL HYPOTHESES

There are no formal statistical hypotheses for this study.

2.1. Multiplicity Adjustment

There will be no formal statistical inference in this study; therefore, there will be no multiplicity adjustment.

3. SAMPLE SIZE DETERMINATION

Approximately 7 participants will be enrolled to ensure 6 participants complete the study. The sample size was selected without statistical considerations. It has been determined adequate to meet the study objectives and is in accordance with the Food and Drug Administration guidance.[1, 2] This sample size is limited based on clinical considerations for this type of study and in order to limit exposure to radioactivity.

4. POPULATIONS FOR ANALYSIS

Data for all participants will be assessed to determine if they meet the criteria for inclusion in each analysis population shown in Table 3 prior to releasing the database. Classifications will be documented per standard operating procedures.

Table 3 Analysis Populations

Population	Description
Screened	Participants who signed informed consent.
Safety Analysis Set	Participants who received the study drug.
PK Analysis Set	Participants who received the study drug and had an adequate number of PK samples collected to derive any ADME (absorption, distribution, metabolism and excretion) parameter and have no protocol deviations that would significantly alter disposition of study drug.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Timing of Analyses

Safety data will be reviewed on an ongoing basis. There will be a production run of tables, figures, and listings (TFLs) after the database has been locked following the study-level EOS.

5.1.2. Programming Environment

SAS® version 9.4 or higher (SAS Institute, Cary, North Carolina) will be used for statistical analyses and for the production of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) data sets as well as TFLs.

5.1.3. Reporting Conventions

Data will be summarized by visit, where applicable. TFL tables of contents, mock-ups, and specifications are provided in a separate document from the SAP. The following reporting conventions will be followed:

- Tables and figures will present summaries/analyses by study visit and time point, as appropriate.
- Table column headers and figure legends will include sample size ("N = xx"), where applicable. Sample sizes reported as part of descriptive statistics ("n") will be the number of non-missing observations.
- Listings will generally include unique subject identifier; study visit/time point; assessment or collection date/time; parameter; and observed value.

5.1.4. General Analysis Conventions

Categorical variables will be summarized using frequencies and percentages. Percentages will be reported to one decimal place.

Continuous variables will be summarized using descriptive statistics (e.g., n, mean, standard deviation (SD), distribution percentiles, range). The number of decimal places for minimums and maximums will be the same as the original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original data plus one, and the number of decimal places for measures of variance will be the same as the source data plus two. See Appendix 6.4.1 (Appendix 4) for summary statistics and precision specifications for PK data.

Data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.

5.1.5. Definitions

Study Drug: IDV184001AN + [^{14}C]-IDV184001AN

Screening Period: Informed consent to Day -1 Clinic Check-In.

Day -1 Clinic Check-In: clinic check-in to date/time of dosing on Day 1.

Study Day 1: day of study drug dosing.

Study day:

- Study day = date of assessment – date of Study Day 1 + 1, for assessments on or after Study Day 1
- Study day = date of assessment – date of Study Day 1, for assessments before Study Day 1

Duration:

- Duration in days = end date – start date + 1
- Duration in minutes = end time – start time

Baseline observation: for a given parameter for a given subject, the last observed value, including unscheduled and repeated assessments, before study drug dosing.

EOS, Subject-Level: Early termination or completion of discharge criteria or completion of a 21-day clinic stay post-dose (ie, Study Day 22).

EOS, Study-Level: Study completion for the last subject.

5.2. Study Conduct and Participant Disposition

Subject disposition summaries will include the number of subjects screened and the number and percentage of subjects who were screen failures, who were otherwise not enrolled, who were enrolled, who were in each analysis population, and who completed the study. For percentages, the number of subjects screened will be the denominator for screen failures, for subjects not otherwise enrolled, and for subjects who were enrolled, and the number of subjects enrolled will be the denominator for the Safety Analysis Set, the PK Analysis Set and for subjects completing the study.

