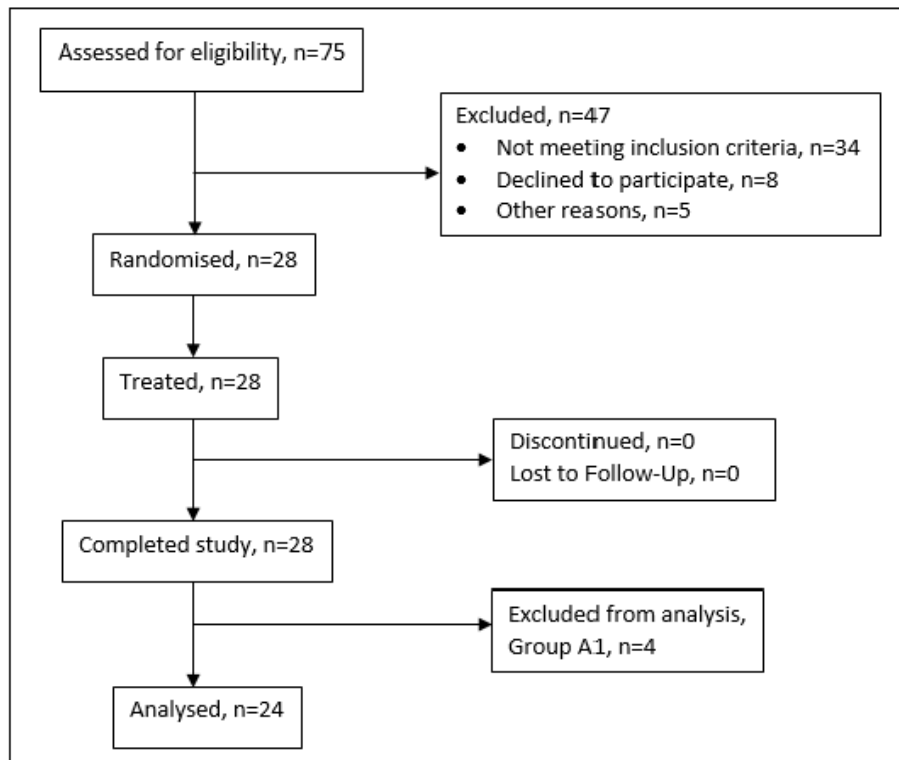
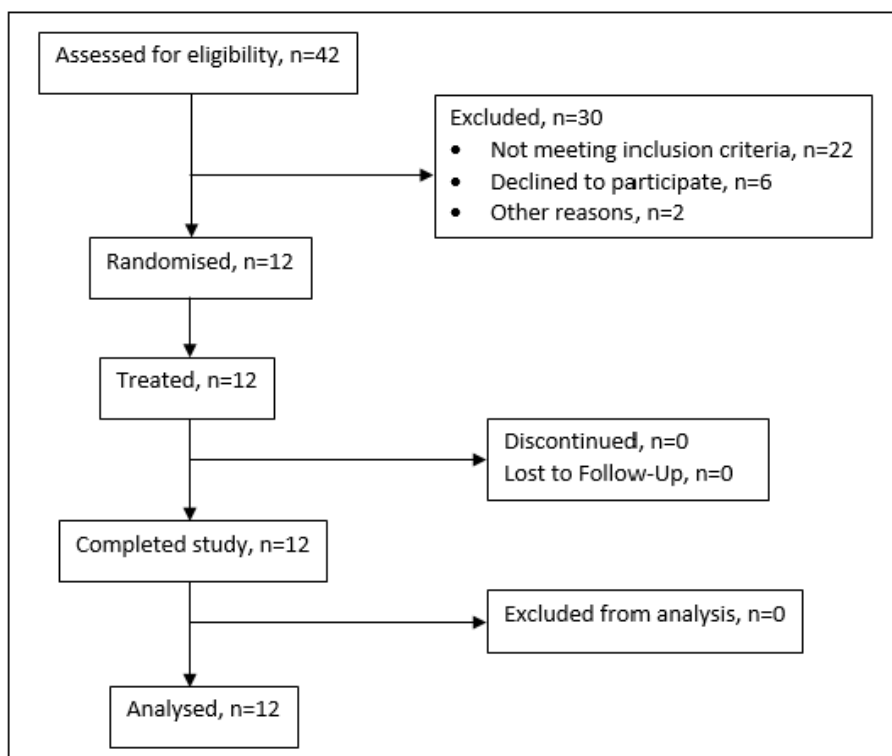


