2. SYNOPSIS

Study Title
AN OPEN-LABEL STUDY TO CHARACTERIZE THE ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION OF A SINGLE ORAL DOSE OF ^{14}C-LENIOLISIB IN HEALTHY MALE SUBJECTS

Study Codes

Sponsor code	: LE 2101
PRA code	: PGG20415-20415X
EudraCT number	: 2021-001807-33

Sponsor
Pharming Technologies BV, Darwinweg 24, 2333 CR Leiden, The Netherlands (Pharming Technologies BV is a subsidiary of Pharming Group NV)
Sponsor's contact : Pierre Peeters, PhD, Clinical Pharmacology Consultant, Curare Consulting

Contract Research Organization and Clinical Site
PRA Health Sciences - Early Development Services, Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands

Principal Investigator
Jan Jaap van Lier, MD

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Study Period : Date of first screening to last follow-up: 15 Oct 2021 to 26 Nov 2021

Clinical Phase : Phase 1

Objectives

Primary	: To determine the total recovery and relative excretion of radioactivity in urine and feces after a single dose of 70 mg ^{14}C-leniolisib, containing 40 µCi of ^{14}C-radioactivity administered as a drinking solution.
Secondary	: To determine the plasma pharmacokinetic (PK) parameters of total ^{14}C-radioactivity and of leniolisib. To evaluate the safety profile of a single 70-mg dose of ^{14}C-leniolisib.

Design and Treatments
This was a Phase 1, single-center, open-label absorption, distribution, metabolism, and excretion study in healthy subjects.

Eligible subjects were admitted to the clinical research unit (CRU) on the afternoon of Day -1 and were dosed the following morning (Day 1), after at least 10 hours fasting.

PK sampling (blood, urine, feces, and vomit [if applicable]) and safety monitoring were conducted at the CRU through minimally 8 days and maximally 12 days post-dose. Collection of urine and feces were discontinued and subjects were discharged from the CRU if ≥90% of the administered dose was recovered and radiocarbon measurements results indicated that 2 consecutive 24-hour samples contained ≤1% of the

administered dose of radioactivity. If the discharge criteria were not met on Day 12, subjects had to return to the CRU for one or more 24-hour visits on Days 19, 26, and 33, until the discharge criteria were met.

Subjects returned to the CRU for an End-of-Study (EOS) visit within 5 days after last sample collection.

Study Schedule

Screening	: Between Day -28 and Day -1 (admission)
Treatment period	: In-house period of minimally 8 days and maximally 12 days, followed by potential 24-hour visits once weekly until criteria were met on Days 19, 26, and/or 33.
Follow-up	: EOS visit within 5 days after last sample collection

Subjects

Six healthy male subjects were planned.

Main Criteria for Inclusion

Age	: 18 to 45 years, inclusive, at screening
Body mass index (BMI)	: 18.5 to 30.0 kg/m^2, inclusive
Subjects	: Healthy male subjects

Study Drug

Active Medication

Active substance	: Leniolisib
Activity	: Inhibitor phosphoinositide 3-kinases subunit of p110δ
Indication/ In development for	: Activated phosphoinositide 3-kinase δ syndrome (APDS)
Strength	: 70 mg (free base)/40 µCi
Dosage form	: Oral, drinking solution
Manufacturer	: Pharmaron
Batch number	: RLM 220

Variables

Pharmacokinetics	: Plasma, urine, and feces (and vomit, if applicable) concentrations of total ^{14}C-radioactivity (TRA) and plasma concentrations of leniolisib PK parameters in plasma of TRA and leniolisib estimated using noncompartmental analysis, as appropriate: C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, k_{el}, $t_{1/2}$, CL/F, V_z/F, Ratio C_{max}, Ratio AUC_{0-t}, and Ratio AUC_{0-inf} PK parameters of TRA in urine, feces, and vomit (if applicable) estimated using noncompartmental analysis, as appropriate: Ae_{urine}, fe_{urine}, Ae_{feces}, fe_{feces}, Ae_{vomit}, fe_{vomit}, cumulative Ae in urine, cumulative fe in urine, cumulative Ae in in feces, cumulative fe in feces, cumulative Ae in vomit (if applicable), cumulative fe in vomit (if applicable), Ae, total (total recovery), and fe, total (total recovery)
Safety	: Adverse events (AEs), clinical laboratory, vital signs, 12-lead electrocardiogram (ECG), physical examination

