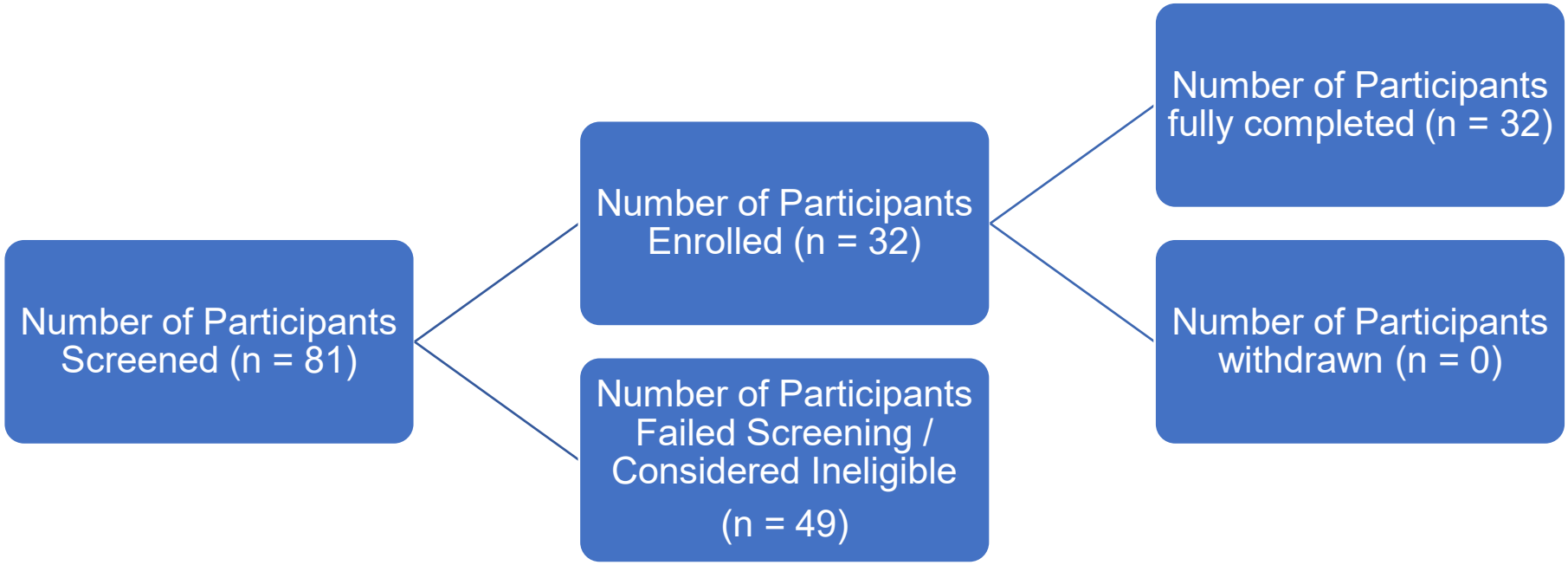
Participant Flow



Baseline Characteristics

Table 11.2.1 Summary of Participant Demographics (Safety Set)

Parameter	Statistic	40 mg IOA-244			80 mg IOA-244			Overall (N=32)
		Males (N=8)	Females (N=8)	Overall (N=16)	Males (N=10)	Females (N=6)	Overall (N=16)	
Height (m)	n	8	8	16	10	6	16	32
	Mean	1.803	1.613	1.708	1.754	1.640	1.711	1.709
	SD	0.0696	0.0489	0.1140	0.0750	0.0494	0.0862	0.0995
Weight (kg)	n	8	8	16	10	6	16	32
	Mean	89.93	64.69	77.31	78.68	69.28	75.16	76.23
	SD	10.445	7.128	15.636	13.249	7.788	12.149	13.817
BMI (kg/m^2)	n	8	8	16	10	6	16	32
	Mean	27.615	24.858	26.236	25.448	25.705	25.544	25.890
	SD	1.9854	2.3353	2.5323	2.7976	1.9109	2.4351	2.4689

