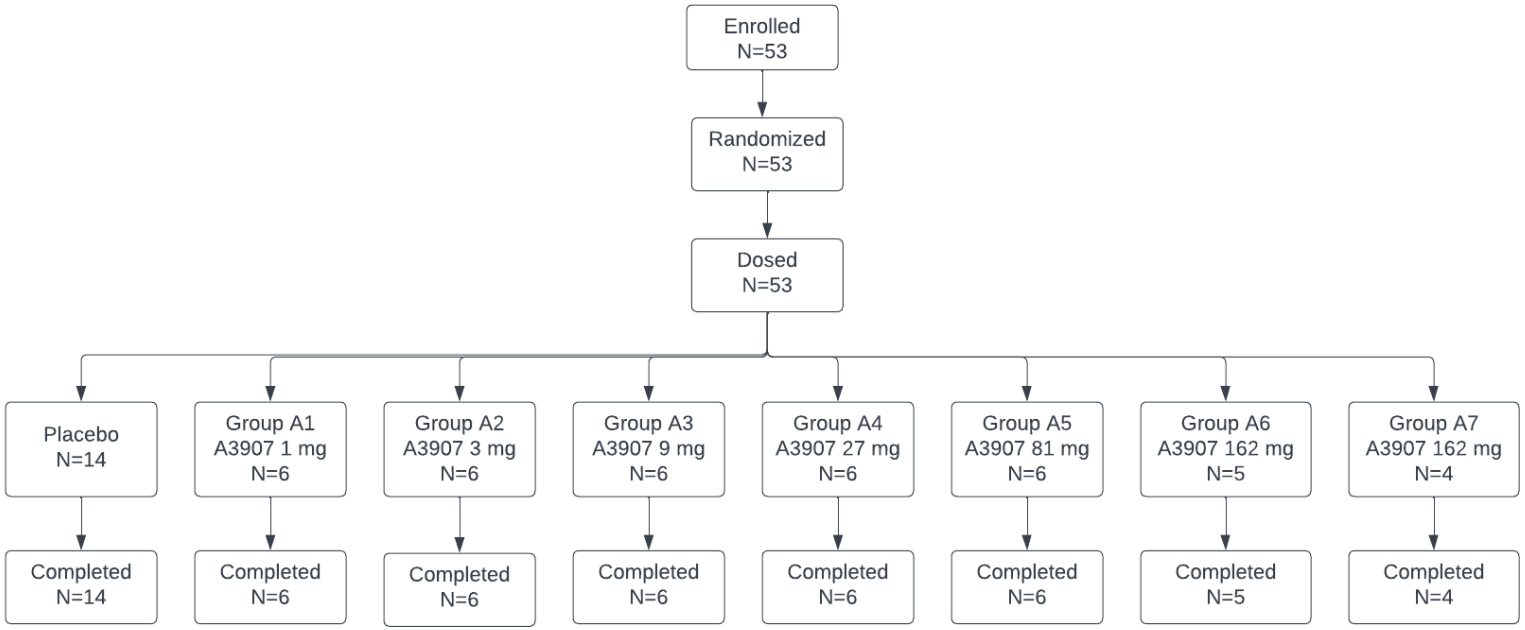
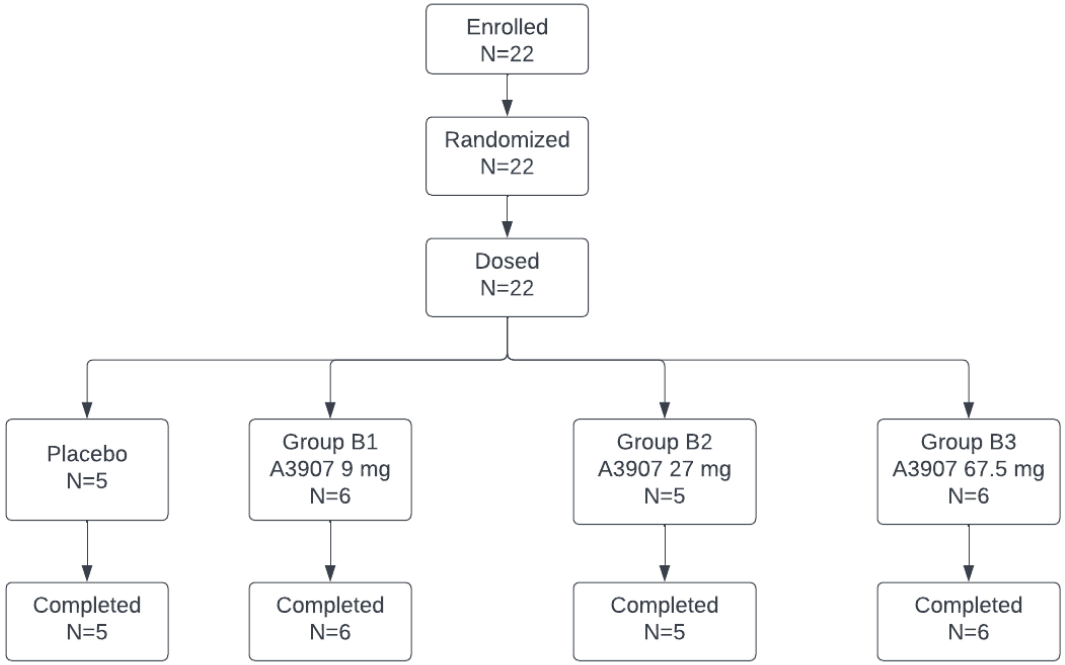
Participant Flow:

