

Online Resource 1: Protocol-to-analysis reconciliation, recruitment explanation, and STROBE checklist

This Online Resource reports the STROBE checklist for cohort studies and differences between the published PABTOX protocol and the present secondary exploratory analysis.

Section 1.1 STROBE checklist

STROBE item	Reporting location
1. Study design in title/abstract	Title; Abstract, Methods
2. Scientific background	Introduction, paragraphs 1–4
3. Objectives and hypotheses	Final Introduction paragraph
4. Study design	Methods: Study design, ethics, and participants
5. Setting and dates	Methods: Study design; Online Resource 1
6. Eligibility and participant selection	Methods; Fig. 1; Table S1.2
7. Outcomes, exposures, and covariates	Methods: PROs, body composition, activity, toxicity, exposure
8. Data sources and measurement	Methods; Online Resources 2 and 3
9. Potential sources of bias	Discussion: limitations; Online Resource 1
10. Study-size rationale	Methods; Table S1.1
11. Handling of quantitative variables	Methods: Statistical analysis; Table S4.1
12. Statistical methods	Methods; Online Resources 4 and 5
13. Participant numbers	Results; Fig. 1; Table S1.2
14. Descriptive data and missingness	Table 1; Tables S2.1–S2.2
15. Outcome data	Table 2; Fig. 2; Tables S2.3–S2.4
16. Main estimates and precision	Fig. 3; Tables S4.2–S4.5
17. Secondary and sensitivity analyses	Online Resources 4 and 5
18. Key findings	Discussion, paragraph 1
19. Limitations	Discussion, final paragraph
20. Overall interpretation	Discussion
21. Generalisability	Discussion, final paragraph
22. Funding	Statements and Declarations

Section 1.2 Protocol-to-analysis reconciliation

Table 1.2 Protocol-to-analysis reconciliation for the present PABTOX secondary analysis

Domain	Published protocol	Realised analysis and manuscript handling
Sample size and principal model	Target sample of 40; development of population PK and PK–PD models for CIPN and potentially neutropenia	The realised cohort comprised 20 participants. This manuscript reports exploratory association analyses; the prespecified population PK–PD model is not reported as a completed analysis.
DLT definition	Clinically relevant CTCAE v5.0 toxicity of grade ≥ 3	No medical-record-derived event reached grade ≥ 3 . Legacy DLT_total and DLT_any variables instead captured toxicities attributed to treatment modification irrespective of grade. They are not interpreted as protocol-defined DLTs. Adverse events were retrospectively abstracted by one researcher from unstructured medical records and mapped to CTCAE v5.0. Laboratory neutropenia was derived separately from absolute neutrophil counts.
Toxicity ascertainment	DLT inventory at T1–T4, described as recorded by oncologists	Realised early sampling extended to approximately 1 h after infusion. The first concentration is described as post-infusion concentration rather than observed ($C_{\max}$).
Post-infusion sampling	First sample scheduled within 10 min after infusion; second sample 16–26 h later	Paired observations were divided by participant into a 60% training subset and 40% hold-out subset. Separate conversion factors were estimated for both sampling periods.
DBS-to-plasma conversion	Relation between both matrices to be investigated in the first ten participants	

Missing data	Multiple imputation and complete-case sensitivity analyses proposed	No explicit imputation was used. Mixed models used available follow-up outcomes; correlations used pairwise complete observations.
PRO modelling	Repeated HRQoL and CIPN measurements planned	Trajectory and baseline-adjusted mixed models were added for the present exploratory analysis.
CT body composition	DXA and BIA specified in the protocol	Available pretreatment CT images were added as exploratory baseline imaging markers.

