W4403

Pharmacokinetics of AC220 and its Active Metabolite AC886, a FLT-3 Inhibitor, Following Sequential Oral Dose Escalation to Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

Ahmed Kousba[1], Joyce James[2], Guy Gammon[2];
[1]BioAgilytix, San Diego, CA, 92121. [2]Ambit Biosciences Corp., San Diego, CA, 92121.

BioAgilytix

ABSTRACT

Purpose:

AC220, a FLT-3 inhibitor, is being investigated for the treatment of Acute Myeloid Leukemia (AML). The objective of this study was to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AC220 and its active metabolite AC886 following once daily escalating oral dosing to patients with relapsed or treatment-refractory AML.

Methods:

This was a phase I open-label, sequential dose escalation study investigating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of AC220 when administered daily to patients with relapsed or refractory AML. AC220 was administered at daily doses ranging from 12 to 450 mg for 14 days followed by a 14-day rest in each 28-day cycle. Two groups of patients received AC220 for 28 days in each 28-day cycle at 200 and 300 mg doses. Plasma samples were analyzed for AC220 and its active metabolite, AC886, using a validated HPLC-MS/MS assay. Individual plasma PK parameters were estimated using standard non-compartmental methods. Dose proportionality was assessed using the linear model and ANOVA model.

Results:

AC220 was fairly rapidly absorbed with median T_{max} values ranging from 1.00 to 5.00 hours. AC220 C_{max} and $AUC_{(0-24)}$ increased in a proportional manner as AC220 dose increases. AC220 median C_{max} values increased from 23.2 (16.9- 29.4) to 849 (535-1220) ng/mL on Day 1 and from 88.5 (54.9-122) to 3660 (886-3790) ng/mL on Day 8 for 12 to 450 mg dose. Corresponding $AUC_{(0-24)}$ increased from 411 (312-511) to 12900 (9030-20500) ng•h/mL on Day 1 and from 1630 (1120-2140) to 58600 (17700-64300) ng•h/mL on Day 8. Metabolite AC886 was readily measurable in plasma and its C_{max} and $AUC_{(0-24)}$ increased proportionally as a function of AC220 dose. $AUC_{(0-24)}$ values of AC886 were typically ~ 4-fold lower than the corresponding values for AC220. Both AC220 and AC886 displayed moderate accumulation following repeated daily dosing of AC220 for 8 days with median accumulation factors (AR) of 3.8 for AC220 and 4.8 for AC886.

Conclusions:

AC220 and its active metabolite, AC886, exhibited favorable PK in humans with systemic exposure that supports once daily dosing. AC220 was fairly rapidly absorbed, and was dose proportional. AC886 was rapidly produced and measurable in plasma following AC220 dosing and was also dose proportional.

Objective

To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AC220 and its active metabolite AC886 following once daily escalating oral dosing to patients with relapsed or treatment-refractory AML.

Introduction

AC220, a potent and selective FLT-3 inhibitor, is being investigated as an oral, once-a-day, monotherapy for treatment of AML.

Acute myeloid leukemia (AML) is the most common acute leukemia affecting adults. ITD mutations in the FLT-3 gene occurring in 25-30% of AML patients and confer poor prognosis, early relapse, and lower survival rate with existing therapies.

American Cancer Society estimate for adult new cases diagnosed with AML in the United States 2011 is approximately 12,950 with approximately 9,050 expected to die of the disease in that year.

This poster presents the PK of AC220 and its active metabolite AC886 in patients with relapsed or treatment-refractory AML.

Materials and Methods

A. Study

A phase I open-label, sequential dose escalation study investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of AC220 in patients with relapsed or refractory AML.

B. Dose

AC220 was administered at doses ranging from 12 to 450 mg for 14 days followed by a 14-day rest in each 28-day cycle (Intermittent Dosing, ID). Two groups of subjects received AC220 for 28 days at 200 and 300 mg doses (Continuous Dosing, CD).

C. Analytical Method

The plasma samples were analyzed for AC220 and its active metabolite, AC886, using a validated HPLC-MS/MS assay.

D. PK Analysis

Plasma PK parameters (C_{max}, T_{max}, and $AUC_{(0-24)}$) of AC220 and its active metabolite, AC886, were determined using WinNonlin Professional 5.2.1 (Pharsight Corp., Mountain View, CA).

