2. SYNOPSIS

Name of Sponsor:	Vifor (International) Inc.
Name of Finished Product:	Vamifeport
Name of Active Ingredient(s):	VIT-2763

Study Title:	[^{14}C]-Vamifeport - A Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion Following a Single Oral Dose in Healthy Male Subjects
Investigators and Study Centres:	Jim Bush, MBChB, PhD, MRCS, FFPM, GFMD This study was conducted at 1 site in the United Kingdom.
Publication(s) (Reference):	None
Studied Period:	31 October 2022 (date of first informed consent) to 15 December 2022 (date of final poststudy observation).
Phase of Development:	Phase 1
Objectives:	Primary Objectives: • To determine the routes and rates of elimination, and mass balance of total radioactivity from [^{14}C]-vamifeport. • To characterise the pharmacokinetics (PK) of vamifeport and total radioactivity following administration of [^{14}C]-vamifeport to healthy male subjects Secondary Objectives: • To derive further PK parameters of vamifeport • To determine, where possible, the quantitative metabolite profiles in plasma, urine, and faeces following [^{14}C]-vamifeport • To determine, where possible, the chemical structure of major metabolites in plasma, urine, and faeces following [^{14}C]-vamifeport administration • To assess the safety and tolerability of a single dose of [^{14}C]-vamifeport when administered to healthy male subjects
Endpoints:	Primary Endpoints: • Recovery of total radioactivity – amount of dose administered recovered in urine (Ae) and percentage of dose administered recovered in urine (fe) in urine, faeces, and total excreta (urine + faeces) • PK parameters including $AUC_{0\text{-infinity}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, and $t_{1/2}$ for vamifeport in plasma and total radioactivity in plasma and whole blood and urinary recovery of vamifeport (Ae and fe) and renal clearance (CL_r) Secondary Endpoints: • Further PK parameters, such as apparent terminal disposition phase rate constant, apparent total clearance, apparent volume of distribution during the terminal disposition phase, and blood to plasma ratios; additional PK parameters may be calculated where appropriate • Quantitative metabolic profiles of vamifeport in plasma and excreta

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	• Identification of vamifeport major metabolites in plasma (>10% relative total drug-related exposure) and excreta (>10% of excreted dose) • Incidence and severity of adverse events (AEs) • Incidence of laboratory abnormalities, based on haematology, clinical chemistry, and urinalysis test results • 12-lead electrocardiogram (ECG) parameters • Vital signs measurements
Methodology:	This was a Phase 1, open-label, non-randomised, single-dose study in healthy male subjects. Potential subjects were screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects were admitted into the study site on Day -1. On the morning of Day 1, all subjects received a single oral dose of 120 mg containing approximately 169 µCi (6.25 MBq) of [^{14}C]-vamifeport in the fasted state. The dose was administered as 2 capsules containing 60 mg [^{14}C]-vamifeport each. Subjects were to be discharged from the study site from Day 5 onwards, upon Investigator decision, regardless of the Schedule of Assessments planned up to Day 7, once the following discharge criteria were met: • Plasma radioactivity levels below the limit of quantitation for 2 consecutive collections, and • ≥90% mass balance recovery, and • <1% of the total radioactive dose was recovered in combined excreta (urine and faeces) in 2 consecutive 24-hour periods If discharge criteria were not met by Day 7, subjects were to remain confined to the study site up to a maximum of Day 14 to continue blood sampling and 24-hour urine and faeces collections for total radioactivity until all discharge criteria were met unless otherwise agreed upon by the Sponsor and Investigator. If criteria were not met by Day 14, subjects may have been asked to collect 24-hour excreta samples on up to 2 further occasions on a residential basis to allow extrapolation of urinary and faecal excretion. If needed, the 2 additional 24-hour residential collections were to start on the morning of Days 21 and 28. If, on the second occasion, the subject had still not met the desired criterion, then the subject was to be discharged from the study, per the Investigator's decision.
Number of Subjects (Planned and Analysed):	Up to 8 subjects were to be enrolled to ensure that a minimum of 6 subjects completed the study. Eight subjects entered and completed the study. Data for all 8 subjects (100%) were included in the PK and safety analysis populations.
Diagnosis and Main Criteria for Inclusion:	Healthy male subjects of any race, aged between 35 and 65 years, inclusive, and with a body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive were selected according to the inclusion and exclusion criteria listed in the protocol.