Online Resource 2: Rationale for selection of body composition markers

Construct and selected marker	Operationalisation in this paper	Analytical position	Why this marker was prioritised	Complementarity and reason alternatives were not prioritised	Key evidence
CT L3 skeletal muscle index (CT-SMI)	L3 skeletal muscle cross-sectional area / height ² (cm ² /m ²)	Primary CT muscle anchor	L3 CT analysis is the most established muscle-quantity approach in oncology because it is tissue-specific, reproducible, and can be extracted from routine staging images. Height indexing improves comparability across body size. Paclitaxel-specific work also links lower muscle mass with greater systemic exposure.	Preferred to raw muscle area because raw area is strongly body-size dependent, and to DXA total lean mass because CT isolates skeletal muscle rather than all non-fat soft tissue. It complements, rather than replaces, DXA ALM/BMI. CT-SMI is not a stand-alone sarcopenia diagnosis.	[1–4,12]
CT L3 total adipose tissue index (CT-TATI)	L3 total adipose tissue area / height ² (cm ² /m ²), using the study segmentation output	Primary CT adiposity anchor	CT-TATI captures the overall abdominal adipose compartment represented on the L3 image and is the closest CT analogue of whole-body adiposity burden. It is more informative than body size alone when patients with similar BMI differ substantially in fat amount and distribution.	Prioritised over VAT alone as the main CT adiposity measure because VAT represents only one depot. It complements DXA FMI: CT provides regional tissue distribution, whereas DXA provides whole-body fat mass.	[1,2,7,8,11]
CT L3 visceral adipose tissue index (CT-VATI)	L3 visceral adipose tissue area / height ² (cm ² /m ²)	Secondary CT adiposity-distribution marker	CT-VATI directly quantifies the visceral depot, which carries distinct metabolic and inflammatory information that is not captured by total adiposity or BMI. It therefore tests a different biological construct from CT-TATI and DXA FMI.	Not used as the sole adiposity marker because patients with similar visceral fat may differ in subcutaneous and total fat burden. It was retained as a complementary depot-specific measure rather than treated as superior to total adiposity.	[1,2,7,8]

Construct and selected marker	Operationalisation in this paper	Analytical position	Why this marker was prioritised	Complementarity and reason alternatives were not prioritised	Key evidence
Mean CT skeletal muscle attenuation	Mean attenuation of segmented L3 skeletal muscle (Hounsfield units)	Exploratory CT muscle-quality marker	Mean muscle attenuation provides information on tissue composition that muscle area cannot provide. Lower attenuation is associated with greater intramuscular lipid content and is widely used as an imaging proxy for myosteatosis.	It complements CT-SMI because muscle quantity and tissue quality are biologically distinct. It was not elevated to a primary marker because attenuation is influenced by acquisition parameters, contrast phase, reconstruction, and segmentation, and it is not a direct measure of muscle function.	[5,13]
DXA appendicular lean mass / BMI (ALM/BMI)	DXA appendicular lean mass divided by BMI at baseline	Primary DXA muscle marker	ALM/BMI was selected as the main DXA muscle construct because it contextualises appendicular lean tissue against body size and adiposity. The FNIH Sarcopenia Project empirically derived ALM/BMI thresholds in relation to weakness, making it relevant in a female cohort with substantial adiposity heterogeneity.	Prioritised over absolute ALM and ALM/height ² for the principal DXA model because those measures may classify larger or more adipose individuals differently. It was analysed as a continuous host-phenotype marker, not as a diagnostic sarcopenia cut-off; ratio-based normalisation can retain adiposity dependence.	[6,7,12]
DXA fat mass index (FMI)	DXA total fat mass / height ² (kg/m ²)	Primary DXA adiposity marker	DXA is a well-established reference technique for whole-body fat and lean soft-tissue assessment. FMI expresses absolute fat mass relative to height, separates adiposity from lean mass, and is therefore more biologically specific than BMI.	Preferred to percentage body fat because percentage fat uses total body mass as its denominator and can change through variation in either fat or lean mass. FMI complements CT-TATI and CT-VATI by providing whole-body rather than single-slice regional adiposity.	[7,8,14]

