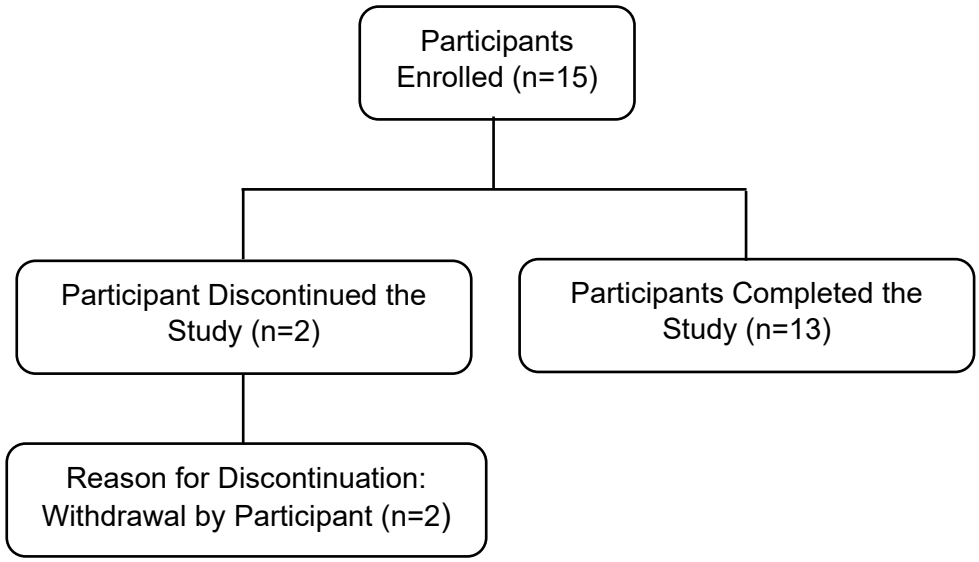
Study Title: A Phase I, open-label, fixed-sequence study to evaluate the effect of a single dose of cyclosporine on the single-dose pharmacokinetics of pralsetinib in healthy subjects

Participants Flow



Baseline Characteristics

Table 1: Baseline Characteristics

Demographic and Baseline Variable	Statistics	Pralsetinib 200 milligrams (mg) (N=15)
Age (years)	n Median Minimum - Maximum	15 42.0 23 - 55
Sex (percentage of participants) Male Female	 n (%) n (%)	 13 (86.7) 2 (13.3)
Race (percentage of participants) White Black or African American	 n (%) n (%)	 9 (60.0) 6 (40.0)
Ethnicity (percentage of participants) Not Hispanic or Latino Hispanic or Latino	 n (%) n (%)	 8 (53.3) 7 (46.7)

Outcome measures

Primary Outcome Measures:

1. Maximum plasma concentration (Cmax) of pralsetinib when administered alone and in combination with cyclosporine measured using noncompartmental methods of analysis at pre-dose and 0.5 hour (h), 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144 h, 192 h, 216 h, 240 h (cyclosporine arm only) and 264 h (cyclosporine arm only) post dose

   Analysis population description: Pharmacokinetics (PK) population included all participants who received at least 1 dose of study drug and had at least 1 evaluable post dose PK sample. Overall number analysed is the number of participants with data available for analysis.

   Table 2: Summarized Pralsetinib Cmax

Treatment	Number of Participants Analysed	Geometric Mean	% Geometric Coefficient of Variation
Pralsetinib 200 mg	15	648	53.6
Pralsetinib 200 mg + Cyclosporine 600 mg	14	955	59.8

Unit of measurement: nanograms per millilitre (ng/mL)

Statistics: Cmax

Treatment	Number of Participants Analysed	Geometric Least Squares Mean (GLSM)	Geometric Mean Ratio (GMR) % (90% CI)	Within-Subject Coefficient of Variation (CV)
Pralsetinib 200 mg	15	648	148 (109, 201)	49.2
Pralsetinib 200 mg + Cyclosporine 600 mg	14	959		

2. Time to maximum concentration (tmax) of pralsetinib when administered alone and in combination with cyclosporine measured using noncompartmental methods of analysis at pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144

h, 192 h, 216 h, 240 h (cyclosporine arm only) and 264 h (cyclosporine arm only) post dose

Analysis population description: PK population included all participants who received at least 1 dose of study drug and had at least 1 evaluable post dose PK sample. Overall number analysed is the number of participants with data available for analysis.

Table 3: Summarized Pralsetinib tmax

Treatment	Number of Participants Analysed	Median	Minimum and Maximum
Pralsetinib 200 mg	15	3.00	2.00 - 3.23
Pralsetinib 200 mg + Cyclosporine 600 mg	14	4.00	3.00 – 8.00

Unit of measurement: h

3. Area under the concentration-time curve (AUC) from hour 0 to the time of the last quantifiable concentration (AUC0-t) of pralsetinib when administered alone and in combination with cyclosporine measured using noncompartmental method of analysis at pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144 h, 192 h, 216 h, 240 h (cyclosporine arm only) and 264 h (cyclosporine arm only) post dose

   Analysis population description: PK population included all participants who received at least 1 dose of study drug and had at least 1 evaluable post dose PK sample. Overall number analysed is the number of participants with data available for analysis.

