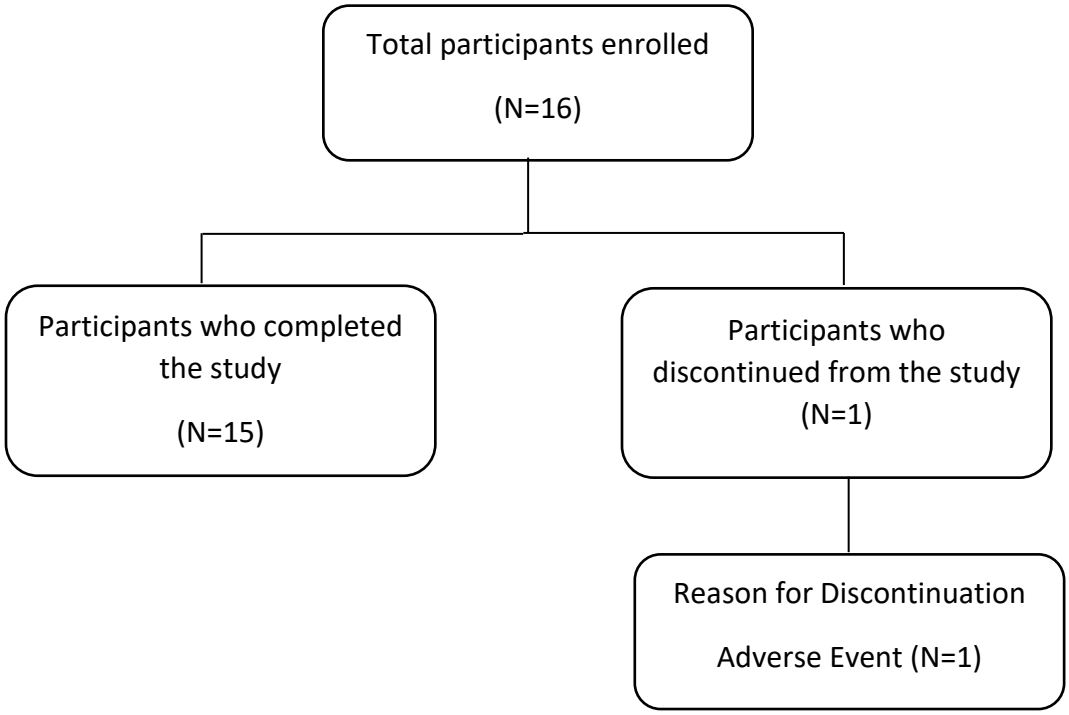
Study Title: A non-randomized, open-label, single-sequence, two-period study to investigate the effect of CYP3A inhibition on the pharmacokinetics of RO6953958 in healthy participants

Participant flow



Baseline Characteristics

Table 1 - Baseline Characteristics

Demographic and Baseline Variable	Statistics	Safety Set
Age (years)	n Mean Standard Deviation [SD]	16 33.2 10.77
Sex (participants) Female Male	 n (%) n (%)	 7 (43.8%) 9 (56.3%)
Race (participants) White Black or African American	 n (%) n (%)	 15 (93.8%) 1 (6.3%)

Ethnicity (participants) Hispanic or Latino Not Hispanic or Latino	 n (%) n (%)	 6 (37.5%) 10 (62.5%)

Treatment groups

Period 1: RO6953958 Alone – Participants received a single oral dose of RO6953958, capsule by mouth, under fed conditions on Day 1.
Period 2: RO6953958 and Itraconazole – Participants received a single oral dose of RO6953958 on Day 4 after repeated administration of itraconazole, twice a day (BID) on Day 1 and once daily (QD) on Days 2-10, under fed conditions.

Outcome Measures

Primary Outcome Measures

1. Maximum observed plasma concentration (C_{max}) of RO6953958, and its metabolites (M1, and M3) measured using non-compartmental methods

   Timeframe: Period 1: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 1, and on Days 2, 3, 4, 5, 6, 7; Period 2: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 4, and on Days 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 18

   Analysis Population Description: Pharmacokinetics (PK) population included all participants who received at least 1 dose of study treatment and who had data from at least 1 post dose sample.