1. Participant Flow

Part A



Part B



2. Baseline Characteristics

Part A

Characteristic	A2	A3	A4	A5	A6	A7	Placebo
Age (Years) Mean (SD)	22.7 (1.5)	38.7 (24.6)	24.3 (6.8)	29.7 (7.0)	29.3 (9.5)	23.3 (5.8)	35.5 (13.6)
Gender	3 M	3 M	3 M	3 M	3M	3 F	5M, 1F
Ethnicity	3 WB	3 WB	2WB, 1WE	3 WB	3WB	2WB, 1WE	5 WB

F = Female; M = Male; SD = Standard Deviation; WB = White British; WE = White European

Characteristic	A2	A3	A4	A5	A6	A7	Placebo
Weight (kg) Mean (SD)	80.2 (2.0)	79.9 (13.9)	89.7 (7.1)	75.8 (16.7)	81.3 (16.7)	62.9 (1.6)	81.9 (10.6)
Height (cm) Mean (SD)	179 (4.5)	176 (10.9)	184 (5.9)	179 (5.5)	182 (8.5)	169 (8.1)	179 (15.6)
BMI (kg/m ²) Mean (SD)	24.9 (0.6)	25.7 (1.4)	26.4 (1.1)	23.6 (3.7)	24.4 (3.0)	22.0 (1.7)	25.5 (2.0)
Oral Temp. (°C) Mean (SD)	36.8 (0.3)	36.7 (0.2)	36.8 (0.1)	36.9 (0.1)	36.7 (0.1)	36.8 (0.2)	36.7 (0.1)
Heart Rate (bpm) Mean (SD)	62.0 (4.0)	66.0 (7.5)	56.7 (2.3)	67.7 (11.5)	57.0 (10.5)	63.7 (14.2)	66.7 (7.9)
Systolic BP (mmHg) Mean (SD)	121 (11.8)	129 (8.1)	128 (25.1)	136 (8.7)	125 (12.0)	110 (10.6)	124 (15.4)
Diastolic BP (mmHg) Mean (SD)	62.7 (5.5)	79.7(3.5)	73.7 (11.0)	78.3 (8.1)	68.7 (7.4)	70.3 (10.0)	76.5 (4.0)

BMI = Body Mass Index; BP = Blood Pressure; bpm = Beats/minute; SD = Standard Deviation.

Part B

Characteristic	B1	B2	B3	Placebo
Age (Years) Mean (SD)	60.3 (5.0)	54.7 (8.1)	58.0 (7.2)	66.0 (7.5)
Gender	2 M, 1F	1 M, 2F	1 M, 2F	1 M, 2F
Ethnicity	3 WB	3 WB	3WB	3 WB

F = Female; M = Male; SD = Standard Deviation; WB = White British; WE = White European

Characteristic	B1	B2	B3	Placebo
Weight (kg) Mean (SD)	87.1 (7.5)	76.6 (13.8)	82.0 (24.9)	78.0 (25.1)
Height (cm) Mean (SD)	172 (10.4)	165 (3.6)	170 (15.0)	167 (11.0)
BMI (kg/m ²) Mean (SD)	29.6 (1.2)	28.3 (6.2)	27.8 (4.8)	28.0 (7.5)
Oral Temp. (°C) Mean (SD)	36.6 (0.3)	36.6 (0.2)	36.8 (0.4)	36.7 (0.2)
Heart Rate (bpm) Mean (SD)	71.3 (15.7)	65.7 (17.6)	58.3 (12.9)	76.7 (19.7)
Systolic BP (mmHg) Mean (SD)	140 (7.2)	126 (12.0)	127 (12.7)	116 (6.1)
Diastolic BP (mmHg) Mean (SD)	84.7 (4.6)	79.0 (10.1)	76.3 (4.9)	73.7 (10.0)

BMI = Body Mass Index; BP = Blood Pressure; bpm = Beats/minute; SD = Standard Deviation.

4. Primary Endpoint: To determine safety & tolerability of ascending single and multiple oral doses of APPA-1 in healthy subjects and osteoarthritis patients.