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Test Product, Dose and Mode of Administration, Lot Number:	Doses of 120 mg containing approximately 169 µCi (6.25 MBq) of [^{14}C]-vamifeport were administered orally as 2 capsules containing 60 mg [^{14}C]-vamifeport each, with a total volume of 240 ml (volume included rinse) room-temperature water. Batch/lot number of active pharmaceutical ingredient (API) (non-radiolabelled vamifeport powder): 0214020E. Batch/lot number of radiolabelled API ([^{14}C]-VIT-2763-3HCl API powder): P/006617. Batch/lot number of unit doses/bottles (2 x [^{14}C]-VIT-2763 capsules (60 mg)): 1M241122.
Duration of Treatment:	A single dose was administered once on Day 1. Overall, subject's study participation could have been up to a maximum of 57 days (including screening to discharge from study).
Statistical Methods:	Analysis Populations: The PK population included all subjects who received a dose of radiolabelled study treatment ([^{14}C]-vamifeport), had at least 1 valid PK concentration, and did not have any major protocol deviations that had an impact on PK data. The safety population included all subjects who received a dose of radiolabelled study treatment ([^{14}C]-vamifeport). The all subjects population included all subjects who signed the Informed Consent Form (ICF) and had any study assessment recorded in the database per the protocol. Statistical Methodology: All plasma (vamifeport and total radioactivity), whole blood (total radioactivity), and urine (vamifeport) PK concentrations and parameters were listed. Summary tables, arithmetic mean (+standard deviation (SD)) figures, overlaying individual figures, and individual figures and time post-dose were provided for plasma and whole blood PK concentrations. All figures were produced on both linear-linear and linear-logarithmic scales. The +SD bars were displayed on the linear-linear scales. Summary tables were provided for all PK parameters, with the exception of diagnostic regression-related PK parameters. Separate summary tables by time intervals were provided for non-radioactive excretion parameters and cumulative excretion parameters. For total radioactivity in blood, plasma, urine, and faeces analysis, individual data and arithmetic mean ±SD were tabulated and presented in graphical form where appropriate. No inferential statistical analyses were planned or performed. All AEs were listed. The frequency of subjects with treatment-emergent adverse events (TEAEs)/treatment-related TEAEs and the number of TEAEs/treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) were summarised overall and by severity. The frequencies of subjects were also summarised separately for TEAEs and treatment-related TEAEs overall by Medical Dictionary for Regulatory

	Activities (MedDRA) system organ class (SOC) and preferred term (PT) and by PT. All clinical laboratory parameters were listed and any values outside the clinical reference ranges were flagged. Summary tables by time point were provided for clinical chemistry and haematology parameters. Summary tables by time point were provided for all vital signs and 12-lead ECG parameters. All vital signs and 12-lead ECG parameter data were listed, with any values outside the clinical reference ranges flagged. All other safety data were listed for the all subjects population. Determination of Sample Size: No formal statistical assessment of sample size was conducted. The sample size chosen for this study is common in human radiolabelled studies and was considered sufficient to achieve the objectives of the study. Eight subjects were to be enrolled and studied as a single group in order that a minimum of 6 subjects completed the study.
Summary of Results:	Subject Disposition: A total of 8 male subjects, aged between 35.0 and 59.0 years, with a mean BMI of 26.71 kg/m^2, entered the study. All 8 subjects (100%) completed the study. All 8 subjects (100%) received a single oral dose of approximately 120 mg [^{14}C]-vamifeport, with exact doses ranging from 115.92 to 119.75 mg vamifeport (free base). The radioactivity of the doses administered ranged from 6.09 to 6.29 MBq. PK Results: Following administration of a single oral dose of [^{14}C]-vamifeport, vamifeport was characterised by a rapid absorption phase, with a median T_{max} of 1 hour post-dose (range from 0.500 to 2.00 hours). Maximum levels of total radioactivity were reached at a similar time to that of vamifeport in whole blood and in 7 of 8 subjects in plasma. After reaching C_{max}, there was a second plasma concentration peak of vamifeport observed between 3 and 4 hours post-dose for 3 subjects and at 1.5 hours post-dose for 1 subject before vamifeport concentrations declined. In addition, 1 subject had a plateau of concentrations from 3 to 4 hours post-dose. Plasma concentrations then declined with a geometric mean $t_{1/2}$ of 4.74 hours and individual $t_{1/2}$ values ranged from 2.54 to 9.20 hours. A second peak or shoulder of vamifeport concentrations was observed in previous studies with this study drug too (VIT-2763-101, VIT-2763-CP-103). Similar concentration-time profiles of total radioactivity were also observed in plasma and whole blood. Vamifeport in plasma was approximately 65% of total radioactivity in plasma ($AUC_{0\text{-inifinity}}$ ratio of 0.653), suggesting the presence of circulating drug-related radiolabelled metabolites. There was low association of radioactivity with red blood cells (whole blood/plasma total radioactivity of 0.568). The overall arithmetic mean recovery of total radioactivity in urine and faeces combined was approximately 98% of the administered radioactive dose through 168 hours post-dose, with urinary excretion being the predominant