Parameter	Statistic	40 mg IOA-244			80 mg IOA-244			Overall (N=32)
		Males (N=8)	Females (N=8)	Overall (N=16)	Males (N=10)	Females (N=6)	Overall (N=16)	
Age at Informed Consent (yrs)	n	8	8	16	10	6	16	32
	Mean	35.3	40.1	37.7	39.1	43.8	40.9	39.3
	SD	7.69	13.18	10.73	8.63	11.34	9.65	10.17
Ethnicity:								
Not Hispanic or Latino	n (%)	8 (100.0)	8 (100.0)	16 (100.0)	10 (100.0)	6 (100.0)	16 (100.0)	32 (100.0)
Race:								
Black or African American	n (%)	0	0	0	2 (20.0)	0	2 (12.5)	2 (6.3)
Asian	n (%)	0	0	0	1 (10.0)	0	1 (6.3)	1 (3.1)
White	n (%)	6 (75.0)	8 (100.0)	14 (87.5)	6 (60.0)	6 (100.0)	12 (75.0)	26 (81.3)
Mixed	n (%)	2 (25.0)	0	2 (12.5)	1 (10.0)	0	1 (6.3)	3 (9.4)

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
Percentages calculated from the number of participants in the Safety Set within a treatment and gender.
Data Source: Table 14.1.2.1

Outcome Measures

Table 11.4.1 Summary of Derived Plasma Roginolisib PK Parameters (PK Set)

Treatment	Summary Statistic[1]	C_{max} (ng/mL)	t_{max} (h)	C_{last} (ng/mL)	t_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$t_{1/2}$ (h)	λ_z (1/h)	CL/F (L/h)	Vz/F (L)	R_{Cmax} fed:fasted	R_{AUCinf} fed:fasted
40 mg IOA-244 Fasted (N=16)	Mean	2330	N/A	72.3	N/A	49800	28200	53100	28.3	0.0287	0.988	34.6		
	SD	676	N/A	59.7	N/A	25500	10300	28500	12.1	0.0123	0.593	13.7		
	Geo. Mean	2230	N/A	60.5	N/A	44000	26400	46700	N/A	0.0265	0.857	32.3		
	Geo. CV%	30.8	N/A	59.7	N/A	57.1	39.3	58.0	N/A	42.6	58.0	38.9		
	Min	1340	0.500	30.6	48.0	14600	12200	15600	11.9	0.0108	0.296	15.8		
	Median	2350	1.00	56.9	120	47800	26900	53800	27.7	0.0251	0.743	31.3		
	Max	3410	2.00	280	123	120000	48100	135000	63.9	0.0585	2.56	68.9		
40 mg IOA-244 Fed (N=16)	Mean	1750	N/A	65.7	N/A	47200	25900	49700	24.9	0.0319	1.03	31.8	0.766	0.960
	SD	469	N/A	36.3	N/A	22100	8870	23800	7.73	0.0149	0.604	8.96	0.105	0.166
	Geo. Mean	1700	N/A	59.5	N/A	42100	24500	44200	N/A	0.0295	0.905	30.7	0.760	0.947
	Geo. CV%	26.5	N/A	44.7	N/A	55.5	36.9	55.7	N/A	39.3	55.7	29.1	13.4	17.4
	Min	1130	2.00	34.1	48.0	14400	11700	15300	9.84	0.0196	0.403	19.3	0.630	0.678
	Median	1610	4.00	55.9	120	47600	23400	50300	24.9	0.0279	0.795	30.5	0.725	0.951
	Max	2780	6.00	178	120	90700	43000	99200	35.3	0.0704	2.61	50.8	0.977	1.34
80 mg IOA-244 Fasted (N=16)	Mean	3560	N/A	87.9	N/A	78400	45300	82300	27.5	0.0270	1.10	41.2		
	SD	596	N/A	69.4	N/A	28600	10100	31900	7.36	0.00734	0.357	12.3		
	Geo. Mean	3520	N/A	68.1	N/A	74100	44300	77300	N/A	0.0261	1.04	39.6		
	Geo. CV%	16.5	N/A	80.9	N/A	34.9	21.4	37.1	N/A	27.6	37.1	28.7		
	Min	2720	0.500	30.6	96.0	43100	31200	43900	17.1	0.0167	0.527	25.3		
	Median	3450	1.00	51.8	120	64200	42200	66400	26.8	0.0259	1.20	37.6		
	Max	4890	4.00	221	120	142000	68700	152000	41.6	0.0406	1.82	69.0		
80 mg IOA-244 Fed (N=16)	Mean	2860	N/A	94.4	N/A	85100	46000	89400	26.8	0.0276	0.973	35.4	0.813	1.13
	SD	422	N/A	75.6	N/A	23500	7050	27400	7.67	0.00683	0.290	6.00	0.123	0.224
	Geo. Mean	2830	N/A	74.9	N/A	82100	45500	85700	N/A	0.0267	0.933	34.9	0.804	1.11
	Geo. CV%	15.5	N/A	74.8	N/A	28.3	16.0	30.8	N/A	26.9	30.8	17.3	14.7	20.6
	Min	1970	4.00	35.6	96.0	49400	31300	50600	17.8	0.0150	0.540	24.1	0.650	0.744
	Median	2870	6.00	51.5	120	82700	46800	84900	23.8	0.0291	0.942	35.5	0.813	1.11
	Max	3710	6.00	317	120	130000	60100	148000	46.2	0.0389	1.58	48.6	1.09	1.51