Reason for study discontinuation will also be summarized by number and percentage of subjects for each reason reported; for the percentage, the number of subjects who discontinued will be the denominator.

Reason for screen failure and other non-enrollment will be summarized in a separate table by number and percentage of subjects for each reason reported; the denominator will be the number of non-enrolled subjects.

5.3. Primary Endpoints Analysis

5.3.1. Definition of Endpoints

The primary endpoints are itemized in Table 2.

5.3.2. Main Analytical Approach

Estimand strategy: Principal stratum.

Analysis set: PK (see Table 3).

Analysis methodology:

For TRA recovery and the percentage of the radioactive dose excreted in the urine, feces, and in both excreta combined (mass balance), based on urine sample weights, fecal homogenate weights, IDV184001-concentration equivalents of TRA in urine and fecal homogenate samples collected at each interval will be used to derive the TRA recovery parameters for each subject using standard non-compartmental methods (see Appendix 6.4.2.2).

For PK analysis, standard non-compartmental methods based on actual sampling times will be used to derive parameters for each subject (see Appendix 6.4.2.1).

Intercurrent events and missing data: Subjects with intercurrent events may be excluded from the PK Analysis Set, to be decided by the sponsor on a case-by-case basis. See Section 6.6.1 (Appendix 6) for details on handling of missing data.

5.4. Secondary Endpoints Analysis

5.4.1. Definition of Endpoints

The secondary endpoints are incidence, seriousness, severity, and relatedness of TEAEs.

5.4.2. Main Analytical Approach

Estimand strategy: Treatment policy.

Analysis set: Safety (see Table 3).

Analysis methodology: Descriptive only.

Intercurrent events and missing data: AEs will be reported regardless of the occurrence of an intercurrent event. See Section 6.6.2 (Appendix 6) for handling of missing AE information.

See Section 5.5.2 for details on AE summaries and listings.

5.5. Tertiary/Exploratory Endpoints Analysis

5.5.1. Definition of Endpoints

[redacted]

5.5.2. Main Analytical Approach

5.6. Other Safety Analyses

5.6.1. Study Drug Exposure

Details of study drug exposure will be listed and summarized. Exposure data will be presented with the same precision as original data in listings, and will be rounded to 2 or 3 decimal places for summarization, depending on the data.

5.6.2. Adverse Events

A TEAE starts at or after study drug dosing. AEs will be coded to a System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). Additional details of the coding process, including the current version of the dictionary, are described in the Data Management Plan.

All AEs will be listed for individual subjects. Listings will include SOC, PT, and reported term; onset date and time, end date, and duration; treatment-emergence, severity, toxicity grade, seriousness and seriousness criteria; relationship to study drug; whether concomitant treatment was given; outcome; and whether the AE resulted in study discontinuation. Duration (days) is calculated as the AE end date – the AE onset date +1; for ongoing AEs, the date of end of study participation will be used as the end date. Duration will be missing if either the start or end date is partially or completely missing. TESAEs, TEAEs leading to study discontinuation, and fatal TEAEs will be listed separately.

The incidence and number of all TEAEs, TESAEs, study drug-related TEAEs and study drug-related TESAEs, severe TEAEs, TEAEs with grade 3 or higher toxicity grade, TEAEs leading to study discontinuation, and fatal TEAEs will be presented in an overall summary table.