Construct and selected marker	Operationalisation in this paper	Analytical position	Why this marker was prioritised	Complementarity and reason alternatives were not prioritised	Key evidence
BIA phase angle	Raw phase angle derived from resistance and reactance (degrees)	Secondary host-phenotype marker	Phase angle is a direct, raw impedance-derived measure that reflects cell-membrane properties, body-cell mass, and fluid distribution. It adds a vulnerability construct not represented by CT or DXA and has been studied in breast cancer in relation to nutritional and clinical status.	Selected over proprietary BIA estimates of muscle or fat because those estimates depend on device-specific prediction equations and hydration assumptions and are not interchangeable with DXA. Phase angle was not interpreted as muscle mass, adiposity, or a diagnostic nutritional measure.	[9,10]
Body mass index (BMI)	Measured body weight / height ² (kg/m ²)	Context and sensitivity marker; not a direct body-composition marker	BMI remains clinically interpretable and relevant to BSA-based chemotherapy dosing and routine oncology documentation. Including it allows direct comparison between conventional body-size assessment and tissue-specific CT, DXA, and BIA markers.	BMI was not treated as a primary body-composition measure because it cannot distinguish muscle from fat, quantify visceral distribution, or identify muscle quality. It was therefore retained as context rather than used as a substitute for measured body composition.	[7,11,14]

Abbreviations: ALM, appendicular lean mass; BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; FMI, fat mass index; HU, Hounsfield units; L3, third lumbar vertebral level; SMI, skeletal muscle index; TATI, total adipose tissue index; VATI, visceral adipose tissue index.

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Online Resource 3 PTX related adverse events as registered by the treating oncologist

	Adverse event Grade 1 (n=125)	Adverse event Grade 2 (n=10)	Total (n=135)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia	4	/	4
CARDIAC DISORDERS			
Palpitations	2	/	2
EYE DISORDERS			
Blurred vision	2	/	2
Dry eye	2	/	2
GASTROINTESTINAL DISORDERS			
Abdominal pain*	3	1	4
Constipation	4	/	4
Diarrhea	6	/	6
Dry mouth	4	/	4
Mucositis oral	2	/	2
Nausea	3	/	3
Vomiting	1	/	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema limbs	1	/	1
Fatigue	17	/	17
INFECTIONS AND INFESTATIONS			
Paronychia	1	/	1
Upper respiratory tract infection	/	1	1
INVESTIGATIONS			
ALT increased*	4	/	4
ALK increased	1	/	1
GGT increased	2	/	2