[1] n = 16 for all parameters.
Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
LLOQ = 30 ng/mL. Values below LLOQ imputed as 0 at pre-first dose and for time points prior to the first quantifiable concentration, and as LLOQ/2 for subsequent post-dose time points.
LLOQ = lower limit of quantitation, N/A = not applicable. **Data Source:** Table 14.4.2.1

Table 11.4.2 Statistical Analysis of Bioavailability - Plasma Roginolisib C_{max} and AUC PK Data - Food Effect (PK Set)

Treatment	Parameter	Number in Comparison	Geometric LSMeans (95% CI)		Geometric LSMean Ratio (90% CI)
			Fasted (N=32)	Fed (N=32)	Fed / Fasted
40 mg IOA-244 (N=16)	C_{max} (ng/mL)	16	2230 (2150, 2320)	1700 (1630, 1760)	0.760 (0.726, 0.795)
	AUC_{0-t} (h*ng/mL)	16	44000 (41700, 46400)	42100 (39900, 44400)	0.956 (0.898, 1.02)
	AUC_{0-inf} (h*ng/mL)	16	46700 (44100, 49400)	44200 (41700, 46800)	0.947 (0.886, 1.01)
80 mg IOA-244 (N=16)	C_{max} (ng/mL)	16	3520 (3330, 3720)	2830 (2680, 2990)	0.804 (0.753, 0.859)
	AUC_{0-t} (h*ng/mL)	16	74100 (69400, 79100)	82100 (76900, 87600)	1.11 (1.03, 1.20)
	AUC_{0-inf} (h*ng/mL)	16	77300 (71900, 83000)	85700 (79800, 92000)	1.11 (1.02, 1.20)

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
Results obtained using an ANOVA with fixed effects of treatment, period, sequence and subject nested within sequence.
ANOVA = analysis of variance
Data Source: Table 14.4.2.5

Table 11.4.3 Statistical Analysis of Plasma Roginolisib T_{max} PK Data (PK Set)

Treatment	Parameter	Number in Comparison	Median (Min, Max)		Median Difference (95% CI[a])	P-Value for Difference[b]
			Fasted (N=32)	Fed (N=32)	Fed vs Fasted	
40 mg IOA-244 (N=16)	t_{max} (h)	16	1.00 (0.500, 2.00)	4.00 (2.00, 6.00)	4.00 (3.00, 5.00)	<.0001
80 mg IOA-244 (N=16)	t_{max} (h)	16	1.00 (0.500, 4.00)	6.00 (4.00, 6.00)	4.00 (3.00, 5.00)	<.0001

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
[a] Confidence interval obtained using Hodges-Lehmann method.
[b] p-value obtained using the Wilcoxon Signed Rank test.
Data Source: Table 14.4.2.6

Table 11.4.4 Statistical Analysis of Plasma Roginolisib Dose Proportionality (PK Set)