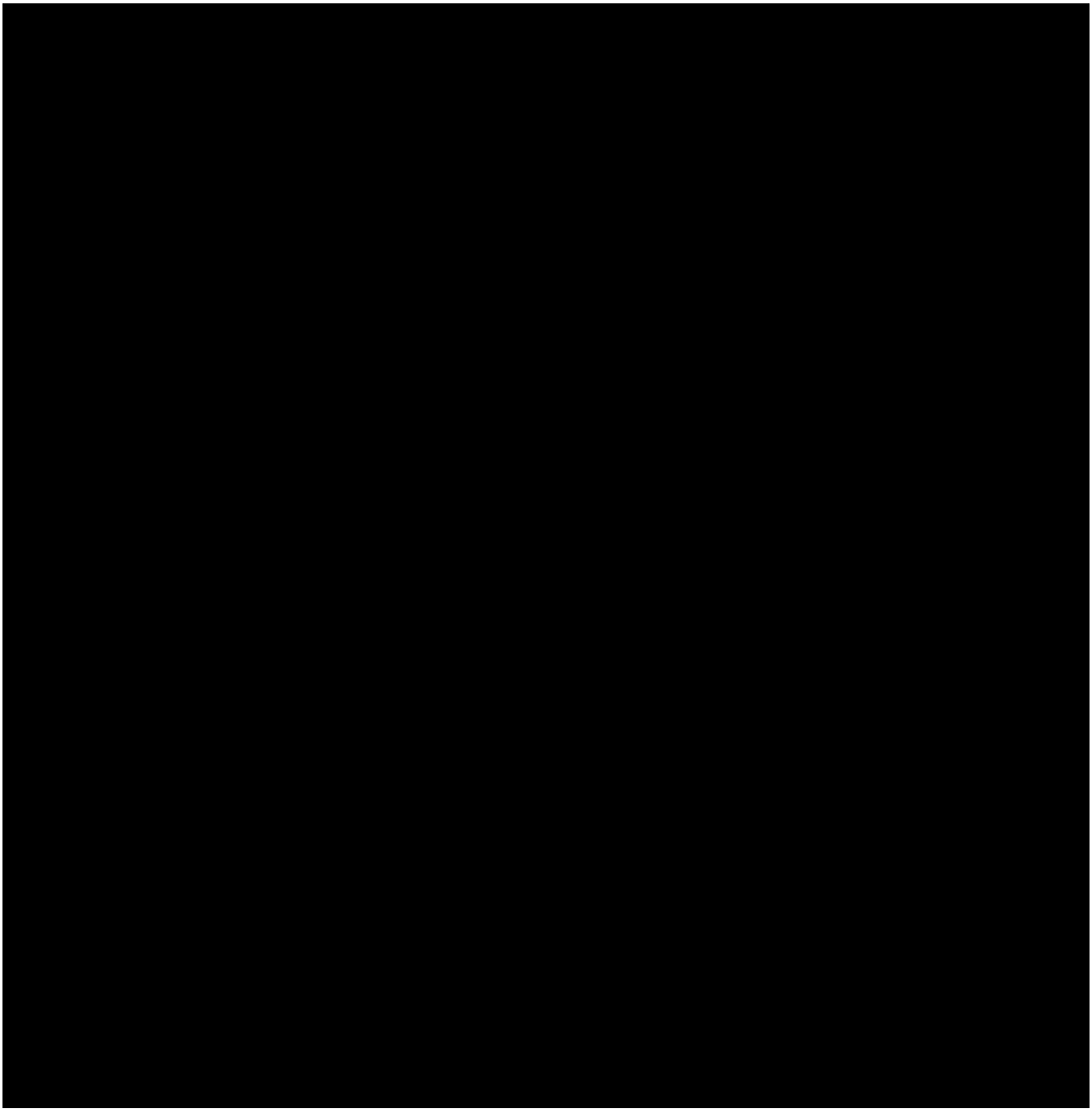
TEAEs, TESAEs, study drug-related TEAEs and study drug-related TESAEs will be summarized by MedDRA SOC and PT, each in descending order of frequency among all subjects (then alphabetically in case of ties). TEAEs will also be summarized by maximum severity and by maximum toxicity within SOC and PT. If an AE is reported more than once by a subject within a SOC and/or PT, the maximum reported level of severity/toxicity will be used at each level of summation in the severity/toxicity summary tables.