   Unit of Measurement: nanogram per millilitre (ng/mL)

   Table 2 – Summarised C_{max} of RO6953958, M1, and M3

	Treatment groups					
	Period 1: RO6953958 Alone (N= 16)			**Period 2: RO6953958 and Itraconazole (N = 15)**		
Analyte	**RO6953958**	**M1**	**M3**	**RO6953958**	**M1**	**M3**

Number of Participants Analysed (n)	16	16	16	15	15	15
Geometric mean	479	202	597	776	36.0	1040
Coefficient of Variation	25.4	32.5	59.6	28.6	49.7	55.5

Statistics: Cmax (RO6953958)

Groups	Period 1: RO6953958 Alone vs. Period 2: RO6953958 and Itraconazole
Number of participants analysed	16
Geometric Least Square (LS) Mean Ratio	1.634
90% Confidence Interval (CI)	(1.471, 1.816)

Statistics: Cmax (M1)

Groups	Period 1: RO6953958 Alone vs. Period 2: RO6953958 and Itraconazole
Number of participants analysed	16
Geometric LS Mean Ratio	0.178
90% CI	(0.154, 0.206)

Statistics: Cmax (M3)

Groups	Period 1: RO6953958 Alone vs. Period 2: RO6953958 and Itraconazole

Number of participants analysed	16
Geometric LS Mean Ratio	1.737
90% CI	(1.602, 1.884)

2. Area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) of RO6953958, and its metabolites (M1, and M3) measured using non-compartmental methods

   Timeframe: Period 1: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 1, and on Days 2, 3, 4, 5, 6, 7; Period 2: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 4, and on Days 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 18

   Analysis Population Description: The PK population included all participants who received at least 1 dose of study drug and who had data from at least 1 post dose sample.

   Unit of Measurement: hour*nanogram per millilitre (h*ng/mL)

   Table 3 – Summarised $AUC_{0\text{-}inf}$ of RO6953958, M1, and M3

	Treatment groups					
	Period 1: RO6953958 Alone (N = 16)			**Period 2: RO6953958 and Itraconazole (N = 15)**		
Analyte	**RO6953958**	**M1**	**M3**	**RO6953958**	**M1**	**M3**
Number of Participants Analysed	16	16	16	15	11	15
Geometric mean	2280	1900	15900	5630	825	112000
Coefficient of Variation	49.4	48.5	67.4	65.6	82.7	63.9

Statistics: $AUC_{0\text{-}inf}$ (RO6953958)

Groups	Period 1: RO6953958 Alone vs. Period 2: RO6953958 and Itraconazole
Number of participants analysed	16
Geometric LS Mean Ratio	2.473
90% CI	(2.187, 2.797)

Statistics: AUC0-inf (M1)

Groups	Period 1: RO6953958 Alone vs. Period 2: RO6953958 and Itraconazole
Number of participants analysed	16
Geometric LS Mean Ratio	0.408
90% CI	(0.328, 0.507)

Statistics: $AUC_{0\text{-}inf}$ (M3)

Groups	Period 1: RO6953958 Alone vs. Period 2: RO6953958 and Itraconazole
Number of participants analysed	16
Geometric LS Mean Ratio	7.042
90% CI	(6.266, 7.913)

3. Area under the concentration-time curve up to last measurable concentration (AUC_{last}) of RO6953958, and its metabolites (M1, and M3) measured using non-compartmental methods

Timeframe: Period 1: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 1, and on Days 2, 3, 4, 5, 6, 7; Period 2: Predose and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose on Day 4, and on Days 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 18

Analysis Population Description: The PK set included all participants who received at least 1 dose of study drug and who had data from at least 1 post dose sample.

Unit of Measurement: h*ng/mL

Table 4 – Summarised AUC_{last} of RO6953958, M1, and M3

	Treatment groups					
	Period 1: RO6953958 Alone (N=16)			**Period 2: RO6953958 and Itraconazole (N=15)**		
Analyte	**RO6953958**	**M1**	**M3**	**RO6953958**	**M1**	**M3**
Number of Participants Analysed	16	16	16	15	15	15
Geometric mean	2250	1830	15700	5570	660	108000
Coefficient of Variation	50.0	48.8	67.4	66.0	88.9	63.6

Secondary Outcome Measures

1. Percentage of participants with adverse events and severity of AEs assessed by the investigator as mild, moderate, or severe

   Timeframe: From screening up to follow up (approximately 9 weeks)

   Analysis Population Description: The safety set included all participants who received at least 1 dose of the study treatment, whether prematurely withdrawn from the study or not.