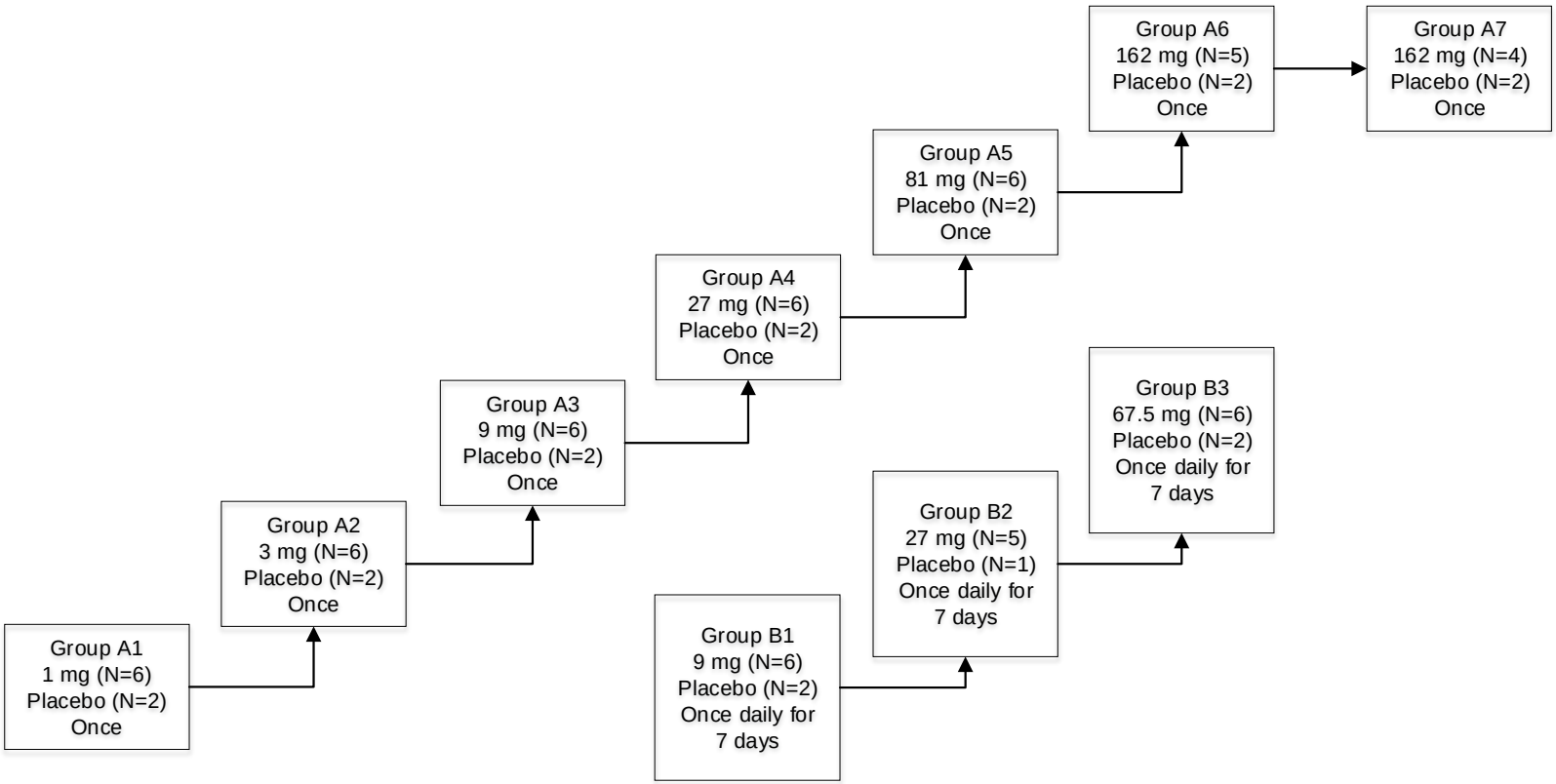
Part A



Part B


Enrolled
N=22
Randomized
N=22
Dosed
N=22
Placebo
N=5
Group B1
A3907 9 mg
N=6
Group B2
A3907 27 mg
N=5
Group B3
A3907 67.5 mg
N=6
Completed
N=5
Completed
N=6
Completed
N=5
Completed
N=6

Dose Levels for Protocol A3907-001



Baseline characteristics

Summary of Screening Demographic Data for Protocol A3907-001 – Part A

Demographic	Placebo (N = 14)	A3907 A1 1 mg (N = 6)	A2 3 mg (N = 6)	A3 9 mg (N = 6)	A4 27 mg (N = 6)	A5 81 mg (N = 6)	A6 162 mg (N = 5)	A7 162 mg (N = 4)	Overall (N = 53)
Age (years)	34.5 (12.00)	40.0 (13.27)	50.7 (9.95)	37.3 (10.52)	39.3 (14.35)	43.8 (13.45)	34.0 (9.82)	26.3 (5.91)	38.2 (12.58)
Sex									
Male	14 (100)	6 (100)	4 (66.7)	5 (83.3)	5 (83.3)	4 (66.7)	5 (100)	4 (100)	47 (88.7)
Female	---	---	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	---	---	6 (11.3)
Race									
White	12 (85.7)	6 (100)	6 (100)	6 (100)	6 (100)	5 (83.3)	5 (100)	4 (100)	50 (94.3)
Asian	1 (7.1)	---	---	---	---	1 (16.7)	---	---	2 (3.8)
Black or African American	1 (7.1)	---	---	---	---	---	---	---	1 (1.9)
Ethnicity									
Not Hispanic or Latino	14 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (100)	4 (100)	53 (100)
Height (cm)	179.8 (8.05)	174.7 (5.05)	177.0 (10.12)	176.5 (10.43)	175.8 (8.91)	168.7 (8.26)	176.4 (5.59)	176.8 (3.77)	176.3 (8.17)
Body Weight (kg)	80.24 (10.669)	77.65 (5.921)	88.62 (14.158)	76.58 (8.317)	80.38 (6.354)	75.70 (14.772)	83.08 (10.963)	85.90 (10.850)	80.68 (10.700)
Body Mass Index (kg/m^2)	24.86 (3.280)	25.48 (1.820)	28.20 (2.832)	24.57 (1.629)	26.02 (1.841)	26.42 (2.942)	26.64 (2.781)	27.55 (3.913)	25.95 (2.844)

n = number of subjects with valid observations; N = number of subjects; SD = standard deviation; % = percentage of subjects with valid observations (n/N×100);
--- = no data recorded
For continuous data, mean (SD) statistics presented; for categorical data, n (%) statistics presented.
Body mass index (kg/m^2) = body weight (kg) / height (m)^2