4.1 Adverse Events

Intensity of AEs by Treatment

Part	N	Intensity	APPA Total Daily Dose (mg)					Placebo	Total
			400	800	1,600	2,400	3,200		
A	28	1. Mild	4	1	2	2		6	15
		2. Moderate							0
		3. Severe	1						1
		Sub-Total	5	1	2	1	0	6	16
B	12	1. Mild			3	9	1	2	15
		2. Moderate			1	3			4
		3. Severe							
		Sub-Total			4	12	1	2	19

Causality of Adverse Events by Treatment

Part	N	Causality	APPA Total Daily Dose (mg)					Placebo	Total
			400	800	1,600	2,400	3,200		
A	28	Possibly Related						2	2
		Unlikely Related							
		Not Related	5	2	2	1			14
		Sub-Total	5	2	2	1	0	6	16
B	12	Possibly Related						1*	1
		Unlikely Related			1	1	1	1	4
		Not Related			3	7			10
		Sub-Total			4	8	1	2	15

4.2 Vital signs

Part A

Vital Sign	Time point	Group and APPA-1 Dose (mg) N=21							Placebo N=7
		A2 800	A3 1,600	A4 1,600	A5 Fasted 2,400	A5 Fed 2,400	A6 3,200	A7 Female 3,200	
Oral Temp. (°C) Mean (SD)	Day 1 Predose	36.6 (0.1)	36.5 (0.1)	36.6 (0.1)	36.5 (0.1)	36.6 (0.2)	36.8 (0.2)	37.2 (0.4)	36.7 (0.2)
	Day 2	36.6 (0.2)	36.7 (0.3)	36.8 (0.2)	36.8 (0.2)	36.6 (0.3)	36.7 (0.1)	36.9 (0.1)	36.6 (0.1)
	Follow Up	36.8 (0.1)	36.7 (0.2)	36.8 (0.2)		36.6 (0.2)	36.8 (0.2)	36.7 (0.2)	36.7 (0.1)
Heart Rate (bpm) Mean (SD)	Day 1 Predose	53.0 (6.0)	57.1 (10.5)	51.1 (3.9)	61.6 (5.8)	56.3 (9.4)	57.4 (8.5)	75.0 (19.4)	57.4 (8.0)
	Day 1 6 hour	59.7 (10.7)	67.3 (12.1)	54.0 (1.0)	63.0 (4.6)	61.3 (5.1)	59.0 (2.6)	70.3 (5.0)	59.9 (7.1)
	Day 2	57.3 (5.1)	58.3 (16.4)	53.7 (1.5)	58.0 (5.0)	54.3 (10.1)	57.0 (11.8)	71.7 (11.0)	62.7 (10.1)
	Follow Up	65.7 (14.6)	63.3 (13.7)	56.3 (4.0)		68.3 (10.5)	62.3 (13.6)	67.7 (16.8)	66.5 (8.8)
Systolic BP (mmHg) Mean (SD)	Day 1 Predose	115 (6.5)	124 (8.2)	120 (10.8)	121 (8.7)	116 (2.9)	123 (11.7)	106 (5.5)	114 (10.9)
	Day 1 6 hour	119 (9.6)	129 (7.0)	135 (12.8)	117 (9.6)	119 (3.2)	117 (13.9)	112 (5.1)	117 (8.4)
	Day 2	122 (10.6)	124 (8.7)	126 (9.5)	121 (6.7)	117 (4.2)	124 (0.0)	103 (3.8)	116 (11.1)
	Follow Up	122 (2.5)	123 (7.0)	125 (13.0)		128 (13.3)	125 (8.0)	114 (7.2)	116 (16.2)
Diastolic BP (mmHg) Mean (SD)	Day 1 Predose	66.3 (3.3)	77.3 (6.4)	72.6 (7.2)	76.9 (7.2)	70.7 (3.9)	73.6 (10.7)	70.3 (3.6)	71.0 (7.5)
	Day 1 6 hour	64.3 (3.2)	73.7 (2.1)	75.0 (7.5)	71.0 (5.3)	65.0 (8.7)	68.0 (15.1)	65.7 (4.0)	68.6 (4.4)
	Day 2	66.3 (3.5)	72.7 (8.4)	70.3 (8.4)	75.7 (3.1)	68.7 (4.5)	69.7 (4.6)	64.3 (6.1)	70.9 (6.1)
	Follow Up	64.7 (8.6)	72.7 (4.9)	73.0 (9.5)		74.3 (5.5)	74.0 (4.4)	73.0 (7.5)	67.5 (5.6)