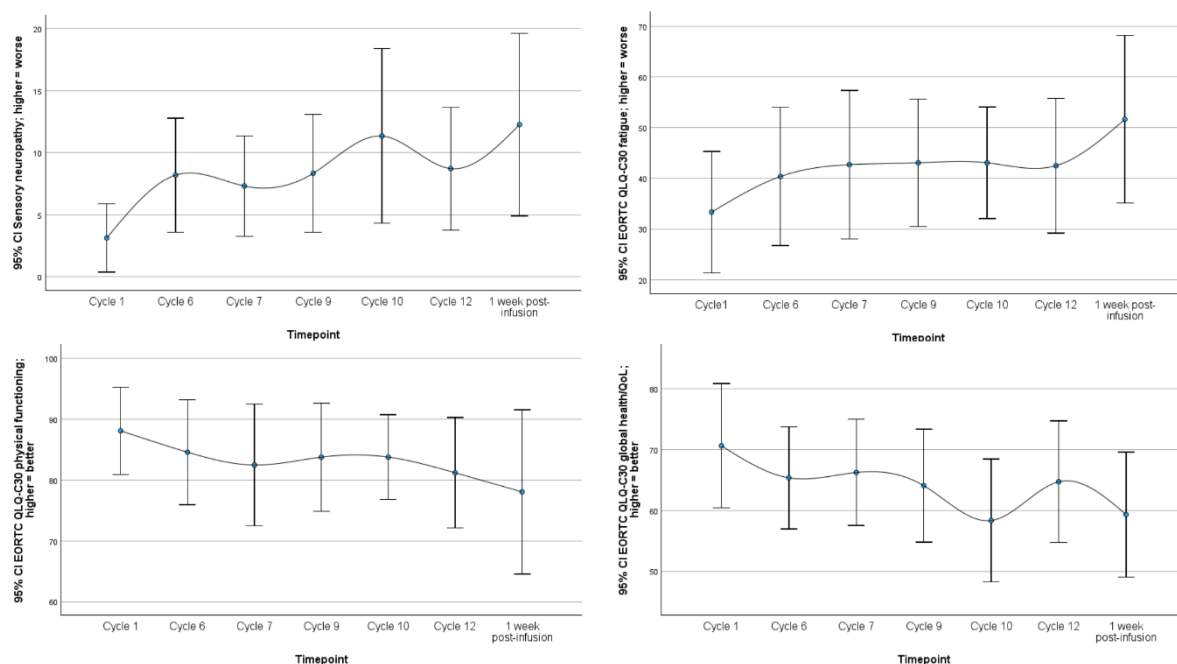
Platelet count decreased	2	1	3
Neutrophil count decreased*	4	/	4
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	2	1	3
Back pain*	/	1	1
Myalgia*	6	1	7
NERVOUS SYSTEM DISORDERS			
Dysgeusia	2	/	2
Headache	3	/	3
Peripheral sensory neuropathy*	14	3	17
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Amenorrhea	2	/	4
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Dyspnea	1	/	2
Epistaxis	9	/	9
Productive cough*	1	/	2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia	4	/	4
Nail discoloration	1	/	1
Nail loss	3	/	3
Pruritus	2	/	2
Rash acneiform	5	/	5
VASCULAR DISORDERS			
Hot flashes	5	/	5
Thromboembolic event	/	1	1

Note. ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; *n*, number of adverse-event episodes. “/” indicates no recorded event in that grade category; “*” identifies an adverse event classified as a dose-limiting toxicity or contributing to treatment modification. The totals refer to adverse-event episodes, not numbers of participants.

Online Resource 4 Patient-reported outcome trajectories during weekly PTX infusion cycles over 12 weeks

Across the scheduled assessments, 70 Day 1 and 71 Day 7 questionnaire sets were completed. From T1D1 to the descriptive T4D7 endpoint, fatigue increased by 19.4 points and CIPN by 10.0 points, while physical functioning declined by 10.4 points and global health status/quality of life by 10.7 points (Online Resource 4). These changes were consistent with clinically important deterioration according to the applicable domain-specific thresholds.

Trajectory models included T1D7 (week 1), T2D1 (week 6), T2D7 (week 7), T3D1 (week 9), T3D7 (week 10), T4D1 (week 12, final PTX infusion), T4D7 (one week after final PTX infusion) (Figure 2). Fatigue differed across categorical assessment occasions ($p=.013$) and increased by an average of 2.60 points per ordered occasion ($p<.001$). CIPN also differed across occasions ($p=.012$) and increased by 1.27 points per ordered occasion ($p<.001$). Categorical occasion effects were not statistically clear for physical functioning or global health status/quality of life, although ordered models indicated declines of 1.49 points ($p=.004$) and 1.54 points ($p=.013$) per successive assessment occasion, respectively.



Note. Panels show sensory neuropathy from the EORTC QLQ-CIPN20 and fatigue, physical functioning, and global health status/quality of life from the EORTC QLQ-C30. Filled circles and solid lines represent estimated marginal means with 95% confidence intervals for the seven occasions included in the categorical linear mixed-effects models. Ordered-occasion coefficients represent change per successive assessment occasion and should not be interpreted as weekly slopes because the intervals between assessments were unequal. EORTC, European Organisation for Research and Treatment of Cancer

Online Resource 5

This Online Resource describes the conversion from DBS concentration to plasma concentration and calculation of time above threshold.