Dose proportionality was examined using a simple linear regression model and an ANOVA model (p value set at $p \geq 0.05$) using GraphPad Prism v 5.01 (GraphPad Inc., CA).

The equation for linear regression is $AUC_{(0-24)}$ or $C_{max} = \mu + ß \times dose$; where µ represents the intercept and ß is the slope of the regression model. If the slope was significantly greater than zero and the intercept was not significantly greater than zero, then evidence of linearity was assumed.

In ANOVA, statistical difference among the group means for dose-normalized C_{max} (i.e., C_{max}/dose) and $AUC_{(0-24)}$ (i.e., $AUC_{(0-24)}$/dose) was utilized for proportionality assessment. If the null hypothesis was achieved (i.e.: no difference between dose groups; ($p \geq 0.05$)), then dose proportionality was assumed.

Results

PK of AC220:

AC220 demonstrated fairly rapid absorption with Day 1 median T_{max} values ranging from 2.00 to 5.00 hours (Figure 1 and Table 1). The median C_{max} increased from 23.2 (16.9-29.4) to 849 (535-1220) ng/mL and the $AUC_{(0-24)}$ increased from 411 (312-511) to 12900 (9030-20500) ng•h/mL as the AC220 dose was increased from 12 to 450 mg.

AC220 T_{max} did not change with repeated dosing (Figure 1 and Table 1). Day 8 median C_{max} values increased from 88.5 (54.9-122) to 3660 (886-3790) ng/mL and median $AUC_{(0-24)}$ values increased from 1630 (1120-2140) to 58600 (17700-64300) ng•h/mL as the AC220 dose was increased from 12 to 450 mg. The median accumulation factor (AR) of AC220 ranged from 1.68 to 6.77 across all dose levels (Table 1).

Both the linear regression and ANOVA models indicate that AC220 exposure on Days 1 and 8 is dose proportional over the range of 12 to 450 mg AC220 (Table 3 and Figures 2 and 3).

PK of AC886:

Metabolite AC886 was readily measurable in plasma with median T_{max} values ranging from 4.00 to 23.8 hours (Figure 2 and Table 2). Day 1 median AC886 C_{max} increased from 3.88 (3.37-4.39) to 189 (62.0-278) ng/mL and the $AUC_{(0-24)}$ increased from 69.9 (51.6-88.1) to 3310 (1240-4900) ng•h/mL as the AC220 dose was increased from 12 to 450 mg.

Day 8 AC886 median C_{max} values increased from 19.6 (19.5-19.7) to 849 (535-1220) ng/mL and the mean $AUC_{(0-24)}$ values increased from 434 (417-451) to 10600 (7450-19700) ng•h/mL as the AC220 dose was increased from 12 to 450 mg. Median accumulation factor (AR) of AC886 ranged from 3.05 to 8.59 across all dose levels (Table 2). $AUC_{(0-24)}$ values of AC886 on Days 1 and 8 were ~ 4-fold lower than the corresponding values for AC220 (Compare Tables 1 and 2).

The exposure of AC886 (C_{max} and $AUC_{(0-24)}$) appeared to be proportional to AC220 doses at 12 to 450 mg AC220 (Table 3 and Figures 4 and 5).

Table 1

Summary Mean Plasma PK Parameters of AC220 in Human Subjects on Days 1 and 8 Following Escalating Oral Doses of AC220

AC220 PK Parameter	12 mg ID			18 mg ID			27 mg ID			40 mg ID		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Day 1												
T_{max}, h	2.00	4.03	6.05	2.00	3.00	8.00	2.00	2.00	8.00	1.00	2.00	4.07
C_{max}, ng/mL	16.9	23.2	29.4	26.8	39.2	45.9	57.8	81.1	108	25.5	74.0	120
C_{max}/Dose, (ng/mL)/mg	2.00	4.03	6.05	2.00	3.00	8.00	2.00	2.00	8.00	1.00	2.00	4.07
$AUC_{(0-24)}$, ng•h/mL	16.9	23.2	29.4	26.8	39.2	45.9	57.8	81.1	108	25.5	74.0	120
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	2.00	4.03	6.05	2.00	3.00	8.00	2.00	2.00	8.00	1.00	2.00	4.07
$T_{1/2}$, h	16.9	23.2	29.4	26.8	39.2	45.9	57.8	81.1	108	25.5	74.0	120
Day 8												
T_{max}, h	1.00	3.50	6.00	2.00	4.00	4.00	1.00	2.00	4.00	1.00	2.92	4.00
C_{max}, ng/mL	54.9	88.5	122	81.9	126	204	42.1	303	499	111	226	302
C_{max}/Dose, (ng/mL)/mg	4.58	7.37	10.2	4.55	7.00	11.3	1.56	11.2	18.5	2.78	5.65	7.55
$AUC_{(0-24)}$, ng•h/mL	1,120	1,630	2,140	1,590	2,420	3,450	554	2,990	7,390	1,390	4,480	5,720
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	93.3	136	178	88.3	134	192	20.5	111	274	34.8	112	143
AR	3.59	3.89	4.19	2.91	3.68	4.84	0.621	1.68	4.25	1.03	3.51	6.98

