2. SYNOPSIS

Study Title

AN OPEN-LABEL, SINGLE SEQUENCE CROSSOVER DRUG-DRUG INTERACTION STUDY TO EVALUATE THE EFFECT OF MULTIPLE ORAL DOSES OF ITRACONAZOLE ON THE PHARMACOKINETICS OF PHA-022121 IN HEALTHY SUBJECTS

Study Codes

Sponsor code : PHA022121-C004
PRA code : PHV19687-19687X
EudraCT number : 2019-005001-49

Sponsor

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Principal Investigator

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Publication : None at time of writing this clinical study report

Study Period : Date of first screening to last follow-up: 26 Feb 2020 – 07 Apr 2020

Clinical Phase : Phase 1

Objectives

Primary : The primary objective of this study was to determine the effect of multiple doses of the cytochrome P450 3A4 (CYP3A4) inhibitor itraconazole on the pharmacokinetics (PK) of PHA-022121 in healthy adult subjects.

Secondary : The secondary objective of this study was to evaluate the safety and tolerability of PHA-022121 alone and in combination with multiple doses of the CYP3A4 inhibitor itraconazole in healthy adult subjects.

Design and Treatments

This was a Phase 1, open-label, fixed sequence study in healthy adult subjects to assess the effect of multiple doses of itraconazole, a potent CYP3A4 and P-glycoprotein inhibitor, at steady-state on the PK of a single dose of PHA-022121.

A target of 14 healthy adult subjects was planned in this study to ensure a minimum of 12 subjects to complete all assigned treatments. Enrollment of additional subjects were allowed if more than 2 dropouts would occur (if these dropouts were unrelated to safety and/or tolerability to the test compound). Thirteen (13) subjects were enrolled and completed the study. The fourteenth subject could not be included in the study because of the SARS-CoV-2 outbreak and resulting lockdown of the study facility. All thirteen enrolled subjects received the following administrations:

- a single dose of 12 mg PHA-022121 alone on Day 1, 0.5 hour after finishing a standard meal

- 200 mg itraconazole twice daily (b.i.d., with 12 hours between administrations) on Day 3, and once daily (q.d.) on Days 4 to 8, 1 hour before start of a standard meal
- a single dose of 12 mg PHA-022121 on Day 7, 0.5 hour after finishing a standard meal

Screening took place from Days -21 to -2, and subjects were admitted to the clinical site on Day -1.

PHA-022121 was made available as a self-microemulsifying drug delivery system (SMEDDS) solution containing 12 mg PHA-022121. Itraconazole was administered as an oral solution of 10 mg/mL.

PHA-022121 was dosed orally on Day 1, 0.5 hour after finishing a standard meal, with 240 mL of non-carbonated water.
Itraconazole was dosed orally from Day 3 up to and including Day 8. On Day 3, subjects received 200 mg itraconazole b.i.d., with approximately 12 hours in between administrations, 1 hour before start of a standard meal. On Days 4 to 8, subjects received oral doses of 200 mg itraconazole q.d. one hour before start of a standard meal. The time of itraconazole dosing was approximately the same on every day.

On Day 7, itraconazole was administered one hour before start of a standard meal with approximately 120 mL non-carbonated water. PHA-022121 was administered 0.5 hour after finishing the standard meal. Therefore, the intake of PHA-022121 on Day 1 and Day 7, took place under fed conditions. 240 mL of water was used to swallow the PHA-022121 SMEDDS solution. Water intake (except for the water to be given to swallow the study drug) was not allowed until 2 hours after dosing.

Subjects were discharged from the clinical site on Day 9 on the condition that all required assessments had been performed and there were no medical reasons for a prolonged stay. The clinical study was completed with an end-of-study (EOS) visit, which took place between 5 and 9 days after the last treatment-defined assessment (or after early withdrawal).

Plasma concentrations of PHA-022121 and its metabolite M2-D were determined predose and over a 48-hour evaluation period after dosing of PHA-022121 on Days 1 and 7.

Trough plasma concentrations of itraconazole and hydroxyitraconazole were determined by taking predose plasma samples on Days 4 to 7, to document exposure to itraconazole and hydroxyitraconazole.

A mandatory pharmacogenomic blood sample was collected from all subjects receiving PHA-022121 for potential exploratory analyses on Day 1, which may be conducted if it was hypothesized that this may help with the interpretation of the clinical data.

The study duration for each subject was maximally 9 days, screening and EOS visit not included.

Safety and tolerability were assessed throughout the study from signing of the informed consent form (ICF) onwards until the subject's last study-related activity.

Specific evaluations and their timing can be found in the Time and Events Schedule.

Study Schedule

Screening	: Between Day -21 and Day -2.
Confinement period	: From Day -1 (admission) to Day 9 (on the condition that all required assessments were performed and there were no medical reasons for a prolonged stay).