1. Conversion from DBS concentration to plasma concentration

Blood-to-plasma (B:P) ratios were calculated using paired dried blood spot (DBS) and plasma concentrations. B:P ratios were calculated as:

$$B:P = \frac{C_{DBS}}{C_{plasma}}$$

where C_{DBS} and C_{plasma} represent the PTX concentrations measured in DBS and plasma, respectively.

To further investigate the influence of sampling time on B:P relationship, B:P ratios obtained from Day 1 samples (within 1 h after infusion end) and Day 2 samples (16–26 h after infusion end) were compared using Wilcoxon signed-rank test. Statistical significance was defined as $p < 0.05$.

The observed B:P ratios are shown in Figure S1. B:P ratios were consistently higher for Day 2 than for Day 1 samples, supporting the use of sampling time-specific conversion factors.

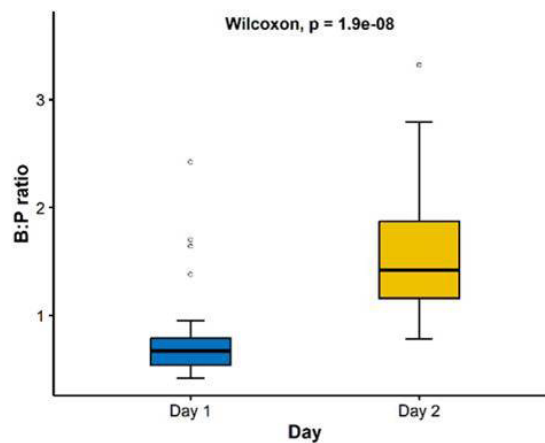


Figure S1. Boxplots of observed blood-to-plasma PTX concentration ratios (B:P ratio) on Day 1 (right after the end of infusion) and Day 2 (16-26h after the end of infusion).

Given the observed sampling time-dependent differences in B:P ratios, the predictive performance of the B:P-ratio approach was subsequently evaluated. Patients with paired DBS and plasma concentrations were randomly assigned to a training dataset (60% of patients) and an independent test dataset (40% of patients). Mean B:P ratios derived from the training dataset were calculated separately for Day 1 and Day 2 and used to predict plasma concentrations in the test dataset:

$$C_{plasma(predicted)} = \frac{C_{DBS(observed)}}{mean\ B:P\ ratio}$$

where $C_{plasma(predicted)}$ represents the predicted PTX plasma concentration, $C_{DBS(observed)}$ represents the observed PTX DBS concentration, and $mean\ B:P\ ratio$ denotes the mean B:P ratio for Day 1 or Day 2.

The predictive performance of the B:P-ratio approach was evaluated using an independent test dataset. Predicted plasma concentrations showed good agreement with observed concentrations

(Figure S2), and the prediction profiles adequately captured the observed concentration–time patterns (Figure S3).

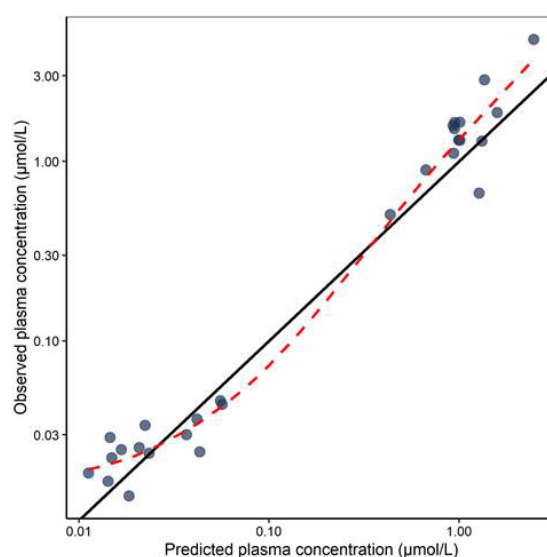


Figure S2. Goodness-of-fit plot comparing predicted and observed PTX plasma concentrations in the independent test dataset. The solid black line represents the line of identity ($y = x$). The dashed red line represents the linear regression fit.