Fed/Fasted	Dose-Normalised Parameter	Geometric LSMeans (95% CI) [Number of Observations]		Geometric LSMean Ratio (90% CI)
		40 mg IOA-244 (N=16)	80 mg IOA-244 (N=16)	80 mg IOA-244/ 40 mg IOA-244
Fasted (N=32)	C_{max}/D (ng/mL/mg)	55.8 (49.3, 63.1) [16]	44.0 (38.9, 49.8) [16]	0.788 (0.682, 0.912)
	AUC_{0-t}/D (h*ng/mL/mg)	1100 (877, 1380) [16]	926 (738, 1160) [16]	0.842 (0.644, 1.10)
	AUC_{0-inf}/D (h*ng/mL/mg)	1170 (924, 1470) [16]	966 (765, 1220) [16]	0.828 (0.629, 1.09)
Fed (N=32)	C_{max}/D (ng/mL/mg)	42.4 (38.0, 47.3) [16]	35.4 (31.7, 39.5) [16]	0.835 (0.734, 0.949)
	AUC_{0-t}/D (h*ng/mL/mg)	1050 (851, 1300) [16]	1030 (830, 1270) [16]	0.976 (0.761, 1.25)
	AUC_{0-inf}/D (h*ng/mL/mg)	1110 (890, 1370) [16]	1070 (862, 1330) [16]	0.969 (0.751, 1.25)

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
Results obtained using an ANOVA on log-transformed dose-normalised parameters with a fixed effect of dose.
ANOVA = analysis of variance
Data Source: Table 14.4.2.7

Table 11.4.5 Summary of Derived Plasma Roginolisib (Free) PK Parameters (PK Set)

Treatment	Summary Statistic[1]	$C_{max,free}$ (ng/mL)	$AUC_{0-t,free}$ (h*ng/mL)	$AUC_{0-inf,free}$ (h*ng/mL)
40 mg IOA-244 Fasted (N=16)	Mean	78.1	1590	1690
	SD	12.2	476	515
	Geo. Mean	77.2	1520	1610
	Geo. CV%	15.5	33.1	32.8
	Min	58.2	858	921
	Median	78.9	1630	1700
	Max	107	2520	2830
40 mg IOA-244 Fed (N=16)	Mean	63.9	1620	1700
	SD	11.9	444	464
	Geo. Mean	62.7	1560	1640
	Geo. CV%	20.6	31.7	31.5
	Min	35.0	765	811
	Median	63.8	1640	1710
	Max	88.4	2230	2320
80 mg IOA-244 Fasted (N=16)	Mean	135	2890	3040
	SD	24.8	763	890
	Geo. Mean	133	2800	2920
	Geo. CV%	18.4	27.0	29.5
	Min	101	1820	1860
	Median	130	2890	3030
	Max	174	4460	5000
80 mg IOA-244 Fed (N=16)	Mean	106	3150	3310
	SD	16.9	809	934
	Geo. Mean	105	3050	3190
	Geo. CV%	14.5	26.2	28.6
	Min	85.3	1840	1890
	Median	100	3040	3130
	Max	158	4850	5040

[1] n = 16 for all parameters.
Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
LLOQ = 30 ng/mL. Values below LLOQ imputed as 0 at pre-first dose and for time points prior to the first quantifiable concentration, and as LLOQ/2 for subsequent post-dose time points.
Free PK parameters derived by multiplying the plasma PK parameters by the unbound fraction (fu)/100.
LLOQ = lower limit of quantitation, PK = pharmacokinetic
Data Source: Table 14.4.2.2

Table 11.4.6 Summary of Derived Urine IOA-244 PK Parameters (PK Set)

Treatment	Summary Statistic[1]	$Ae_{(0-120)}$ (ng)	$fe_{(0-120)}$ (%)	CL_R (L/h)
40 mg IOA-244 Fasted (N=16)	Mean	10100000	25.3	0.274
	SD	2940000	7.34	0.129
	Geo. Mean	9780000	24.5	0.250
	Geo. CV%	27.3	27.3	45.2
	Min	6370000	15.9	0.127
	Median	9160000	22.9	0.239
	Max	17300000	43.2	0.576
40 mg IOA-244 Fed (N=16)	Mean	10600000	26.4	0.312
	SD	2100000	5.24	0.141
	Geo. Mean	10300000	25.8	0.284
	Geo. CV%	22.1	22.1	46.9
	Min	6250000	15.6	0.143
	Median	11100000	27.9	0.307
	Max	13800000	34.6	0.628
80 mg IOA-244 Fasted (N=16)	Mean	19100000	23.9	0.302
	SD	4720000	5.90	0.0645
	Geo. Mean	18600000	23.2	0.296
	Geo. CV%	25.2	25.2	21.1
	Min	12300000	15.3	0.211
	Median	18300000	22.9	0.294
	Max	29200000	36.5	0.442
80 mg IOA-244 Fed (N=16)	Mean	21600000	27.0	0.318
	SD	5510000	6.88	0.0825
	Geo. Mean	20900000	26.1	0.306
	Geo. CV%	28.7	28.7	29.2
	Min	12000000	15.0	0.180
	Median	22900000	28.7	0.318
	Max	29900000	37.3	0.445