Statistical Methods

PK parameters	: Descriptive statistics for all relevant PK parameters of TRA and leniolisib in plasma: N, arithmetic mean, coefficient of variation (CV), SD, minimum, maximum, median, geometric mean, geometric CV

: Descriptive statistics for all relevant PK parameters of TRA in urine, feces, and vomit (if applicable): N, arithmetic mean, CV, SD, minimum, maximum, and median

: Individual TRA cumulative amount and percentage of dose data per collection interval for urine, feces, and total were tabulated together with descriptive statistics. Individual urine, feces, and total mass balance parameters were tabulated together with descriptive statistics. An arithmetic mean graph of cumulative TRA excretion in urine and feces and total recovery (percentage of dose) by time, and individual cumulative TRA excretion by time plots, were provided.

Safety parameters : Descriptive statistics

Results

Subject Disposition

A total of 19 subjects were screened and 6 of these subjects were included in the study. All subjects completed the study as per protocol and were included in the safety and PK set.

Demographics

A total of 6 male subjects between 23 and 43 years of age and with a BMI between 22.6 and 25.6 kg/m^2 participated in the study. A total of 4 subjects were white and 2 subjects were Asian. None of the 6 subjects were of Hispanic or Latino ethnicity.

Pharmacokinetics

Mass Balance

Overall, the arithmetic mean recovery of TRA was 92.5% (SD: 2.3%) of the administered dose of ^{14}C-leniolisib within 168 hours after dosing. Radioactivity was predominately excreted in feces (67.0% [SD: 4.1%]). Excretion in urine was 25.5% (SD: 3.9%) (Table S 1). Excretion was relatively fast, with on average, 69.6% of the administered dose of ^{14}C-leniolisib already excreted in urine (25.1%) and feces (44.5%) within 48 hours post-dose.

Pharmacokinetics

The median t_{max} for both TRA and leniolisib was 0.5 hours. The geometric mean $t_{1/2}$ for TRA was 32.8 hours, which was substantially longer than the geometric mean $t_{1/2}$ for leniolisib, which was 6.39 hours (Table S 2 and Table S 3). The C_{max}, AUC_{0-t}, and AUC_{0-inf} for TRA were higher than those for leniolisib, with geometric mean ratios of leniolisib over TRA of 0.87, 0.74, and 0.68, respectively (Table S 4).

The concentration-time profiles for both TRA and leniolisib exhibited a rapid increase within the first 0.5 hours post-dose in all subjects, suggesting a very rapid absorption of ^{14}C-leniolisib.

Table S 1 Excretion Parameters of Total ^{14}C-Radioactivity in Urine, Feces, and Total Recovery

Statistic (N=6)	Cum. fe_{Urine} (%)	Cum. fe_{Feces} (%)	Cum. $fe_{Urine+Feces}$ (%)	Cum. Ae_{Urine} (mgEq)	Cum. Ae_{Feces} (mgEq)	Cum. $Ae_{Urine+Feces}$ (mgEq)
Arithmetic mean	25.5	67.0	92.5	17.9	46.9	64.8
SD	3.9	4.1	2.3	2.8	2.8	1.7
CV%	15.2	6.1	2.5	15.5	5.9	2.6
Median	25.5	67.6	92.6	17.8	47.5	64.8
Minimum	19.8	61.5	89.0	13.8	43.0	62.3
Maximum	31.2	73.0	95.3	22.0	50.9	66.7

Cum. = cumulative; N=number of subjects; SD=standard deviations; CV=coefficient of variation

Table S 2 Summary Statistics of the Main Pharmacokinetic Parameters for Total ^{14}C-Radioactivity in Plasma