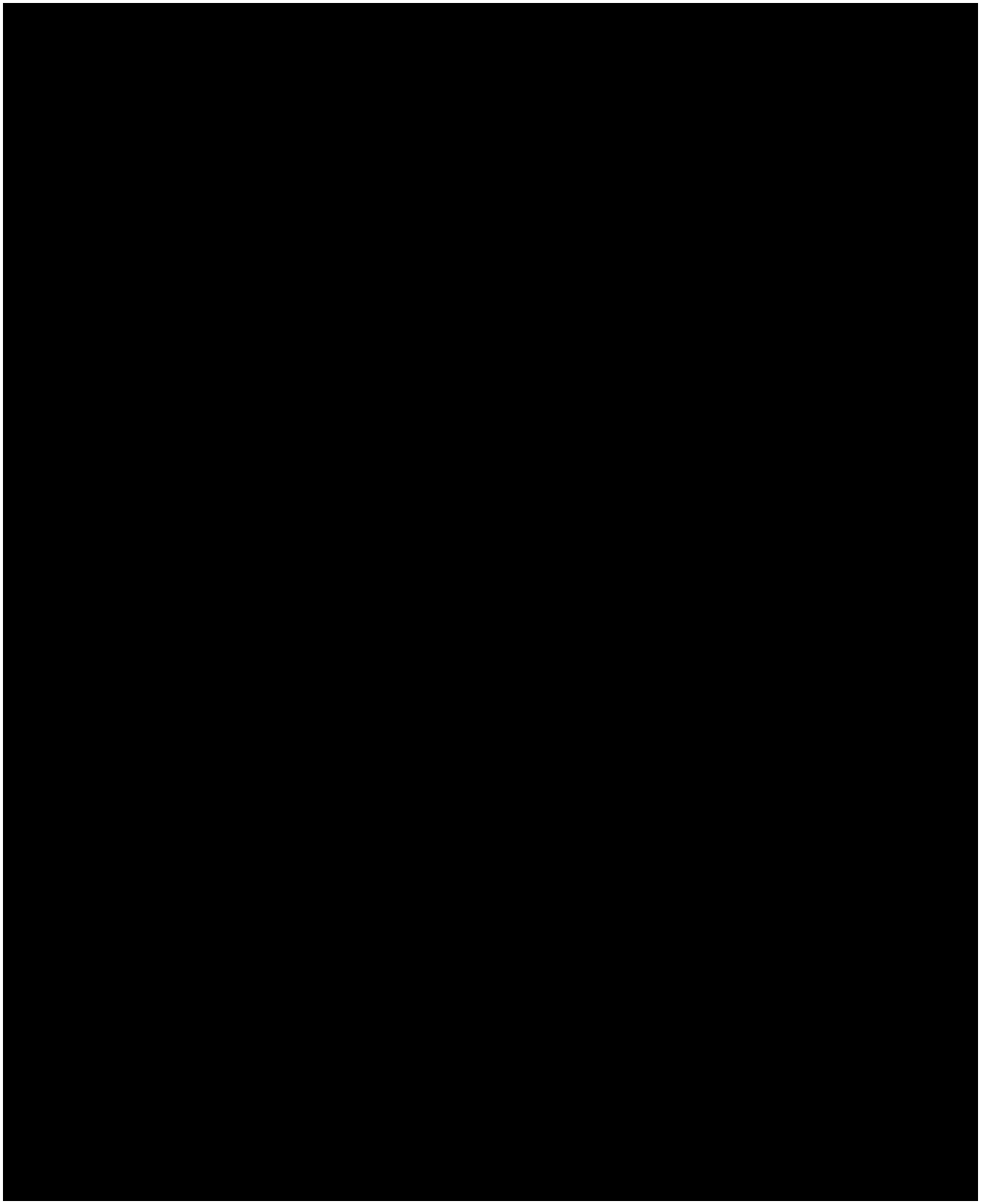
Incidence and number of TEAEs will also be summarized by PT only (ie, not SOC), sorted by descending frequency among all subjects.

Non-TEAEs are defined as AEs that started before study drug dosing. Non-TEAEs will be summarized for the Safety Analysis Set.