Part B

Vital Sign	Time point	Group and APPA-1 Daily Dose (mg) N=9			Placebo N=3
		B1 1,600	B2 2,400	B3 3,200	
Oral Temp. (°C) Mean (SD)	Day 1 Predose	36.7 (0.3)	36.5 (0.1)	36.5 (0.1)	36.6 (0.1)
	Day 2	36.8 (0.2)	36.7 (0.2)	36.8 (0.3)	36.6 (0.1)
	Day 7	36.9 (0.4)	36.8 (0.2)	36.6 (0.2)	36.5 (0.1)
	Day 14 Predose	36.7 (0.2)	36.5 (0.1)	36.7 (0.1)	36.5 (0.1)
	Day 21	36.5 (0.4)	36.6 (0.1)	36.6 (0.2)	36.8 (0.4)
Heart Rate (bpm) Mean (SD)	Day 1 Predose	61.1 (13.0)	63.3 (17.6)	51.4 (7.9)	66.4 (5.2)
	Day 1 6 hour	62.0 (13.5)	67.0 (22.9)	64.0 (7.9)	70.3 (6.4)
	Day 2	62.7 (10.6)	64.0 (13.1)	55.0 (9.2)	67.7 (8.0)
	Day 7	63.3 (10.7)	65.0 (20.1)	54.3 (12.4)	69.3 (9.8)
	Day 14 Predose	63.7 (11.0)	62.0 (19.7)	54.0 (11.3)	65.7 (7.8)
	Day 21	66.7 (16.6)	67.3 (17.2)	58.7 (7.6)	75.0 (15.1)
Systolic BP (mmHg) Mean (SD)	Day 1 Predose	130 (5.1)	125 (17.1)	113 (6.2)	126 (7.2)
	Day 1 6 hour	119 (2.6)	122 (6.7)	102 (11.4)	118 (13.2)
	Day 2	133 (6.2)	121 (13.6)	110 (6.5)	121 (13.0)
	Day 7	140 (6.7)	125 (12.3)	112 (4.4)	123 (1.0)
	Day 14 Predose	132 (8.9)	122 (5.5)	115 (9.1)	119 (6.7)
	Day 21	136 (19.2)	117 (10.8)	115 (7.2)	121 (9.3)
Diastolic BP (mmHg) Mean (SD)	Day 1 Predose	75.2 (3.5)	78.8 (9.5)	71.9 (5.3)	76.6 (9.2)
	Day 1 6 hour	73.7 (3.2)	78.3 (3.5)	63.7 (9.3)	73.0 (5.6)
	Day 2	82.0 (9.0)	79.3 (7.6)	71.7 (4.0)	79.0 (6.6)
	Day 7	81.3 (3.5)	76.3 (8.0)	73.3 (1.5)	74.7 (9.0)
	Day 14 Predose	79.7 (7.2)	78.7 (6.7)	72.3 (9.0)	73.7 (10.0)
	Day 21	80.0 (5.3)	73.0 (6.6)	65.3 (6.8)	74.7 (5.5)