Table 4: Summarized Pralsetinib AUC0-t

Treatment	Number of Participants Analysed	Geometric Mean	% Geometric Coefficient of Variation
Pralsetinib 200 mg	15	9840	65.1
Pralsetinib 200 mg + Cyclosporine 600 mg	13	16900	71.6

Unit of measurement: hours*nanograms per millilitre (h*ng/mL)

Statistics: AUC0-t

Treatment	Number of Participants Analysed	GLSM	GMR % 90% CI	Within-Subject CV
Pralsetinib 200 mg	15	9840	179 (131, 245)	48.0

Pralsetinib 200 mg + Cyclosporine 600 mg	13	17600		

4. AUC from Hour 0 to “192,” where “192” is a common nominal timepoint across participants of pralsetinib when administered alone and in combination with cyclosporine measured using noncompartmental method of analysis at pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144 h, and 192 h post dose

   Analysis population description: PK population included all participants who received at least 1 dose of study drug and had at least 1 evaluable post dose PK sample. Overall number analysed is the number of participants with data available for analysis.

Table 5: Summarized Pralsetinib AUC0-192

Treatment	Number of Participants Analysed	Geometric Mean	% Geometric Coefficient of Variation
Pralsetinib 200 mg	15	9940	64.2
Pralsetinib 200 mg + Cyclosporine 600 mg	14	17900	71.5

Statistics: AUC0-192

Treatment	Number of Participants Analysed	GLSM	GMR % (90% CI)	Within-Subject CV
Pralsetinib 200 mg	15	9940	181 (136, 241)	45.3
Pralsetinib 200 mg + Cyclosporine 600 mg	14	18000		

5. AUC from time zero to infinity (AUC0-∞) of pralsetinib when administered alone and in combination with cyclosporine measured using noncompartmental methods of analysis at pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144 h, 192 h, 216 h, 240 h (cyclosporine arm only) and 264 h (cyclosporine arm only) post dose

   Analysis population description: PK population included all participants who received at least 1 dose of study drug and had at least 1 evaluable post dose PK sample. Overall number analysed is the number of participants with data available for analysis.

Table 6: Summarized Pralsetinib AUC0-∞

Treatment	Number of Participants Analysed	Geometric Mean	% Geometric Coefficient of Variation
Pralsetinib 200 mg	15	9970	64.4
Pralsetinib 200 mg + Cyclosporine 600 mg	14	18000	71.6

Unit of measurement: h*ng/mL

Statistics: AUC0-∞

Treatment	Number of Participants Analysed	GLSM	GMR % (90% CI)	Within-Subject CV
Pralsetinib 200 mg	15	9970	181 (136, 241)	45.4
Pralsetinib 200 mg + Cyclosporine 600 mg	14	18000		

6. Apparent terminal elimination half-life (t1/2) of pralsetinib when administered alone and in combination with cyclosporine measured using noncompartmental methods of analysis at pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 144 h, 192 h, 216 h, 240 h (cyclosporine arm only) and 264 h (cyclosporine arm only) post dose

   Analysis population description: PK population included all participants who received at least 1 dose of study drug and had at least 1 evaluable post dose PK sample. Overall number analysed is the number of participants with data available for analysis.

   Table 7: Summarized Pralsetinib t1/2

Treatment	Number of Participants Analysed	Median	Minimum and Maximum
Pralsetinib 200 mg	15	14.0	9.36- 44.4
Pralsetinib 200 mg + Cyclosporine 600 mg	14	14.3	11.3- 26.5

Secondary Outcome Measures:

1. Number of participants with treatment emergent adverse events (TEAEs) and severity of TEAEs measured using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v 5.0) from study initiation up to follow up at Day 38

   Analysis population description: Safety population included all participants who received at least 1 dose of study drug.

   Table 8: Summary of AEs

	Pralsetinib 200 mg (N=15)	**Pralsetinib 200 mg + Cyclosporine 600 mg (N=14)**
Participants with TEAEs [number (%)]	3 (20.0%)	4 (28.6%)
Participants with serious TEAEs [number (%)]	0 (0.0%)	0 (0.0%)
Grade 1 [number (%)]	3 (20.0%)	3 (21.4%)
Grade 2 [number (%)]	0 (0.0%)	1 (7.1%)
Grade 3[number (%)]	0 (0.0%)	1 (7.1%)

2. Number of participants with abnormal electrocardiogram (ECG) parameter measured using triplicate 12-lead ECG at screening, check-in (Day -1) Days 1, 2, 5, 9, 10, 11, 14, 18 and at discharge (Day 21)

   Analysis population description: Safety population included all participants who received at least 1 dose of study drug. Overall number analysed is the number of participants with data available for analysis.

   Table 9: Summary of Abnormal ECG Parameters Reported as AE

	Pralsetinib 200 mg (N=15)	**Pralsetinib 200 mg + Cyclosporine 600 mg (N=14)**
Participants with Abnormal ECG Parameters	0 (0.0%)	1 (7.1%)

Adverse Events

Table 10: Adverse Events by System Organ Class and Preferred Term

System Organ Class	Preferred Term	Pralsetinib 200 mg n (%) (N=15)	Pralsetinib 200 mg + Cyclosporine 600 mg n (%) (N=14)
Gastrointestinal disorders	Constipation	**3 (20.0%)**	**0 (0.0%)**
	Nausea	**0 (0.0%)**	**1 (7.1%)**
Investigations	Alanine aminotransferase increased	**0 (0.0%)**	**1 (7.1%)**
	Aspartate aminotransferase increased	**0 (0.0%)**	**1 (7.1%)**
Blood and lymphatic system disorders	Neutropenia	**0 (0.0%)**	**1 (7.1%)**
Cardiac disorders	Palpitations	**0 (0.0%)**	**1 (7.1%)**
Vascular disorders	Flushing	**0 (0.0%)**	**1 (7.1%)**