See Section 6.6.2 (Appendix 6) for details on handling of missing AE information.

5.6.3. Additional Safety Assessments





5.7. Other Analyses

5.7.1. Demographics and Anthropometrics

Demographics and anthropometrics will be summarized separately for the safety and PK analysis sets, if different. Parameters to be summarized will include age, race, ethnicity, and height/weight/body mass index.

5.7.2. Medical History

Relevant medical history will be coded using MedDRA (refer to the Data Management Plan) and will be listed for the safety analysis set.

5.7.3. Prior and Concomitant Medications and Therapies

Medications and therapies will be collected from screening through EOS and will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug Dictionary (WHO-DD). Additional details of the coding process, including the current version of the dictionary, are described in the Data Management Plan. Prior medications and therapies ended before dosing or were taken by subjects who were never dosed. All other medications and therapies will be considered concomitant.

Prior and concomitant medications and therapies will be summarized separately for the safety analysis set. The summary of incidence (number and percentage of subjects reporting the medication or therapy at least once) will be sorted alphabetically by therapeutic class (ATC level 2) and standardized medication/therapy name.

See Section 6.6.3 (Appendix 6) for details on handling missing information on medications and therapies.

5.7.4. Protocol Deviations

Protocol deviations will be identified and documented prior to database lock and will be summarized by category (eg, prohibited medication, out-of-window assessment) and type (eg, important, not important), per the Protocol Deviation Assessment Tool for the study, for the safety analysis set. Deviations that occur in subjects who were not in the safety analysis set, if any, will be summarized separately. All protocol deviations will be listed.

5.8. Interim Analyses

Not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: List of Abbreviations

Abbreviation	Term
%DoseAe	percent of administered dose excreted/recovered within a given collection interval
ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
Ae_{t1-t2}	amount of total radioactivity excreted/recovered within a given collection interval
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from 0 to infinity
$AUC_{extrap(\%)}$	area under the curve extrapolated as a percentage of the total $AUC_{0-\infty}$
AUC_{last}	area under the curve from dosing to the last measured concentration
BLQ	below limit of quantitation
[redacted]	[redacted]
C_{max}	maximum plasma concentration
CL/F	apparent total clearance of drug from plasma after oral administration
CL_r	renal clearance
CRF	Case Report Form
CSR	clinical study report
Cum%Dose	cumulative percent of dose excreted/recovered
CumAe	cumulative amount of total radioactivity excreted/recovered
CV	coefficient of variation
[redacted]	[redacted]
EOS	end of study
HPLC	high-performance liquid chromatography
λ_z	terminal elimination rate constant
µCi	microcurie
MedDRA	Medical Dictionary for Regulatory Activities
$MRAUC_{0-\infty}$	metabolic ratio of $AUC_{0-\infty}$
MRC_{max}	metabolic ratio of C_{max}
PK	pharmacokinetic(s)
PT	Preferred Term
[redacted]	[redacted]
$RAUC_{last\ (plasma)}$	ratio of unlabeled plasma drug AUC_{last} to plasma TRA AUC_{last}
$RC_{max\ (plasma)}$	ratio of unlabeled plasma drug C_{max} to plasma TRA C_{max}
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
$T_{1/2}$	apparent terminal half-life
T_{max}	time of maximum plasma concentration
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TRA	total radioactivity
V_z/F	apparent volume of distribution during the terminal elimination phase after oral administration
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2: Changes to Protocol-Planned Analyses

The following are changes from the protocol that are in the SAP:

Protocol:	SAP (changes in bold):
[redacted]	

6.3. Appendix 3: Definition and Use of Visit Windows in Reporting

No windowing will be used for summaries. Analysis visits will be visits denoted in the Case Report Form (CRF). An early termination visit will be counted as a scheduled visit if it occurs on a scheduled visit study day; otherwise, it will be counted as an unscheduled visit. If a participant has more than 1 assessment for a given visit, the most recent non-missing assessment will be used for summaries.