AC220 PK Parameter	60 mg ID			90 mg ID			135 mg ID			200 mg ID		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Day 1												
T_{max}, h	2.00	2.00	4.00	2.00	2.00	2.00	2.00	3.00	9.00	4.00	4.00	6.00
C_{max}, ng/mL	98.3	176	271	85.7	98.9	256	243	347	410	227	255	479
C_{max}/Dose, (ng/mL)/mg	1.64	2.93	4.52	0.952	1.10	2.84	1.80	2.57	3.04	1.14	1.28	2.40
$AUC_{(0-24)}$, ng•h/mL	1,730	2,120	2,820	1,240	1,440	3,450	3,340	4,890	7,720	3,390	4,350	8,420
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	28.8	35.3	47.0	13.8	16.0	38.3	24.7	36.3	57.2	17.0	21.8	42.1
$T_{1/2}$, h	16.6	24.0	37.1	28.1	28.1	28.1	10.1	18.3	26.5	12.7	32.8	35.3
Day 8												
T_{max}, h	2.00	2.00	6.00	4.00	6.00	8.00	2.00	4.00	4.00	4.00	5.00	23.8
C_{max}, ng/mL	346	436	835	490	741	992	575	818	969	824	1,190	1,930
C_{max}/Dose, (ng/mL)/mg	5.77	7.27	13.9	5.44	8.23	11.0	4.26	6.06	7.18	4.12	5.95	9.65
$AUC_{(0-24)}$, ng•h/mL	6,090	9,840	12,000	9,580	14,800	20,000	5,880	9,190	15,100	16,300	21,600	38,700
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	102	164	200	106	164	222	43.6	68.1	112	81.5	108	194
AR	2.19	5.05	5.69	5.80	6.77	7.73	1.09	1.96	2.09	2.00	4.46	6.20

AC220 PK Parameter	200 mg CD			300 mg ID			300 mg CD			450 mg ID		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Day 1												
T_{max}, h	2.00	2.00	8.00	2.00	3.00	6.00	2.00	2.00	8.00	2.00	4.00	4.00
C_{max}, ng/mL	216	434	863	362	514	866	478	592	1,250	535	849	1,220
C_{max}/Dose, (ng/mL)/mg	1.08	2.17	4.32	2.00	1.71	2.89	1.59	1.97	4.17	1.19	1.89	2.71
$AUC_{(0-24)}$, ng•h/mL	3,740	5,990	12,600	26.8	9,810	13,800	6,470	11,300	16,000	9,030	12,900	20,500
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	18.7	30.0	63.0	2.00	32.7	46.0	21.6	37.7	53.3	20.1	28.7	45.6
$T_{1/2}$, h	10.4	21.2	53.1	26.8	22.2	22.2	23.6	32.9	45.5	18.4	34.5	50.7
Day 8												
T_{max}, h	2.00	2.00	4.50	1.83	2.00	8.67	1.00	2.00	6.00	0.00	1.00	2.00
C_{max}, ng/mL	919	1,410	2,380	566	2,340	3,320	1,390	2,620	2,630	886	3,660	3,790
C_{max}/Dose, (ng/mL)/mg	4.60	7.03	11.9	1.89	7.78	11.1	4.63	8.73	8.77	1.97	8.13	8.42
$AUC_{(0-24)}$, ng•h/mL	12,200	25,200	46,200	12,300	42,300	68,000	30,200	48,400	52,900	17,700	58,600	64,300
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	61.0	117	231	41.0	141	227	101	161	176	39.3	130	143
AR	1.61	3.73	6.55	1.57	4.39	6.99	3.97	4.48	4.67	1.96	3.14	4.54