Follow-up : 5 to 9 days after the last treatment-defined assessment.

Subjects

A total of 14 healthy male and female subjects were to be included in the study.

Main Criteria for Inclusion

Age : 18 to 60 years, inclusive, at screening
Weight : Not less than 50.0 kg, inclusive, at screening
Body mass index (BMI) : 18.0 to 30.0 kg/m^2, inclusive, at screening
Subjects : Healthy male and female subjects

Investigational Product

Active medication (1)

Active substance : PHA-022121
Activity : Competitive human B_2 receptor antagonist
In development for : Hereditary angioedema
Strength : 12 mg PHA-022121
Dosage form : Oral solution
Manufacturer : NextPharma
Batch number : 228324

Active medication (2)

Active substance : Itraconazole (Trisporal)
Activity : Azole antifungal (used here as CYP3A4 and P-glycoprotein inhibitor)
Strength : 10 mg/mL
Dosage form : Oral solution
Manufacturer : Janssen
Batch number : JIB5200

Variables

Safety : Adverse events (AEs), clinical laboratory, vital signs, 12-lead electrocardiogram (ECG), physical examination

PK : Plasma PHA-022121, metabolite M2-D and itraconazole concentrations
: Plasma PK parameters estimated using noncompartmental analysis (NCA), as appropriate:
: For PHA-022121 and metabolite M2-D on Day 1 and Day 7: C_{max}, t_{max}, $t_{½}$, AUC_{last}, AUC_{∞}, λ_z, CL/F (PHA-022121 only), and V_z/F (PHA-022121 only); Ratio $C_{max, M2\text{-}D/PHA\text{-}022121}$, Ratio $AUC_{last, M2\text{-}D/PHA\text{-}022121}$, and Ratio $AUC_{\infty, M2\text{-}D/PHA\text{-}022121}$
: For itraconazole and hydroxyitraconazole on Days 4 to 7: C_{trough} before the morning dose

Statistical Methods

Sample size calculation : A sample size of 14 subjects was planned to explore and estimate the effect of multiple doses of itraconazole on the PK parameters of PHA-022121 in healthy volunteers.
The actual intra-subject variability (CV) for the PK parameters C_{max} and AUC_{∞} of PHA-022121 was unknown. Though, assuming an intra-subject CV of no more

	than 25%, a sample size of 12 subjects was considered sufficient to detect, with at least 80% power, a 30% increase in C_{max} or AUC_{∞} of PHA-022121 after co-administration with itraconazole, compared to administration of the PHA-022121 alone, using a 2-sided test with alpha=0.10. Two (2) additional subjects were added to allow for possible dropouts.
Safety parameters	: Descriptive statistics
PK parameters	: Descriptive statistics for all relevant PK parameters: n, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and % coefficient of variation (CV%)

Results

Subject Disposition

A total of 31 subjects were screened, and 13 of these subjects were included in the study (Table S-1). No subjects were withdrawn or dropped out during the course of the study. All 13 subjects included in the study completed the study as per protocol.

Fourteen (14) subjects were originally planned to enter the study. However, the study was put on hold due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) pandemic. All 13 subjects who were dosed at that time had evaluable PK data. As this was more than the 12 evaluable subjects required to meet the study objectives, the study was considered complete and no additional subjects were included in the study.

The disposition of the participants is given below.

Table S-1 Summary of Subject Disposition

	Number of Participants
Screened volunteers	31
Screening failures	11
Vital signs	4
BMI	3
Medical history	2
Physical examination	1
Lab values	1
Approved but not dosed	7
Rejected in clinical research center	4
Personal reasons	2
Not turned up	1
	Total
Participants receiving study drug	13
Completed participants	13
Safety Analysis Set	13
Pharmacokinetic Concentration Set	13
Pharmacokinetic Analysis Set	13

Demographics

A total of 12 male subjects and 1 female subject between 18 and 60 years of age and with a BMI between 20.8 kg/m^2 and 28.9 kg/m^2 participated in the study. A total of 11 subjects were White and 2 subjects were of

multiple race (1 subject was White+Black or African American and 1 subject was White+Asian). One (1) out of 13 subjects was of Hispanic or Latino ethnicity.

Safety

A total of 19 treatment-emergent adverse events (TEAEs) were reported by 10 (76.9%) subjects. Of these, 4 were reported by 4 subjects (30.8%) after administration of PHA-022121 alone, 12 were reported by 9 subjects (69.2%) after administration of itraconazole alone, and 3 were reported by 2 subjects (15.4%) after administration of PHA-022121 combined with itraconazole.