Summary of Screening Demographic Data for Protocol A3907-001 – Part B

Demographic	Placebo (N = 5)	A3907 B1 9 mg (N = 6)	A3907 B2 27 mg (N = 5)	A3907 B3 67.5 mg (N = 6)	Overall (N = 22)
Age (years)	29.6 (15.34)	30.2 (15.22)	36.4 (15.39)	47.2 (13.56)	36.1 (15.62)
Sex					
Male	5 (100)	5 (83.3)	5 (100)	5 (83.3)	20 (90.9)
Female	---	1 (16.7)	---	1 (16.7)	2 (9.1)
Race					
White	4 (80.0)	4 (66.7)	4 (80.0)	6 (100)	18 (81.8)
Black or African American	1 (20.0)	1 (16.7)	1 (20.0)	---	3 (13.6)
Multiple	---	1 (16.7)	---	---	1 (4.5)
Ethnicity					
Not Hispanic or Latino	5 (100)	6 (100)	5 (100)	6 (100)	22 (100)
Height (cm)	174.8 (9.15)	175.5 (10.73)	174.6 (4.72)	176.3 (6.09)	175.4 (7.54)
Body Weight (kg)	79.02 (10.619)	78.43 (11.717)	86.98 (6.073)	86.32 (10.195)	82.66 (10.123)
Body Mass Index (kg/m^2)	25.80 (2.327)	25.55 (3.969)	28.58 (2.457)	27.75 (3.098)	26.90 (3.147)

n = number of subjects with valid observations; N = number of subjects; SD = standard deviation; % = percentage of subjects with valid observations (n/N×100);
--- = no data recorded
For continuous data, mean (SD) statistics presented; for categorical data, n (%) statistics presented.
Body mass index (kg/m^2) = body weight (kg) / height $(m)^2$

Primary outcome measures

Summary of Treatment-Related Adverse Events in Any Treatment Group in Protocol A3907-001 – Part A

System Organ Class Preferred Term	Placebo (N = 14)	A3907 A1 1 mg (N = 6)	A2 3 mg (N = 6)	A3 9 mg (N = 6)	A4 27 mg (N = 6)	A5 81 mg (N = 6)	A6 162 mg (N = 5)	A7 162 mg (N = 4)	A3907 All Doses (N = 39)
Overall TEAEs	4 (28.6)	---	2 (33.3)	2 (33.3)	1 (16.7)	5 (83.3)	3 (60.0)	3 (75.0)	16 (41.0)
Gastrointestinal disorders	4 (28.6)	---	2 (33.3)	2 (33.3)	1 (16.7)	3 (50.0)	3 (60.0)	3 (75.0)	14 (35.9)
Diarrhoea	4 (28.6)	---	1 (16.7)	2 (33.3)	---	3 (50.0)	3 (60.0)	3 (75.0)	12 (30.8)
Abdominal pain	---	---	1 (16.7)	---	1 (16.7)	1 (16.7)	---	---	3 (7.7)
Abdominal distension	---	---	---	---	---	---	---	1 (25.0)	1 (2.6)
Abdominal pain lower	---	---	---	---	---	---	---	1 (25.0)	1 (2.6)
Dyschezia	---	---	---	---	---	---	---	1 (25.0)	1 (2.6)
Nervous system disorders	---	---	---	1 (16.7)	---	2 (33.3)	---	---	3 (7.7)
Headache	---	---	---	1 (16.7)	---	1 (16.7)	---	---	2 (5.1)
Dizziness	---	---	---	---	---	1 (16.7)	---	---	1 (2.6)
Lethargy	---	---	---	---	---	1 (16.7)	---	---	1 (2.6)
Cardiac disorders	---	---	---	---	---	---	1 (20.0)	---	1 (2.6)
Rhythm idioventricular	---	---	---	---	---	---	1 (20.0)	---	1 (2.6)
Skin and subcutaneous tissue disorders	---	---	---	---	---	---	1 (20.0)	---	1 (2.6)
Cold sweat	---	---	---	---	---	---	1 (20.0)	---	1 (2.6)

n = number of subjects with an adverse event; N = number of subjects; % = percentage of subjects with an adverse event (n/N×100); --- = no data recorded
The n (%) statistics presented.
1 subject had a Bristol Stool Form Scale Type 6 stool (fluffy pieces with ragged edges, a mushy stool) on Day 2. Clinical site staff did not record this stool as an adverse event (AE) in the database. The principal investigator confirmed that this omission was made in error and the stool should have been recorded as an AE. Following database lock, it was confirmed that the subject received placebo.
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that started during or after dosing, or started prior to dosing and increased in severity after dosing.
A treatment-related TEAE was defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