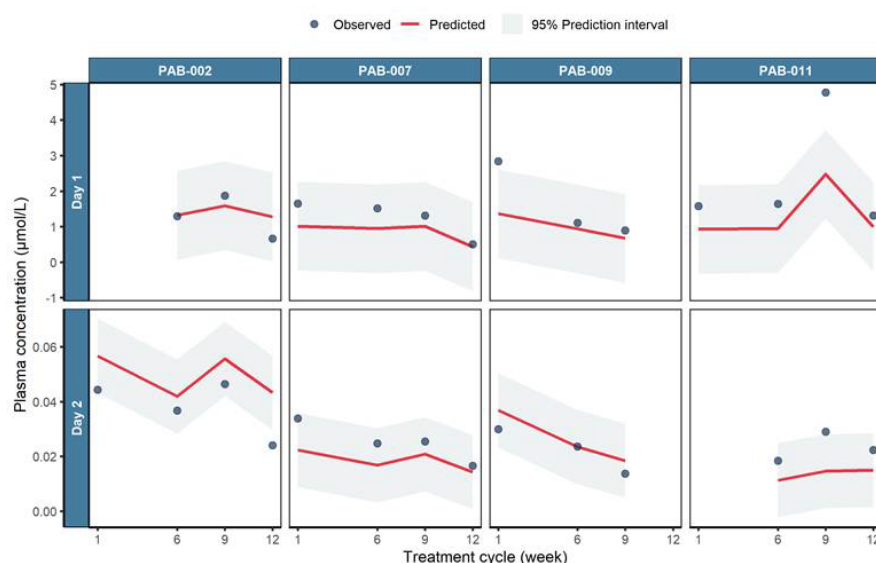


Figure S3. Comparison of observed and predicted PTX plasma concentrations in the independent test dataset. Blue points represent observed plasma concentrations, the red solid line represents the median prediction, and the shaded grey area indicates the 95% prediction interval. Panels are stratified by patient ID and sampling occasions (Day 1 and Day 2).

Subsequently, for patients without concurrent plasma measurements, plasma concentrations were estimated from DBS concentrations using the corresponding mean Day 1 and Day 2 B:P ratios. These estimated plasma concentrations were then incorporated into the exposure analyses.

2. Calculation of time above threshold

To characterize PTX exposure, the duration during which plasma concentrations remained above the clinically relevant threshold of 0.05 µmol/L was estimated for each treatment cycle (1). This analysis was performed using the measured or B:P-ratio-derived plasma concentrations described above.

For each treatment cycle, the plasma concentrations measured on Day 1 and Day 2 were defined as $C_{post-infusion}$ and $C_{delayed-samples}$, respectively. Assuming a one-compartment model with first-order elimination, the apparent elimination rate constant (k_e) was calculated as:

$$k_e = \frac{\ln(C_{post-infusion}/C_{delayed-samples})}{\Delta t}$$

Where Δt represents the time interval between the two samples.

The concentration–time profile after the end of infusion was described by:

$$C(t) = C_{post-infusion} e^{-k_e t}$$

As concentrations immediately following infusion were well above 0.05 µmol/L, exposure above the threshold was assumed to begin at the start of infusion. Consequently, $T_{c>0.05}$ was estimated by solving the equation for $C(t) = 0.05 \mu\text{mol/L}$:

$$T_{c>0.05} = \frac{\ln(C_{post-infusion}/0.05)}{k_e}$$

Descriptive statistics of the estimated PTX exposure metrics are summarized in Table S1. Overall exposure metrics were comparable across treatment occasions, with no evidence of progressive accumulation during weekly PTX treatment.

Table S1. Descriptive statistics of PTX exposure metrics across all treatment occasions.