   Unit of Measurement: percentage of participants

Table 5 – Summary of AEs

	Treatment			
	Period 1: RO6953958 Alone (N=16)	**Period 2: Itraconazole Alone (N=16)**	**Period 2: RO6953958 and Itraconazole (N=15)**	**Overall (N=16)**
Participants with Adverse events	31.3	37.5	66.7	75.0
Mild	31.3	31.3	60.0	62.5
Moderate	0.0	6.3	6.7	12.5
Severe	0.0	0.0	0.0	0.0

2. Concentrations of itraconazole and its metabolite hydroxy-itraconazole measured using non-compartmental methods

   Timeframe: Period 2: Days 2, 3, 4, 6, 8, and 10

   Analysis Population Description: The PK set included all participants who received at least 1 dose of study drug and who had data from at least 1 post dose sample. Overall number of participants analysed is the number of participants with data available for analysis.

   Unit of Measurement: milligrams per millilitre (mg/mL)

   Table 6 – Summary of concentration of Itraconazole in Period 2

Period 2: RO6953958 and Itraconazole	Day 2	Day 3	Day 4	Day 6	Day 8	Day 10
Number of Participants Analysed	16	16	16	15	15	15
Geometric Mean	173	119	173	218	283	346

Coefficient of Variation	28.8	35.5	19.2	20.8	24.6	18.8

Table 7 – Summary of concentration of hydroxy-itraconazole in Period 2

Period 2: RO6953958 and Itraconazole	Day 2	Day 3	Day 4	Day 6	Day 8	Day 10
Number of participants analysed	16	16	16	15	15	15
Geometric Mean	426	445	552	649	771	951
Coefficient of Variation	22.4	26.7	15.2	22.0	25.9	24.7

Adverse Events

Adverse events were checked in all participants who received at least one dose of study treatment.

Table 8 - Adverse Events by System Organ Class and Preferred Term

System Organ Class	Preferred Term	Period 1: RO6953958 Alone n (%) (N=16)	Period 2: Itraconazole Alone n (%) (N=16)	Period 2 RO6953958 and Itraconazole n (%) (N=15)	Overall (N=16)
Cardiac disorders	Palpitations	**1 (6.3%)**	**0**	**0**	**1 (6.3)**
Eye disorders	Blepharitis	**0**	**1 (6.3%)**	**0**	**1 (6.3)**
	Visual impairment	**1 (6.3%)**	**0**	**0**	**1 (6.3)**
Gastrointestinal disorders	Abdominal pain	**1 (6.3%)**	**1 (6.3%)**	**0**	
	Abdominal pain upper	**0**	**1 (6.3%)**	**0**	**1 (6.3)**
	Aphthous ulcer	**1 (6.3%)**	**0**	**1 (6.7%)**	**1 (6.3)**
	Constipation	**0**	**1 (6.3%)**	**0**	**1 (6.3)**

	Nausea	**0**	**0**	**1 (6.7%)**	**1 (6.3)**
	Vomiting	**0**	**0**	**1 (6.7%)**	**1 (6.3)**
General disorders and administration site conditions	Chest pain	**0**	**1 (6.3%)**	**0**	**1 (6.3)**
	Oedema	**0**	**1 (6.3%)**	**0**	**1 (6.3)**
	Sensation of foreign body	**0**	**1 (6.3%)**	**0**	**1 (6.3)**
Infections and infestations	COVID-19	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
Injury, poisoning and procedural complications	Ligament sprain	**1 (6.3%)**	**0**	**0**	**1 (6.3%)**
Musculoskeletal and connective tissue disorders	Back pain	**0**	**1 (6.3%)**	**1 (6.7%)**	**2 (12.5)**
	Myalgia	**0**	**0**	**2 (13.3)**	**2 (12.5)**
Nervous system disorders	Headache	**0**	**2 (12.5)**	**5 (33.3)**	**7 (43.8)**
	Presyncope	**0**	**0**	**2 (13.3)**	**2 (12.5)**
	Dizziness	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
	Sleep paralysis	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
	Somnolence	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
Psychiatric disorders	Abnormal dreams	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
	Insomnia	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
Renal and urinary disorders	Dysuria	**1 (6.3%)**	**0**	**0**	**1 (6.3%)**

Respiratory, thoracic and mediastinal disorders	Epistaxis	**1 (6.3%)**	**1 (6.3%)**	**0**	**2 (12.5)**
	Sinus congestion	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**
Skin and subcutaneous tissue disorders	Dermatitis	**0**	**2 (12.5)**	**1 (6.7%)**	**2 (12.5)**
	Dermatitis acneiform	**1 (6.3%)**	**0**	**0**	**1 (6.3%)**
Vascular disorders	Hot flush	**0**	**1 (6.3%)**	**0**	**1 (6.3%)**
	Orthostatic hypotension	**0**	**0**	**1 (6.7%)**	**1 (6.3%)**