4.3 Electrocardiography

Part A

ECG Parameter	Time point	Group and APPA Dose (mg) N=21							Placebo N=3
		A2 800	A3 1,600	A4 1,600	A5 Fasted 2,400	A5 Fed 2,400	A6 3,200	A7 Female 3,200	
PR Interval (ms) Mean (SD)	Day 1 Predose	185 (21.9)	139 (20.0)	170 (26.2)	162 (25.0)	172 (14.0)	164 (12.2)	150 (32.2)	160 (27.3)
	Day 1, 1 hour	191 (25.7)	135 (13.0)	166 (25.0)	171 (17.9)	163 (23.0)	163 (13.6)	149 (27.2)	161 (25.3)
	Day 1, 3 hours				167 (19.0)	161 (22.1)	166 (17.1)	146 (26.0)	162 (39.8)
	Day 1, 6 hours	178 (19.3)	128 (9.2)	156 (23.1)	159 (27.7)	163 (24.4)	163 (13.0)	139 (13.3)	161 (34.9)
	Day 1, 12 hrs				161 (22.0)	168 (21.6)	159 (19.0)	148 (29.1)	163 (42.3)
	Day 2	185 (19.6)	139 (22.7)	162 (20.3)	159 (23.4)	165 (25.0)	168 (21.1)	143 (11.0)	158 (26.0)
	Follow Up	181 (22.3)	147 (32.5)	168 (27.5)		162 (15.9)	159 (13.0)	149 (28.1)	150 (24.7)
QRS Interval (ms) Mean (SD)	Day 1 Predose	101 (3.1)	94.0 (8.7)	96.0 (10.6)	102 (7.2)	103 (8.3)	96.7 (7.6)	88.0 (5.3)	95.7 (13.3)
	Day 1, 1 hour	98.0 (4.0)	95.3 (4.6)	99.3 (4.2)	98.0 (12.2)	101 (9.0)	98.7 (3.1)	88.7 (9.5)	95.4 (12.3)
	Day 1, 3 hours				100 (8.0)	96.0 (10.6)	102 (2.0)	84.7 (6.1)	93.0 (14.0)
	Day 1, 6 hours	96.7 (4.6)	94.7 (6.1)	100 (6.0)	101 (9.5)	101 (8.1)	98.0 (3.5)	88.0 (6.0)	96.3 (14.3)
	Day 1, 12 hrs				103 (11.7)	101 (9.9)	94.7 (6.1)	86.7 (10.1)	91.5 (11.4)
	Day 2	103 (8.1)	94.7 (4.2)	97.3 (7.0)	102 (12.2)	105 (9.9)	96.0 (7.2)	86.7 (5.0)	94.6 (12.0)
	Follow Up	100 (10.0)	95.3 (7.0)	94.7 (8.1)		105 (15.0)	95.3 (6.4)	91.3 (8.1)	97.3 (16.3)
QTc Interval (ms) Mean (SD)	Day 1 Predose	386 (26.3)	391 (16.8)	381 (17.8)	390 (22.1)	383 (33.1)	400 (10.4)	415 (5.7)	403 (21.5)
	Day 1, 1 hour	386 (20.0)	423 (13.7)	389 (4.9)	409 (18.5)	401 (10.7)	398 (4.9)	414 (20.8)	406 (14.8)
	Day 1, 3 hours				403 (17.0)	401 (24.0)	401 (15.3)	416 (12.7)	401 (15.8)
	Day 1, 6 hours	394 (18.3)	410 (14.6)	389 (13.2)	406 (7.6)	403 (14.1)	386 (18.8)	413 (4.2)	408 (11.8)
	Day 1, 12 hrs				394 (21.7)	384 (19.6)	390 (18.1)	406 (6.1)	390 (6.9)
	Day 2	391 (24.8)	413 (5.5)	387 (8.0)	392 (16.6)	382 (22.8)	398 (15.1)	407 (9.7)	402 (16.4)
	Follow Up	395 (25.2)	411 (13.6)	377 (23.4)		405 (22.6)	389 (20.8)	412 (22.2)	413 (22.7)
QTcB Interval (ms) Mean (SD)	Day 1 Predose	388 (25.6)	409 (11.5)	376 (21.1)	395 (18.8)	383 (35.5)	404 (37.6)	416 (11.8)	401 (26.1)
	Day 1, 1 hour	381 (19.5)	418 (25.0)	384 (10.2)	412 (15.4)	401 (10.3)	402 (5.1)	412 (21.0)	406 (14.3)
	Day 1, 3 hours				399 (12.8)	397 (15.3)	389 (9.0)	410 (11.0)	399 (10.8)
	Day 1, 6 hours	398 (15.6)	403 (15.7)	384 (14.3)	405 (11.0)	401 (16.2)	378 (24.0)	416 (7.0)	406 (11.5)
	Day 1, 12 hrs				408 (17.1)	378 (26.3)	383 (14.0)	402 (7.3)	383 (15.6)
	Day 2	397 (24.0)	404 (14.9)	384 (3.8)	388 (14.2)	381 (15.9)	399 (12.2)	403 (13.6)	395 (16.1)
	Follow Up	393 (34.6)	408 (2.8)	379 (18.2)		399 (29.1)	391 (24.4)	416 (19.6)	409 (25.1)