6.4. Appendix 4: Endpoint Derivations

6.4.1. Mass Balance and PK Endpoints

Individual plasma, and whole blood, urine, and feces samples are collected according to the schedules outlined in Section 10.4 of the protocol.

6.4.1.1. Urine and Feces Mass Balance and PK Parameters

TRA recovery and the percent of the radioactive dose excreted in the urine and feces from pre-dose to at least 168 hours, as applicable, will be assessed on a per participant basis. Mass balance will be calculated as a sum of the percent of the TRA recovered in urine and feces relative to the administered radioactive dose. If emesis occurs, the calculation of mass balance may take into account any radioactivity recovered in the vomitus as appropriate.

Urine, feces, and urine + feces parameters to be calculated are shown in Table 6. Additional parameters may be calculated if required.

Table 5 Mass Balance and PK Parameters : TRA – Urine, Feces, and Urine + Feces

Parameter	Definition
$Ae_{t1\text{-}t2}$	Amount of total radioactivity excreted/recovered within a given collection interval
CumAe	Cumulative amount of total radioactivity excreted/recovered
%DoseAe	Percent of administered dose excreted/recovered within a given collection interval
Cum%Dose	Cumulative percent of dose excreted/recovered
CL_r	Renal clearance. $CL_r = CumAeAe_{t1\text{-}t2}/AUC$, where both $CumAeAe_{t1\text{-}t2}$ and AUC are determined over matched time interval (urine only)

6.4.1.2. Plasma and Whole Blood PK Parameters

Plasma and whole blood PK parameters to be calculated are shown in Table 5. Additional parameters may be calculated if required.

Table 6 PK Parameters: TRA, Unlabeled Plasma IDV184001, and Unlabeled Plasma M12 – Plasma and Whole Blood

Parameter	Definition
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
AUC_{last}	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule

Parameter	Definition
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinite time
$AUC_{extrap(\%)}$	Percent of the area under the concentration-time curve due to extrapolation
λ_z	Terminal phase rate constant
$t_{1/2}$	Apparent terminal half-life
CL/F	Apparent total clearance after oral (extravascular) administration, calculated as Dose/ $AUC_{0-\infty}$ (parent only)
V_z/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as Dose/($AUC_{0-\infty} \times \lambda_z$) (parent only)
$MRAUC_{0-\infty}$	Metabolic ratio of the metabolite $AUC_{0-\infty}$ to the parent $AUC_{0-\infty}$
MRC_{max}	Metabolic ratio of the metabolite C_{max} to the parent C_{max}
$RAUC_{last\ (plasma)}$	Ratio of unlabeled plasma drug AUC_{last} to plasma TRA AUC_{last}
$RC_{max\ (plasma)}$	Ratio of unlabeled plasma drug C_{max} to plasma TRA C_{max}

To calculate the slope of the terminal phase (λ_z), the following acceptance criteria will be used:

- Rsq ≥ 0.80
- Minimum of three time points in the terminal phase (not including C_{max})
- AUC_{0-inf} will be calculated if the percentage of AUC extrapolation ($AUC_{extrap(\%)}$) is <=20%

Actual sampling times will be used in PK parameter calculations.

6.4.1.3. Metabolite Identification, Profiling and Quantitation

IDV184001 metabolite identification, profiling and quantitation will be performed on plasma, urine, and fecal samples from pre-dose to at least 168 hours, as applicable, containing sufficient amounts of radioactivity. For metabolite profiling in urine and feces, collected samples will be pooled across the time intervals for each subject to account for ~90% of the radioactivity excreted in a given matrix. Pooling will be conducted in proportion to the amount (weight or volume) of excreta collected in each sampling period. For metabolite profiling in collected plasma, samples will be pooled across time points for each subject according to the AUC pooling formula.[3] Typically, ≥ 90% of the radioactivity contained within a pooled matrix is extracted for analysis. The percent of dose in urine and feces and % of AUC in plasma represented by each of the metabolites will be calculated. Radiochromatographic peaks from high-performance liquid chromatography (HPLC) coupled with radiodetection will be integrated and the quantity of each identified metabolite is reported as % dose for excreta and % AUC in plasma, relative to total radioactivity. The % of AUC plasma will also be calculated relative to % of AUC for parent.