AR - Accumulation Factor calculated from ratio of Day 8 mean $AUC_{(0-24)}$/Day 1 $AUC_{(0-24)}$
CD - Continuous Dosing (28-days on cycle)
ID - Intermittent Dosing (14-day on and 14-day off cycle)

Table 2

Summary Mean Plasma PK Parameters of AC886 in Human Subjects on Days 1 and 8 Following Escalating Oral Doses of AC220

AC886 PK Parameter	12 mg ID			18 mg ID			27 mg ID			40 mg ID		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Day 1												
T_{max}, h	8.00	16.0	24.1	2.00	14.0	24.0	2.00	6.00	23.8	2.00	6.00	24.2
C_{max}, ng/mL	3.37	3.88	4.39	3.32	7.45	10.2	9.04	14.6	16.8	18.3	45.1	82.9
C_{max}/Dose, (ng/mL)/mg	0.281	0.323	0.366	0.184	0.414	0.567	.0335	0.541	0.622	0.458	1.13	2.07
$AUC_{(0-24)}$, ng•h/mL	51.6	69.9	88.1	47.0	142	210	158	242	326	354	948	1,710
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	4.30	5.82	7.34	2.61	7.86	11.7	5.85	8.96	12.1	8.85	23.7	42.8
$T_{1/2}$, h	ND	ND	ND	40.6	40.6	40.6	79.2	79.2	79.2	62.0	68.2	74.5
Ratio Median $AUC_{(0-24)}$ AC886/AC220	-	0.170	-	-	0.225	-	-	0.170	-	-	0.702	-
Day 8												
T_{max}, h	8.00	15.9	23.8	0.00	1.00	2.00	1.00	4.00	6.08	2.92	4.00	24.1
Cmax, ng/mL	19.5	19.6	19.7	886	3,660	3,790	35.9	105	199	72.2	145	261
C_{max}/Dose, (ng/mL)/mg	1.63	1.63	1.64	1.97	8.13	8.42	1.33	3.89	7.37	1.81	3.63	6.53
$AUC_{(0-24)}$, ng•h/mL	417	434	451	414	970	1,400	565	1,020	3,890	1,670	3,010	4,950
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	34.8	36.2	37.6	39.3	130	143	20.9	37.8	144	41.8	75.3	124
AR	4.73	6.74	8.74	1.96	3.14	4.54	2.57	4.21	16.9	2.59	3.05	4.72
Ratio Median $AUC_{(0-24)}$ AC886/AC220	-	0.266	-	-	0.401	-	-	0.341	-	-	0.672	-

AC886 PK Parameter	12 mg ID			18 mg ID			27 mg ID			40 mg ID		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Day 1												
T_{max}, h	4.00	4.00	8.00	4.00	23.8	24.0	4.00	8.50	24.0	6.00	8.92	23.8
C_{max}, ng/mL	12.2	34.5	82.3	13.4	30.6	39.3	42.5	88.7	318	51.4	85.7	182
C_{max}/Dose, (ng/mL)/mg	0.203	0.575	1.37	0.149	0.340	0.437	0.315	0.657	2.36	0.257	0.429	0.910
$AUC_{(0-24)}$, ng•h/mL	263	743	1,590	223	578	791	806	1,520	6,300	960	1,500	3,620
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	4.38	12.4	26.5	2.48	6.42	8.79	5.97	11.3	46.7	4.80	7.50	18.1
$T_{1/2}$, h	59.3	59.3	59.3	ND	ND	ND	ND	ND	ND	ND	ND	ND
Ratio Median $AUC_{(0-24)}$ AC886/AC220	-	0.350	-	-	0.401	-	-	0.311	-	-	0.345	-
Day 8												
T_{max}, h	2.00	6.00	24.0	4.00	6.00	8.00	2.00	4.00	4.00	4.00	6.00	8.00
C_{max}, ng/mL	41.5	109	481	156	274	391	171	212	698	266	428	905
C_{max}/Dose, (ng/mL)/mg	0.692	1.82	8.02	1.73	3.04	4.34	1.27	1.57	5.17	1.33	2.14	4.53
$AUC_{(0-24)}$, ng•h/mL	924	2,290	9,850	3,310	5,430	7,540	1,200	4,170	14,600	5,650	8,790	17,400
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	15.4	38.2	164	36.8	60.3	83.8	8.89	30.9	108	28.3	43.9	87.0
AR	1.91	3.51	13.3	4.18	8.59	13.0	0.857	5.17	8.85	3.35	5.53	11.6
Ratio Median $AUC_{(0-24)}$ AC886/AC220	-	0.233	-	-	0.367	-	-	0.454	-	-	0.407	-