ECG Parameter	Time point	Group and APPA Dose (mg) N=21							Placebo N=3
		A2 800	A3 1,600	A4 1,600	A5 Fasted 2,400	A5 Fed 2,400	A6 3,200	A7 Female 3,200	
Heart Rate (bpm) Mean (SD)	Day 1 Predose	52.0 (6.6)	54.0 (13.9)	50.0 (3.6)	58.0 (10.4)	53.7 (10.1)	56.0 (11.5)	64.3 (12.2)	54.9 (7.4)
	Day 1, 1 hour	51.3 (3.2)	62.7 (9.0)	52.7 (4.9)	62.3 (9.0)	63.0 (2.0)	56.3 (5.9)	59.3 (7.6)	54.6 (6.7)
	Day 1, 3 hours				57.0 (4.6)	60.3 (9.0)	55.7 (10.7)	57.7 (9.0)	58.3 (3.9)
	Day 1, 6 hours	57.0 (4.6)	63.7 (15.3)	55.7 (1.5)	63.0 (2.6)	60.7 (2.1)	58.0 (10.6)	66.7 (6.1)	61.1 (7.4)
	Day 1, 12 hrs				54.7 (8.1)	53.0 (5.0)	56.3 (14.0)	62.0 (6.6)	54.8 (7.4)
	Day 2	59.0 (6.1)	63.0 (14.7)	51.0 (2.6)	56.7 (4.2)	52.3 (7.6)	57.3 (11.1)	62.0 (11.5)	58.7 (8.6)
	Follow Up	62.0 (18.2)	62.7 (13.2)	53.3 (1.5)		62.0 (3.5)	59.7 (13.1)	69.0 (14.7)	64.8 (8.0)

Part B

ECG Parameter	Time point	Group and APPA-1 Daily Dose (mg) N=9			Placebo, N=3
		B1 1,600	B2 2,400	B3 3,200	
PR Interval (ms) Mean (SD)	Day 1 Predose	165 (12.9)	149 (9.0)	153 (22.5)	180 (26.9)
	Day 1, 6 hours	163 (13.6)	135 (21.2)	145 (17.5)	187 (22.0)
	Day 1, 12 hrs	152 (16.4)	145 (12.1)	145 (23.2)	182 (15.1)
	Day 2	158 (13.9)	142 (14.0)	147 (24.2)	187 (22.7)
	Day 7	160 (10.6)	151 (17.9)	151 (22.5)	184 (14.0)
	Day 14 Predose	143 (5.0)	155 (12.2)	144 (10.6)	190 (16.0)
	Day 21	160 (25.0)	142 (19.1)	147 (18.6)	181 (29.1)
QRS Interval (ms) Mean (SD)	Day 1 Predose	88.0 (7.2)	86.7 (9.9)	94.7 (4.2)	83.3 (1.2)
	Day 1, 6 hours	90.7 (11.4)	89.3 (11.4)	95.3 (5.0)	82.7 (1.2)
	Day 1, 12 hrs	85.3 (5.0)	86.7 (13.3)	94.7 (3.1)	80.7 (1.2)
	Day 2	83.3 (9.9)	90.0 (5.3)	92.7 (4.6)	81.3 (2.3)
	Day 7	84.0 (8.7)	86.0 (4.0)	94.7 (6.1)	80.7 (3.1)
	Day 14 Predose	89.3 (10.3)	82.0 (3.5)	93.3 (3.1)	82.7 (5.0)
	Day 21	86.0 (7.2)	84.7 (13.3)	92.7 (6.4)	82.0 (2.0)
QTc Interval (ms) Mean (SD)	Day 1 Predose	421 (15.7)	428 (19.0)	416 (8.4)	426 (23.1)
	Day 1, 6 hours	423 (19.6)	419 (60.5)	414 (25.0)	426 (21.9)
	Day 1, 12 hrs	417 (12.3)	415 (41.8)	417 (12.7)	418 (23.2)
	Day 2	416 (15.9)	417 (33.1)	414 (10.0)	415 (18.5)
	Day 7	418 (28.0)	416 (25.3)	408 (17.5)	431 (27.3)
	Day 14 Predose	415 (10.0)	405 (26.8)	430 (33.2)	405 (27.6)
	Day 21	411 (29.8)	415 (12.0)	415 (23.0)	418 (28.4)
QTcB Interval (ms) Mean (SD)	Day 1 Predose	414 (14.2)	424 (15.0)	414 (10.5)	426 (21.2)
	Day 1, 6 hours	423 (14.5)	426 (39.9)	413 (20.6)	420 (29.7)
	Day 1, 12 hrs	413 (15.7)	411 (41.9)	414 (10.4)	408 (26.6)
	Day 2	415 (16.0)	420 (36.2)	407 (11.3)	419 (11.0)
	Day 7	418 (25.0)	417 (25.0)	412 (17.5)	428 (24.7)
	Day 14 Predose	415 (14.0)	397 (43.1)	421 (14.5)	406 (26.7)
	Day 21	415 (14.0)	397 (43.1)	421 (14.5)	406 (26.7)
Heart Rate (bpm) Mean (SD)	Day 1 Predose	63.3 (14.0)	63.3 (17.7)	54.0 (10.8)	67.3 (13.6)
	Day 1, 6 hours	65.3 (17.2)	68.0 (26.5)	58.3 (11.0)	73.3 (9.0)
	Day 1, 12 hrs	64.7 (8.6)	65.0 (25.4)	59.3 (12.9)	72.3 (11.7)
	Day 2	61.0 (10.6)	62.3 (18.2)	55.3 (9.1)	67.0 (6.6)
	Day 7	65.0 (11.1)	59.3 (12.4)	53.3 (10.6)	73.0 (5.3)
	Day 14 Predose	60.7 (9.5)	61.0 (16.5)	57.0 (5.6)	62.0 (7.0)
	Day 21	65.7 (17.0)	63.3 (14.8)	57.0 (9.2)	72.0 (11.5)