6.4.1.4. Whole Blood to Plasma Partitioning Ratio

The ratio of TRA concentration equivalents in whole blood relative to plasma at each time-matched determination of TRA in whole blood and plasma from pre-dose to at least 168 hours, as applicable, will be calculated.

6.5. Appendix 5: Statistical Methodology Details

Statistical programming, including urine and feces PK parameters, will be done using SAS® version 9.4 (or higher). Plasma and whole blood PK parameters will be calculated using Phoenix™ WinNonlin® (Version 8.3.4 or higher, Certara, LP).

6.5.1.1. Concentrations and Concentration Equivalents

For plasma and whole blood, listings of individual TRA concentration equivalents and unlabeled IDV184001 and M12 concentrations from pre-dose to at least 168 hours, as applicable, at scheduled collection times points will include nominal time point, sampling date and time, time since dosing, deviation from scheduled sampling time, permitted time window, and concentration (or concentration equivalent) of each analyte. A separate listing will show unscheduled collections. Time since dosing (hour) will be calculated as the sampling date and time – dosing date and time and will be rounded to two decimal places. For scheduled time points, time deviation (minute) will be calculated as sampling date and time – (dosing date and time + nominal sampling time).

For urine and feces, listings of individual TRA concentration equivalents from pre-dose to at least 168 hours, as applicable, at scheduled collection intervals will include collection interval, start and end date and time of the interval, weight collected, and concentration equivalent.

Concentrations and concentration equivalents will be reported in listings with the same precision as the source data provided by the bioanalytical laboratory. Data will be summarized using arithmetic means, SDs, medians, ranges, and coefficients of variation (CVs) by analyte and nominal time point or collection interval. Means, ranges, and medians will be reported to three significant digits; SDs will be reported to four significant digits; and CVs will be rounded to 1 decimal place.

Individual and mean (± SD) concentrations and concentration equivalents in whole blood and plasma versus time plots will be presented on linear and semi-logarithmic scales. The x-axis will represent actual time since dosing in individual plots and nominal time point in mean plots.

Methods for handling concentration and concentration equivalent values reported as below limit of quantitation (BLQ) are described in Section 6.6.1 (Appendix 6).

6.5.1.2. Mass Balance and PK Parameters

Mass balance and PK parameters will be reported with the following precision in data listings: C_{max} will be reported with the same precision as the source data; T_{max}, ratios, and percentages will be reported to 2 decimal places, and reporting precision for mass balance and all other PK parameters (λ_z, CL/F, V_z/F, $Ae_{t1\text{-}t2}$, CumAe, and CL_r) will depend on the minimum observed value. For parameters with minimum observed value ≥ 100, observed values will be rounded to the nearest integer. For parameters with minimum observed value < 100 but ≥ 10, observed values will be rounded to the nearest tenth. For parameters with minimum observed value < 10 but ≥ 1, observed values will be rounded to the nearest hundredth. For parameters with minimum observed value < 1, observed values will be rounded to the nearest thousandth. If any of these rounding rules cannot be applied due to lack of precision in the source data, the source data precision will be used.

Summary tables of mass balance and PK parameters will show arithmetic and geometric means and CVs, SDs, medians, and ranges by analyte. Means, ranges, and medians will be

reported to three significant digits; SDs will be reported to four significant digits; CVs will be rounded to 1 decimal place, and ratios will be rounded to 2 decimal places. Only median and range will be reported for T_{max}.

Individual and mean (± SD) percent of Cum%Dose in urine, feces, and urine + feces versus time plots will be presented on linear scales. The x-axis will represent the nominal endpoint of the collection interval in both individual and mean plots.