	T1	T2	T3	T4	Overall
$C_{post-infusion}$ (µmol/L)	2.090 (1.612 - 2.635)	1.515 (1.253 - 1.698)	1.274 (1.046 - 1.868)	1.267 (0.900 - 1.651)	1.572 (1.170 - 2.141)
$C_{delayed-samples}$ (µmol/L)	0.030 (0.023 - 0.033)	0.024 (0.020 - 0.025)	0.020 (0.017 - 0.025)	0.023 (0.018 - 0.024)	0.023 (0.020 - 0.030)
$T_{c>0.05}$ (hour)	18.542 (18.082 - 19.568)	19.174 (18.019 - 20.402)	17.505 (17.139 - 19.232)	18.477 (16.031 - 20.197)	18.447 (17.188 - 18.812)

Note. Data are presented as median (IQR). $C_{post-infusion}$, plasma concentration measured after the end of infusion (Day 1); $C_{delayed-samples}$, plasma concentration measured 16-26h after infusion (Day 2); $T_{c>0.05}$, estimated duration above the threshold concentration of 0.05 µmol/L.

All statistical analyses and graphical visualizations were performed in R (version 4.5.2, R Foundation for Statistical Computing, Vienna, Austria).

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Online resource 6 Complete clinical-context association result

Table OR6 reports all Spearman rank correlations underlying Fig. 4. Analyses used pairwise-complete observations. Table OR6 reports the binary sensitivity analysis comparing participants with versus without any toxicity-related treatment modification.

Table OR6. Spearman rank correlations for the exploratory clinical-context analyses

Predictor	Relative dose intensity ρ / N / p	Treatment-modification count ρ / N / p	Total adverse-event count ρ / N / p
Observed immediate post-infusion concentration	0.096 / 20 / .686	0.131 / 20 / .582	0.237 / 20 / .315
Baseline BMI	-0.541 / 20 / .014	0.081 / 20 / .733	0.252 / 20 / .284
Baseline ALM/BMI	0.306 / 16 / .249	-0.448 / 16 / .082	-0.064 / 16 / .813
Baseline ALMI	-0.324 / 16 / .221	-0.072 / 16 / .791	0.233 / 16 / .384
Baseline lean mass	-0.212 / 17 / .414	-0.096 / 17 / .714	0.168 / 17 / .518
Baseline fat mass	-0.300 / 16 / .259	0.272 / 16 / .307	0.256 / 16 / .339
Baseline fat-free mass	-0.113 / 17 / .666	-0.133 / 17 / .611	0.185 / 17 / .478
Baseline BIA visceral fat	-0.462 / 19 / .046	0.156 / 19 / .524	0.220 / 19 / .366
Baseline phase angle	0.130 / 18 / .608	0.103 / 18 / .684	0.079 / 18 / .756
Δ BMI	0.456 / 17 / .066	-0.156 / 17 / .549	0.394 / 17 / .117
Δ ALM/BMI	0.222 / 14 / .445	0.146 / 14 / .619	-0.445 / 14 / .111
Δ ALMI	0.150 / 14 / .610	0.118 / 14 / .688	-0.106 / 14 / .719
Δ lean mass	0.612 / 14 / .020	-0.062 / 14 / .832	-0.256 / 14 / .377
Δ fat mass	0.134 / 14 / .647	0.049 / 14 / .869	0.366 / 14 / .198
Δ fat-free mass	0.409 / 14 / .146	-0.257 / 14 / .376	-0.079 / 14 / .789
Δ BIA visceral fat	0.365 / 15 / .181	-0.008 / 15 / .979	0.389 / 15 / .152
Δ phase angle	0.032 / 15 / .909	-0.087 / 15 / .757	0.061 / 15 / .828
Mean steps/day	0.338 / 18 / .170	0.140 / 18 / .580	-0.368 / 18 / .133
Mean counts/min	0.275 / 18 / .269	0.005 / 18 / .983	-0.255 / 18 / .307

Note: In the analysis dataset, treatment-modification count and any treatment modification were coded as DLT_total and DLT_any, respectively. P-values are two-sided nominal exploratory values without multiplicity correction.