4.4 Telemetry

Telemetry was performed on day 1 in Part A; mean, minimum and maximum heart rates were within normal limits.

4.5 Clinical Laboratory Tests

During the study there were no clinically significant abnormalities in clinical data (haematology, coagulation, biochemistry and urinalysis).

5. Secondary Endpoint: To determine the single and multiple oral dose pharmacokinetics of APPA-1 constituents (paeonol/apocynin) in health subjects and osteoarthritis patients.

5.1 Part A

Geometric mean plasma pharmacokinetic parameters of PAEONOL and APOCYNIN following single oral dose of APPA in healthy male and female volunteers - summary

Group Dose level Status Gender No. of Subjects Parameter	A2 800 mg Fasted M n=3	A3 1600 mg Fasted M n=3	A4 1600 mg Fasted M n=3	A5 TP1 2400 mg Fasted M n=3	A5 TP2 2400 mg Fed M n=3	A6 3200 mg Fasted M n=3	A7 3200 mg Fasted F n=3
PAEONOL							
T _{max} * (h)	2.417 (0.92-3.92)	1.417 (1.42-2.42)	1.417 (1.42-1.42)	0.917 (0.67-0.95)	3.917 (1.92- 3.92)	1.417 (0.92-3.92)	2.417 (1.42-4.92)
C _{max} (ng/mL)	21.4 (156.6)	224 (615.2)	296 (93.0)	858 (43.4)	101 (311.4)	449 (765.3)	990 (122.9)
AUC ₀₋₂₄ (ng.h/mL)	79.8 (51.0)	625 (142.2)	496 (100.5)	1530 (77.0)	449 (177.5)	2030 (157.9)	2510 (153.3)
T _{1/2} (h)	2.960 (31.4)	7.343 [n=1]	5.011 (36.3)	7.093 [n=1]	3.854 (64.1) [n=2]	8.013 (18.1)	5.185 (14.5) [n=2]
APOCYNIN							
T _{max} * (h)	1.917 (0.67-11.92)	1.167 (0.92-1.42)	0.925 (0.92-0.93)	0.917 (0.67-0.95)	1.417 (0.92-1.92)	0.667 (0.67-0.92)	0.667 (0.67-0.92)
C _{max} (ng/mL)	8.42 (71.5)	9.55 (45.9)	4.21 (37.4)	6.41 (31.7)	5.62 (19.1)	10.6 (261.4)	33.0 (3651.6)
AUC ₀₋₂₄ (ng.h/mL)	16.2 [n=1]	12.5 [n=1]	NC	21.1 (4.4)	41.4 [n=1]	17.2 (17.9)	80.1 (16.5) [n=2]
T _{1/2} (h)	1.658 [n=1]	1.086 [n=1]	NC	2.008 [n=1]	NC	0.936 (41.4) [n=2]	1.540 (29.1) [n=2]