[1] n = 16 for all parameters.
Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
LLOQ = 3 ng/mL. Values below LLOQ imputed as 0.
LLOQ = lower limit of quantitation
Data Source: Table 14.4.2.3

Table 11.4.7 Summary of Derived Faecal Roginolisib PK Parameters (PK Set)

Treatment	Summary Statistic[1]	$Aef_{(0\text{-}120)}$ (ng)	$fef_{(0\text{-}120)}$ (%)
40 mg IOA-244 Fasted (N=16)	Mean	136000	0.341
	SD	84800	0.212
	Geo. Mean	98400	0.246
	Geo. CV%	129.8	129.8
	Min	11500	0.0288
	Median	144000	0.359
	Max	295000	0.737
40 mg IOA-244 Fed (N=16)	Mean	134000	0.335
	SD	93500	0.234
	Geo. Mean	107000	0.269
	Geo. CV%	117.2	117.2
	Min	0.00	0.00
	Median	126000	0.315
	Max	303000	0.757
80 mg IOA-244 Fasted (N=16)	Mean	302000	0.377
	SD	245000	0.306
	Geo. Mean	191000	0.239
	Geo. CV%	170.8	170.8
	Min	15100	0.0189
	Median	251000	0.313
	Max	860000	1.07
80 mg IOA-244 Fed (N=16)	Mean	268000	0.335
	SD	237000	0.296
	Geo. Mean	172000	0.215
	Geo. CV%	146.8	146.8
	Min	21000	0.0263
	Median	201000	0.251
	Max	818000	1.02

[1] n = 16 for all parameters.
Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
LLOQ = 30 ng/mL. Values below LLOQ imputed as 0.
LLOQ = lower limit of quantitation
Data Source: Table 14.4.2.4

Table 11.4.8 Summary of CD63 Basophil Activation Percentage Inhibition Derived PD Parameters (PD Set)

Treatment	Summary Statistic[1]	E_{max} (%)	t_{Emax} (h)	E_{min} (%)	$t_{above\ 50\%}$ (%)	$AUEC_{0-24}$ (h*%)	$AUEC_{0-t}$ (h*%)
40 mg IOA-244 Fasted (N=16)	n	15	15	15	15	15	15
	Mean	36.86	N/A	-2.39	N/A	436.348	707.483
	SD	16.790	N/A	4.348	N/A	270.0556	501.2668
	CV%	45.6	N/A	-181.7	375	61.89	70.85
	Min	8.4	1	-12.0	0	130.30	95.10
	Median	39.30	2.0	0.00	0.0	409.717	760.403
	Max	71.2	8	0.0	5	928.58	1716.01
40 mg IOA-244 Fed (N=16)	n	16	16	16	16	16	16
	Mean	30.59	N/A	-5.59	N/A	393.948	762.617
	SD	15.912	N/A	14.680	N/A	289.4528	679.3603
	CV%	52.0	N/A	-262.4	400	73.47	89.08
	Min	7.3	1	-59.8	0	-164.68	24.92
	Median	30.85	4.0	-1.00	0.0	388.384	580.066
	Max	67.8	8	0.0	12	1073.85	2713.77
80 mg IOA-244 Fasted (N=16)	n	16	16	16	16	16	15
	Mean	65.61	N/A	-6.50	N/A	999.975	2056.031
	SD	26.157	N/A	19.727	N/A	647.4958	2153.8452
	CV%	39.9	N/A	-303.5	173	64.75	104.76
	Min	0.0	0	-79.8	0	0.00	344.80
	Median	66.60	1.0	0.00	5.4	923.305	1475.709
	Max	100.0	6	0.0	99	2350.00	7150.00
80 mg IOA-244 Fed (N=16)	n	16	16	16	16	16	15
	Mean	57.63	N/A	-2.24	N/A	995.626	2060.962
	SD	27.453	N/A	4.504	N/A	619.4171	1745.5716
	CV%	47.6	N/A	-200.7	167	62.21	84.70
	Min	0.0	0	-13.4	0	0.00	64.14
	Median	55.75	4.0	0.00	1.5	864.425	1336.727
	Max	100.0	8	0.0	99	2350.00	7150.00