Parameter (unit)	Statistic	
C_{max} (ngEq/mL)	Geometric mean (geom. CV%)	3606 (23.5)
	Min - Max	2761 - 5139
T_{max} (h)	Median	0.50
	Min - Max	0.25 - 0.75
AUC_{0-inf} (h.ngEq/mL)	Geometric mean (geom. CV%)	23371 (26.5)
	Min - Max	15271 - 34351
$t_{1/2}$ (h)	Geometric mean (geom. CV%)	32.8 (176.9)
	Min - Max	8.08 - 118

CV=coefficient of variance; geom=geometric; Max=maximum; Min=minimum

Table S 3 Summary Statistics of the Main Pharmacokinetic Parameters for Leniolisib in Plasma

Parameter (unit)	Statistic	
C_{max} (ng/mL)	Geometric mean (geom. CV%)	3153 (36.6)
	Min - Max	2086 - 4677
T_{max} (h)	Median	0.50
	Min - Max	0.25 - 0.75
AUC_{0-inf} (h.ng/mL)	Geometric mean (geom. CV%)	16008 (36.5)
	Min - Max	9154 - 23786
$t_{1/2}$ (h)	Geometric mean (geom. CV%)	6.39 (30.3)
	Min - Max	4.43 - 9.13

CV=coefficient of variance; geom=geometric; Max=maximum; Min=minimum

Table S 4 Summary Statistics of C_{max} and AUC Leniolisib/Total ^{14}C-Radioactivity Ratios

Parameter (unit)	Statistic	
Ratio C_{max}	Geometric mean (geom. CV%)	0.87 (24.4)
	Min - Max	0.67 - 1.26
Ratio AUC_{0-t}	Geometric mean (geom. CV%)	0.74 (28.5)
	Min - Max	0.43 - 0.93
Ratio AUC_{0-inf}	Geometric mean (geom. CV%)	0.68 (33.7)
	Min - Max	0.37 - 0.91

CV=coefficient of variance; geom=geometric; Max=maximum; Min=minimum

Safety

A total of 8 TEAEs were reported by 5 (83.3%) subjects. All TEAEs were Grade 1 (mild) and considered unrelated to the study drug. The most frequently reported TEAEs were diarrhea and myalgia, both events were reported once by 2 (33.3%) subjects each. There were no deaths, serious AEs, or withdrawals due to AEs reported during the study. All TEAEs were transient and resolved without sequelae by follow-up.

No changes or trends of clinical significance were seen for clinical laboratory, vital signs, 12-lead ECGs, and physical examinations.

A single oral dose of 70 mg leniolisib containing 1.5 MBq radioactivity appears to be safe and well tolerated in this group of healthy male subjects.

Conclusions

Pharmacokinetics

- After single oral administration of 70 mg ^{14}C-leniolisib, the arithmetic mean recovery of TRA was 92.5% of the administered dose of ^{14}C-leniolisib within 168 hours after dosing.
- TRA was predominately excreted in feces (67.0%) and the remainder in urine (25.5%).
- Excretion was relatively fast, with on average, 69.6% of the administered dose of ^{14}C-leniolisib already excreted in urine (25.1%) and feces (44.5%) within 48 hours post-dose.
- The median t_{max} for both TRA and leniolisib was 0.5 hours.
- The geometric mean $t_{1/2}$ for TRA of 32.8 hours was substantially longer than the geometric mean $t_{1/2}$ for leniolisib, which was 6.39 hours.
- The C_{max}, AUC_{0-t}, and AUC_{0-inf} geometric mean ratios of leniolisib over TRA were 0.87, 0.74, and 0.68, respectively.

Safety

- A single 70 mg oral dose of ^{14}C-leniosilib was safe and well tolerated in this group of male healthy subjects.
- All TEAEs were transient, unrelated to study drug, and resolved without sequelae by follow-up.
- Most frequently reported TEAEs were diarrhea and myalgia, both events were reported once by 2 (33.3%) subjects each.
- There were no deaths or serious AEs and no withdrawals due to AEs reported during the study.
- No changes or trends of clinical significance were seen for clinical laboratory, vital signs, 12-lead ECGs, and physical examinations.