5.2 Part B

Geometric mean plasma pharmacokinetic parameters of PAEONOL and APOCYNIN following multiple oral dose of APPA-1 for 14 days to osteoarthritis patients (day 1 – day 14)

Group Dose level Status	B1 800 mg b.i.d Fed	B2 1200 mg b.i.d Fed	B3 1600 mg b.i.d Fed	B1 800 mg b.i.d Fed	B2 1200 mg b.i.d Fed	B3 1600 mg b.i.d Fed
No. of Subjects Parameter	n=3	n=3	n=3	n=3	n=3	n=3
PAEONOL	Day 1			Day 14		
T _{max} * (h)	2.917 (0.92-4.92)	0.917 (0.67-2.42)	2.917 (0.93-4.92)	2.917 (2.33-3.92)	2.917 (2.42-5.00)	2.917 (2.42-2.92)
C _{max} (ng/mL)	11.4 (45.7)	60.7 (170.6)	80.7 (78.2)	17.5 (100.5)	79.8 (34.4)	250 (217.7)
T _{1/2} (h)	NC	3.076 (37.0) [n=2]	3.086 (46.8) [n=2]	5.371 [n=1]	9.126 (109.0)	13.599 (22.8)
AUC _{tau} (ng.h/mL)	48.1 (20.2)	184 (98.9)	394 (39.5)	82.1 (63.5)	353 (59.1)	917 (120.9)
APOCYNIN	Day 1			Day 14		
T _{max} * (h)	NC	1.183 (0.92-1.45) [n=2]	0.933 (0.68-1.93)	0.650 [n=1]	0.917 (0.92-0.92) [n=2]	1.325 (0.23-2.42) [n=2]
C _{max} (ng/mL)	NC	4.04 (116.5) [n=2]	7.61 (746.8)	1.66 [n=1]	3.95 (92.0) [n=2]	11.8 (13.7) [n=2]
T _{1/2} (h)	NC	NC	NC	NC	NC	NC
AUC _{tau} (ng.h/mL)	NC	NC	43.2 [n=1]	NC	NC	15.8 (36.1) [n=2]

6. Adverse Events

6.1 Summary of all reported Adverse Events by treatment

Part A

System Organ Class	Preferred Term	N=21 APPA-1 No. Sub (No. AE)	N=7 Placebo No. Sub (No. AE)
Cardiac disorders	Palpitations	0 (0)	1 (3)
Gastrointestinal disorders	Toothache	0 (0)	1 (1)
General disorders and administration site conditions	Peripheral coldness	1 (1)	0 (0)
Injury, Poisoning and Procedural Complication	Injuries	0 (0)	1 (1)
	Thermal Burn (SAE)	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders	Limb discomfort	1 (2)	0 (0)
Nervous system disorders	Headache	1 (1)	1 (1)
	Paraesthesia	2 (2)	0 (0)
Renal and urinary disorders	Pyuria	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal blistering	1 (1)	0 (0)
Vascular disorders	Hypertension	1 (1)	0 (0)
Total		9 (10)	4 (6)

Part B

System Organ Class	Preferred Term	N=9 APPA-1 No. Sub (No. AE)	N=3 Placebo No. Sub (No. AE)
Gastrointestinal disorders	Constipation	1 (1)	0 (0)
	Diarrhoea	1 (1)	0 (0)
	Dyspepsia	1 (2)	0 (0)
Infections and infestations	Rhinitis	1 (1)	0 (0)
	Urinary tract infection	1 (1)	0 (0)
Injury, Poisoning and Procedural Complication	Administration Site Erythema	1 (1)	0 (0)
Investigations	Grip strength decreased	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders	Arthralgia	0 (0)	1 (1)
	Back Pain	1 (1)	0 (0)
	Myalgia	1 (1)	0 (0)
	Neck Pain	1 (1)	0 (0)
	Pain in Extremity	0 (0)	1 (1)
Nervous system disorders	Dizziness	1 (1)	0 (0)
	Headache	2 (2)	0 (0)
Skin & subcutaneous tissue disorders	Skin exfoliation	1 (1)	0 (0)
Total		14 (15)	2 (2)