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
LLOQ - 30 ng/mL. BLQ values imputed as 0.
The n of 15 for the 40 mg IOA-244 Fasted treatment is because it was not possible to calculate inhibition results for Participant 019 Period 1 due to missing baseline data
BLQ = below the limit of quantification, LLOQ = lower limit of quantitation, N/A = Not applicable. **Data Source:** Table 14.5.2.1

Adverse Events

There were no severe AEs, SAEs, events leading to death or withdrawal during the study. A total of 9 TEAEs were reported by 6 (18.8%) participants following oral doses of IOA-244. All events were mild or moderate and considered not related to study drug. The most commonly occurring event was headache, reported by 4 (12.5%) participants across the study. Review of the TEAE profiles demonstrated a low incidence of TEAEs, with no clear food or dose-related changes/trends following study drug.

Table 12.2.1 Overall Summary of TEAEs by Severity and Relationship (Safety Set)

	40 mg IOA-244			80 mg IOA-244			Total Across Study (N=32)
	Fasted (N=16)	Fed (N=16)	Overall (N=16)	Fasted (N=16)	Fed (N=16)	Overall (N=16)	
Number of TEAEs	2	2	4	1	4	5	9
Number of Study Drug-Related TEAEs[a]	0	0	0	0	0	0	0
Number (%) of participants reporting at least one:							
TEAE	1 (6.3)	2 (12.5)	3 (18.8)	1 (6.3)	3 (18.8)	3 (18.8)	6 (18.8)
Serious TEAE	0	0	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0	0
Number (%) of participants with TEAE by severity:							
Mild	1 (6.3)	0	1 (6.3)	1 (6.3)	2 (12.5)	2 (12.5)	3 (9.4)
Moderate	0	2 (12.5)	2 (12.5)	0	1 (6.3)	1 (6.3)	3 (9.4)
Severe	0	0	0	0	0	0	0
Number (%) of participants with TEAE by relationship to study drug:							
Reasonable Possibility	0	0	0	0	0	0	0
No Reasonable Possibility	1 (6.3)	2 (12.5)	3 (18.8)	1 (6.3)	3 (18.8)	3 (18.8)	6 (18.8)

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
A participant with multiple adverse events is counted only once at the maximum level of severity or the strongest relationship to study drug within a treatment.
Percentages calculated from the number of participants in the Safety Set within a treatment.
[a] Study Drug-Related defined as a causality of Reasonable Possibility.
TEAE = treatment emergent adverse event
Data Source: Table 14.3.1.1

Table 12.2.2 TEAEs in each Treatment Group by System Organ Class and Preferred Term (Safety Set)

SYSTEM ORGAN CLASS Preferred Term	Number of Events / Number (%) of Participants						
	40 mg IOA-244			80 mg IOA-244			Total Across Study (N=32)
	Fasted (N=16)	Fed (N=16)	Overall (N=16)	Fasted (N=16)	Fed (N=16)	Overall (N=16)	
GASTROINTESTINAL DISORDERS:							
Constipation	0	0	0	0	1 / 1 (6.3)	1 / 1 (6.3)	1 / 1 (3.1)
Nausea	0	0	0	0	1 / 1 (6.3)	1 / 1 (6.3)	1 / 1 (3.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:							
Malaise	1 / 1 (6.3)	0	1 / 1 (6.3)	0	0	0	1 / 1 (3.1)
NERVOUS SYSTEM DISORDERS:							
Headache	1 / 1 (6.3)	2 / 2 (12.5)	3 / 3 (18.8)	1 / 1 (6.3)	1 / 1 (6.3)	2 / 1 (6.3)	5 / 4 (12.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS:							
Dysmenorrhoea	0	0	0	0	1 / 1 (6.3)	1 / 1 (6.3)	1 / 1 (3.1)

Treatment: A single dose of 40 mg (Group 1) or 80 mg (Group 2) IOA-244 in both the fed and fasted states across two treatment periods.
A participant is counted only once per system organ class and preferred term within a treatment.
Percentages calculated from the number of participants in the Safety Set within a treatment.
MedDRA version 27.0.
Data Source: Table 14.3.1.2