A total of 3 TEAEs were considered to be possibly related to itraconazole; one subject reported pruritis and abdominal pain after administration of itraconazole alone, and 1 subject reported abdominal pain after administration of itraconazole alone. None of the TEAEs was considered to be related to administration of PHA-022121 alone or in combination with itraconazole as judged by the Investigator.

All 19 TEAEs reported during the study were of mild severity (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1). None of the TEAEs were of Grade 2 or higher.

Most frequently reported TEAEs (reported by at least 2 subjects overall) were in the system organ class (SOC) of:

- Skin and Subcutaneous Tissue Disorders (6 TEAEs reported by 6 subjects [46.2%] overall; 1 TEAE reported by 1 subject [7.7%] after administration of PHA-022121 alone, 5 TEAEs reported by 5 subjects [38.5%] after administration of itraconazole alone, and no TEAEs were reported after administration of PHA-022121 combined with itraconazole).
- Gastrointestinal Disorders (7 TEAEs reported by 4 subjects [30.8%] overall; 1 TEAE reported by 1 subject [7.7%] after administration of PHA-022121 alone, 5 TEAEs reported by 4 subjects [30.8%] after administration of itraconazole alone, and 1 TEAE reported by 1 subject [7.7%] after administration of PHA-022121 combined with itraconazole).
- Respiratory, thoracic and mediastinal disorders (2 TEAEs reported by 2 subjects [15.4%] overall; 1 TEAE reported by 1 subject [7.7%] after administration of PHA-022121 alone, no TEAEs were reported after administration of itraconazole alone, and 1 TEAE reported by 1 subject [7.7%] after administration of PHA- 022121 combined with itraconazole).

Most frequently reported TEAEs (reported by at least 2 subjects overall) by preferred term (PT) were:

- Dry skin (4 events reported by 4 subjects [30.8%] overall; 1 event reported by 1 subject [7.7%] after administration of PHA-022121 alone, 3 events reported by 3 subjects [23.1%] after administration of itraconazole alone, and no events reported after administration of PHA-022121 combined with itraconazole).
- Diarrhea (3 events reported by 3 subjects [23.1%] overall; 1 event reported by 1 subject [7.7%] after administration of PHA-022121 alone, 2 events reported by 2 subjects [15.4%] after administration of itraconazole alone, and no events reported after administration of PHA-022121 combined with itraconazole).
- Abdominal pain (2 events reported by 2 subjects [15.4%] overall; no events reported after administration of PHA-022121 alone, 2 events reported by 2 subjects [15.4%] after administration of itraconazole alone, and no events reported after administration of PHA-022121 combined with itraconazole).
- Dry throat (2 events reported by 2 subjects [15.4%] overall; 1 event reported by 1 subject [7.7%] after administration of PHA-022121 alone; no events reported after administration of itraconazole alone, and 1 event reported by 1 subject [7.7%] after administration of PHA-022121 combined with itraconazole).

Other TEAEs that were reported only once during the study were dermatitis contact, pruritus, dyspepsia, frequent bowel movements, feeling cold, arthralgia, headache, insomnia.

There were no deaths or serious AEs reported during the study, and there were no AEs that led to withdrawal from the study. All TEAEs were transient and resolved without sequelae by follow-up.

There were no clinically relevant findings with respect to clinical laboratory, vital signs, ECG, or physical examinations.

Overall, administration of PHA-022121 alone or in combination with itraconazole appeared to be well tolerated in a group of healthy subjects.

Conclusions

Pharmacokinetics

- PHA-022121:
  Co-administration of itraconazole led to a significant decrease in the rate of elimination of PHA-022121 when administered after a standard meal, resulting in a 2.2-fold higher C_{max} and a 12-fold higher AUC_{last}. Median t_{max} shifted from 1.00 hour when PHA-022121 was taken alone to 3.00 hours when PHA-022121 was co-administered with itraconazole. The mean $t_{1/2}$ of PHA-022121 increased from 4.31 hours when PHA-022121 was administered alone to 41.3 hours when PHA-022121 was co-administered with itraconazole.
- M2-D:
  Administration of a single 12 mg dose of PHA-022121 after a standard meal in the presence of itraconazole resulted in a 25% lower mean value for C_{max} and in a 4 times higher mean value for AUC_{last} of M2-D compared to a single 12 mg PHA-022121 intake without itraconazole.
  Median t_{max} shifted from 2.00 hours when PHA-022121 was taken alone to 24.03 hours when PHA-022121 was co-administered with itraconazole.
- The M2-D mean terminal half-life was 4.75 hours when PHA-022121 was taken alone. The half-life of M2-D could not be accurately determined when PHA-022121 was co-administered with itraconazole.

Safety

- A single oral dose of 12 mg PHA-022121 alone or combined with itraconazole was well tolerated in healthy subjects.
- There were no clinically relevant findings with respect to clinical laboratory, vital signs, ECG, or physical examinations.