Summary of Treatment-Related Adverse Events in Any Treatment Group in Protocol A3907-001 – Part B

System Organ Class Preferred Term	Placebo (N = 5)	A3907 B1 9 mg (N = 6)	A3907 B2 27 mg (N = 5)	A3907 B3 67.5 mg (N = 6)	A3907 All Doses (N = 17)
Overall TEAEs	---	5 (83.3)	1 (20.0)	6 (100)	12 (70.6)
Gastrointestinal disorders	---	4 (66.7)	1 (20.0)	6 (100)	11 (64.7)
Diarrhoea	---	4 (66.7)	1 (20.0)	5 (83.3)	10 (58.8)
Abdominal discomfort	---	1 (16.7)	---	1 (16.7)	2 (11.8)
Abdominal pain	---	1 (16.7)	---	1 (16.7)	2 (11.8)
Dyspepsia	---	1 (16.7)	---	---	1 (5.9)
Nausea	---	1 (16.7)	---	---	1 (5.9)
Nervous system disorders	---	2 (33.3)	---	2 (33.3)	4 (23.5)
Headache	---	2 (33.3)	---	2 (33.3)	4 (23.5)

n = number of subjects with an adverse event; N = number of subjects; % = percentage of subjects with an adverse event (n/N×100); --- = no data recorded
The n (%) statistics presented.
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1.
A treatment-emergent adverse event (TEAE) was defined as an adverse event that started during or after the first dose, or started prior to the first dose and increased in severity after the first dose.
A treatment-related TEAE was defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

Secondary outcome measures

Summary of Plasma PK Parameters Following Single Doses – Part A (PK Analysis Population)

Parameter	Cohort A1 1 mg N = 6	Cohort A2 3 mg N = 6	Cohort A3 9 mg N = 6	Cohort A4 27 mg N = 6	Cohort A5 81 mg N = 6	Cohort A6 162 mg N = 5	Cohort A7 162 mg N = 4
AUC_{0-t} (h*ng/mL)	22.89 (57.78%)	55.31 (71.27%)	166.2 (35.98%)	619.8 (34.33%)	1594 (59.57%)	1687 (41.97%)	1962 (51.27%)
AUC_{0-inf} (h*ng/mL)	27.48 (51.37%)	88.46 (15.61%)	171.4 (34.72%)	625.9 (34.20%)	1613 (59.48%)	1703 (41.68%)	1975 (51.26%)
C_{max} (ng/mL)	2.143 (40.57%)	5.240 (41.98%)	12.37 (29.31%)	57.11 (29.35%)	169.9 (67.46%)	161.1 (48.31%)	185.2 (63.84%)
t_{max} (h)	5.5 (5.0 - 8.1)	8.0 (5.0 - 8.0)	6.5 (5.0 - 8.0)	5.0 (5.0 - 8.0)	5.0 (5.0 - 8.1)	5.0 (5.0 - 5.0)	5.0 (5.0 - 5.0)
$t_{1/2}$ (h)	5.67 (0.9359)	4.99 (0.6915)	6.95 (1.441)	5.71 (0.7318)	6.65 (1.941)	6.27 (1.375)	5.69 (1.329)
CL/F (L/h)	40.06 (18.99)	34.22 (5.353)	55.21 (20.38)	45.1 (14.34)	56.81 (29.90)	101.53 (41.44)	88.79 (37.22)
V_z/F (L)	319.83 (140.8)	243.83 (30.76)	550.11 (213.1)	363.92 (101.7)	513.26 (261.4)	926.79 (470.9)	720.59 (307.6)

Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{0-inf}=area under the plasma concentration-time curve from time 0 to infinity, as determined $AUC_{0-last}+C_{last}/\lambda_z$; AUC_{0-t}=area under the plasma concentration-time curve from time 0to the last measurable concentration (C_{last}), as determined using the linear up/log-down trapezoidal rule; CL/F=apparent clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation; max=maximum, min=minimum; N=number of subjects; PK=pharmacokinetic; SD=standard deviation; $t_{½}$=apparent terminal elimination half-life; t_{max}=time to maximum plasma concentration; Vz/F=apparent volume of distribution

AUCs and C_{max} are presented as geometric mean (geometric CV%); t_{max} is presented as Median (Min, Max); other parameters are presented as mean (SD). NC = Not calculated
For Cohort A2, only calculated AUC_{0-inf}, $t_{1/2}$, CL/F, V_z/F, and AUC_{0-inf}/Dose are shown (N = 4)

Summary of Plasma PK Parameters Following Multiple Doses – Part B (PK Analysis Population)

Parameter	Cohort B1 9 mg QD N = 6		Cohort B2 27 mg QD N = 5		Cohort B3 67.5 mg QD N = 6	
	Day		Day		Day	
	1	7	1	7	1	7
AUC_{tau} (h*ng/mL)	149.6 (82.68%)	197.3 (79.62%)	411.6 (46.41%)	420.2 (53.83%)	785.8 (57.83%)	714.5 (62.36%)
C_{max} (ng/mL)	14.88 (96.73%)	16.69 (68.63%)	42.08 (50.99%)	40.84 (64.84%)	79.02 (68.52%)	68.41 (72.02%)
C_{min} (ng/mL)	NC	1.615 (136.7%)	NC	2.667 (90.80%)	NC	5.576 (81.92%)
t_{max} (h)	8.0 (5.0 - 12)	6.0 (6.0 - 12)	5.0 (5.0 - 8.0)	6.0 (6.0 - 8.0)	5.5 (5.0 - 8.0)	6.0 (6.0 - 12)
$t_{1/2}$ (h)	5.81 (1.132)	6.69 (1.647)	4.98 (1.151)	7.06 (2.626)	5.61 (1.077)	8.37 (3.032)
CL/F (L/h)	73.34 (51.57)	54.69 (32.10)	70.83 (30.49)	71.33 (37.25)	97.42 (56.90)	109.11 (69.07)
V_z/F (L)	646.42 (573.9)	519.88 (332.9)	513.26 (282.0)	800.97 (739.8)	780.41 (453.6)	1542.87 (1536)
AR_AUC_{tau}	NC	1.159 (24.80%)	NC	1.021 (71.81%)	NC	0.9092 (32.66%)
AR_C_{max}	NC	1.122 (32.60%)	NC	0.9706 (113.2%)	NC	0.8658 (36.56%)
LI	NC	1.05 (0.2193)	NC	1.1 (0.6796)	NC	0.86 (0.2379)

Abbreviations: AR=accumulation ratio; AUC=area under the plasma concentration-time curve; AUC_{tau}=area under the plasma concentration-time curve over a dosing interval (Day 7); CL/F=apparent clearance; C_{max}=maximum plasma concentration; C_{min}=minimum concentration observed over a dosing interval; CV=coefficient of variation; LI=linearity factor; max=maximum; min=minimum; N=number of subjects; PK=pharmacokinetic; QD=once daily; SD=standard deviation;$t_{½}$=apparent terminal elimination half-life; t_{max}=time to maximum plasma concentration; V_z/F=apparent volume of distribution

AUCs, C_{max}, and C_{min} are presented as geometric mean (geometric CV%); t_{max} is presented as Median (Min, Max); other parameters are presented as mean (SD). NC = Not calculated
For Cohort B1 Day 1, only calculated AUC_{tau}, $t_{1/2}$, CL/F, V_z/F, and AUC_{tau}/Dose are shown (N = 5)
For Cohort B1 Day 7, only calculated AR_AUC_{tau} is shown (N = 5)