AC886 PK Parameter	12 mg ID			18 mg ID			27 mg ID			40 mg ID		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Day 1												
T_{max}, h	4.00	7.00	23.8	6.00	23.9	24.0	4.00	8.00	24.0	6.00	23.8	24.0
C_{max}, ng/mL	18.0	99.0	529	34.7	124	140	41.3	74.7	323	62.0	189	278
C_{max}/Dose, (ng/mL)/mg	0.09	0.495	2.65	0.116	0.413	0.467	0.138	0.249	1.08	0.138	0.420	0.618
$AUC_{(0-24)}$, ng•h/mL	297	1,970	10,700	670	1,940	2,560	338	1,480	6,210	1,240	3,310	4,900
$AUC_{(0-24)}$/Dose, (ng•h/mL)/mg	1.49	9.85	53.5	2.23	6.45	8.53	1.13	4.93	20.7	2.76	7.36	10.9
$T_{1/2}$, h	30.1	43.2	56.2	ND	ND	ND	ND	ND	ND	ND	ND	ND
Ratio Median $AUC_{(0-24)}$ AC886/AC220	-	0.329	-	-	0.198	-	-	0.131	-	-	0.257	-
Day 8												
T_{max}, h	2.00	4.00	8.00	0.250	6.92	24.0	1.00	4.00	8.17	0.00	4.00	4.00
Cmax, ng/mL	152	339	1,310	239	493	633	235	268	667	417	523	922
Cmax/Dose, (ng/mL)/mg	0.760	1.69	6.55	0.797	1.64	2.11	0.783	0.893	2.22	0.927	1.16	2.05
AUC(0-24), ng•h/mL	2,290	5,090	28,100	5,330	11,200	13,700	4,830	5,280	14,700	7,450	10,600	19,700
AUC(0-24)/Dose, (ng•h/mL)/mg	11.5	25.5	141	17.8	37.4	45.7	16.1	17.6	49.0	16.6	23.6	43.8
AR	0.627	3.57	11.2	5.24	5.82	7.96	3.96	5.60	15.6	4.08	5.95	6.01
Ratio Median $AUC_{(0-24)}$ AC886/AC220	-	0.202	-	-	0.265	-	-	0.109	-	-	0.181	-

Figure 2

C_{max} of AC220 Versus AC220 Dose in Human Subjects Following Oral Administration of AC220 on Days 1 and 8

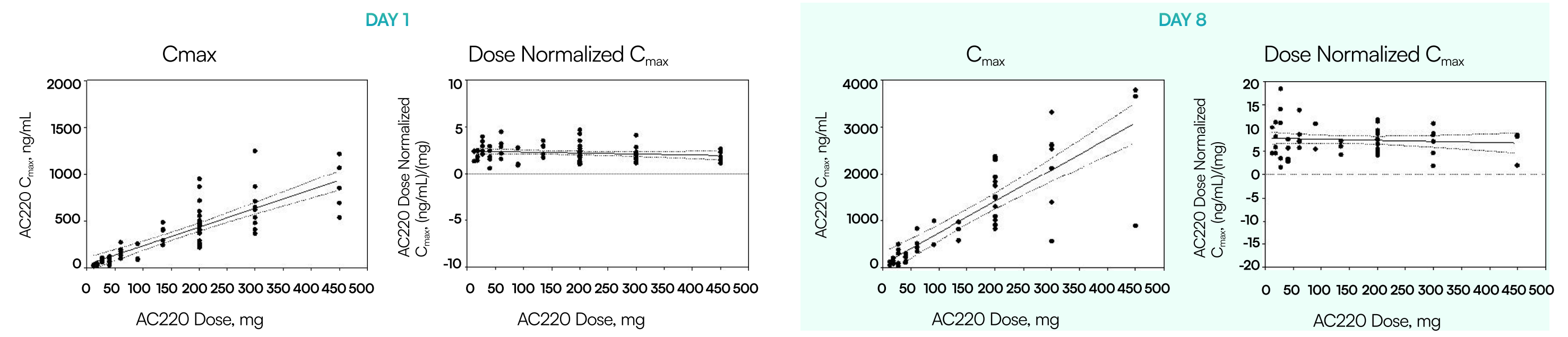


Figure 3

$AUC_{(0-24)}$ of AC220 Versus AC220 Dose in Human Subjects Following Oral Administration of AC220 on Days 1 and 8