	route of excretion for drug-related radioactivity (74.05%) and faecal excretion contributing 24.07%. Urinary excretion was initially rapid with 45.08% of the administered dose recovered over the first 4 hours post-dose, and the majority recovered up to 48 hours post-dose (73.58%). Faecal excretion of drug-related radioactivity was slower, with the majority of radioactivity recovered up to 72 hours post-dose (21.58%). Radioactivity, albeit at low levels, was detected up until the 120 to 144 hours collection period in urine (3 subjects) and up until the 144 to 168 hours collection period in faeces (2 subjects). The geometric mean percentage of approximately 120 mg [^{14}C]-vamifeport recovered in urine was 17.1% through 120 hours post-dose, with the elimination of vamifeport deemed completed for all subjects by 72 hours as no further vamifeport was present in the urine samples collected from 72 hours onwards. The geometric mean CL_r of vamifeport was 2.97 l/h. Safety Results: Overall, single oral doses of approximately 120 mg (169 µCi) of [^{14}C]-vamifeport were well tolerated, with no deaths, no TEAEs leading to discontinuation, and no serious adverse events (SAEs) during the study. Overall, 3 (37.5 %) subjects had 4 TEAEs during the study. All the TEAEs were considered mild, and none were considered related to [^{14}C]-vamifeport. There were no findings in clinical laboratory, vital signs, or ECG parameter data that were considered clinically significant and reported as a TEAE.
Conclusions:	• Following single oral administration of approximately 120 mg of [^{14}C]-vamifeport, vamifeport appeared rapidly in plasma, with a median T_{max} of 1 hour. Plasma concentrations declined with a geometric mean $t_{1/2}$ of approximately 4.74 hours. • The PK profiles of vamifeport and total radioactivity were broadly similar where both analytes were quantifiable. • Radioactivity was generally detected in whole blood up to 16 hours post-dose. Radioactivity in plasma was generally detected up to 24 hours post-dose. Differences were associated with the mean limits of detection, which were 33.6 and 15.2 ng Eq/g, in blood and plasma, respectively. • Vamifeport in plasma was approximately 65% of total radioactivity in plasma ($AUC_{0\text{-infinity}}$ ratio of 0.653), suggesting the presence of circulating drug-related radiolabelled metabolites. • The geometric mean whole blood/plasma ratio for total radioactivity was approximately 0.568 for $AUC_{0\text{-infinity}}$, suggesting there was no preferential binding or uptake of drug-related radioactivity into blood cells over time. • The overall mean recovery of total radioactivity in urine and faeces was 98.12% following a single oral dose of approximately 120 mg (169 µCi) of [^{14}C]-vamifeport. • The primary route of excretion of total radioactivity was in urine, with 74.05% excreted. This means that the kidneys play a major role in filtering and/or secreting the radioactively labelled parent compound and its labelled metabolites from the system. Faeces accounted for 24.07% of the

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	total radioactivity excretion resulting from either non-absorbed parent compound or its metabolites secreted into bile and not being reabsorbed. • Single oral doses of approximately 120 mg (169 µCi) of [^{14}C]-vamifeport were well tolerated by the subjects in this study.
Final Report Date:	19 July 2023