Methods for handling concentration and concentration equivalent values reported as BLQ are described in Section 6.6.1 (Appendix 6).

6.6. Appendix 6: Methods to Manage Missing Data

6.6.1. BLQ PK Concentrations and Concentration Equivalents

Concentration and/or concentration equivalent values that are reported as BLQ will be presented as "BLQ" in concentration and concentration equivalent listings. For summary statistic calculations, concentration and/or concentration equivalent values that are reported as BLQ will be set to zero.

For PK parameter derivations and individual subject linear-scale concentration and concentration equivalent versus time profiles, all concentrations and concentration equivalents that are BLQ prior to the first quantifiable concentration or concentration equivalent will be set to zero. All other plasma or blood BLQ values will be set to missing, and all other urine or feces BLQ values will be set to zero. BLQ values will be excluded from semi logarithmic-scale plots of concentrations and concentration equivalents versus time. No concentration or concentration equivalent estimates will be imputed for missing sample values.

6.6.2. AEs

Missing AE Severity

Missing AE severity must be queried until resolution. In the unlikely event that resolution is not possible, missing severity will be imputed as "severe" in summaries.

Missing AE Relationship to Study Drug

Missing relationship to study drug for a TEAE must be queried until resolution. In the unlikely event that resolution is not possible, missing relationship will be imputed as "related" in summaries.

Missing AE Seriousness

Missing AE seriousness must be queried until resolution. Seriousness cannot be imputed as "serious" since doing so would affect the reconciliation between the trial database and the serious adverse event registry.

Missing AE Toxicity Grade

Missing AE toxicity grade must be queried until resolution, where applicable. There will be no imputation for missing toxicity.

Missing AE Start Date/Time Information

Note: partial times will not be recorded in the CRF.

For the Safety Analysis Set, an AE will be considered treatment emergent under the following conditions:

- Missing start year, month, day, time unless it can be deduced from non-missing components of AE end date that the AE ended before dosing.

- Missing start month, day, time if start year is equal to or after year of dosing, unless it can be deduced from non-missing components of AE end date that AE ended before dosing.

- Missing start day and time if start year is after year of dosing or if start year is equal to year of dosing and month is equal to or after month of dosing, unless AE end date is before date of dosing.

- Missing start time if start date is on or after date of dosing.

6.6.3. Medications and Therapies

Missing Start and End Date/Time Information for Medications and Therapies

Note: partial times will not be recorded in the CRF.

Prior vs. concomitant status will be assigned as follows:

Non-missing end date, missing end time

- If end date is before date of dosing, medication/therapy is prior.
- If end date is equal to or after date of dosing, medication/therapy is concomitant.

Non-missing end year and month, missing end day

- If end year is before year of dosing, medication/therapy is prior.
- If end year is equal to year of dosing and end month is before month of dosing, medication/therapy is prior.
- If end year is equal to year of dosing and end month is equal to or after month of dosing, medication/therapy is concomitant.
- If end year is after year of dosing, medication/therapy is concomitant.

Non-missing end year, missing end month and day

- If end year is before year of dosing, medication/therapy is prior.
- If end year is equal to or after year of dosing, medication/therapy is concomitant.

Missing end year, month, and day

- Medication/therapy is concomitant if subject was dosed; otherwise, medication/therapy is prior.

6.7. Appendix 7: Data Set Descriptions

Trial data sets will consist of CRF exports and external data files. External files may be used for protocol deviations, for example.

7. REFERENCES

1. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies Guidance for Industry, May 2022.

2. Penner N, Klunk LJ, Prakash C. Human radiolabeled mass balance studies: objectives, utilities and limitations. Biopharm Drug Dispos 2009;30(4):185-203. doi: 10.1002/bdd.661.

3. Hamilton RA, Garnett WR, Kline BJ. Determination of mean valproic acid serum level by assay of a single pooled sample. Clin Pharmacol Ther 1981;29(3):408-13. doi: 10.1038/clpt.1981.56.