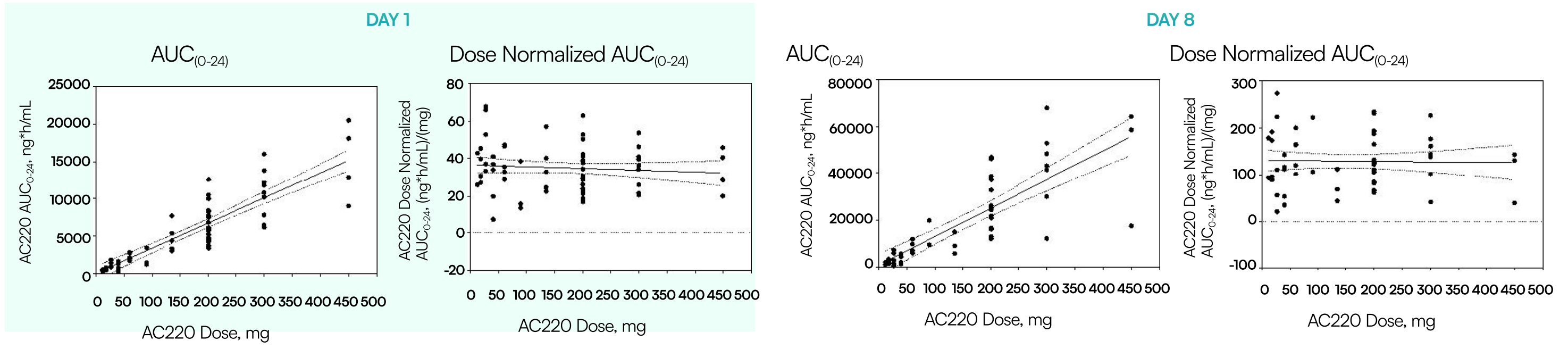


Figure 4

C_{max} of AC886 Versus AC220 Dose in Human Subjects Following Oral Administration of AC220 on Days 1 and 8

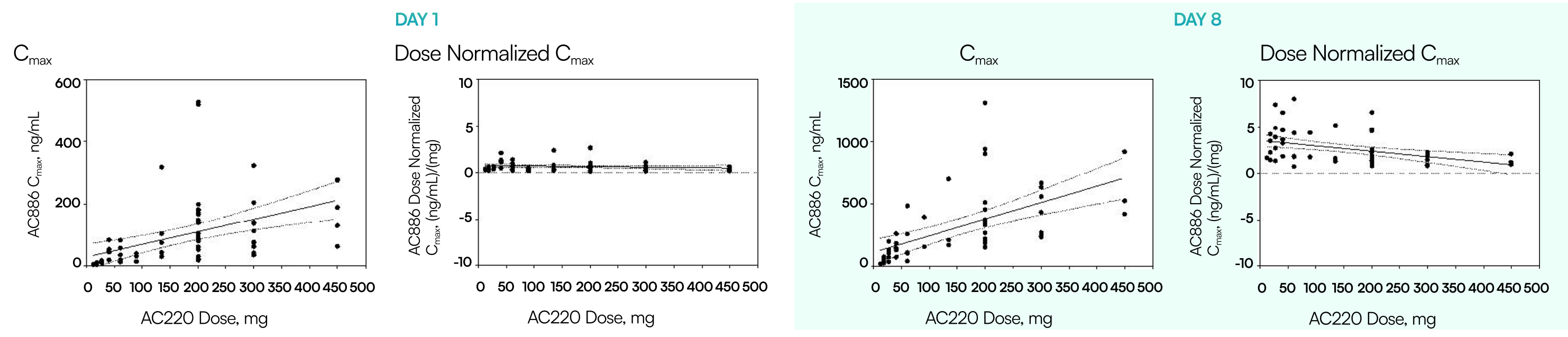


Figure 5

$AUC_{(0-24)}$ of AC886 Versus AC220 Dose in Human Subjects Following Oral Administration of AC220 on Days 1 and 8

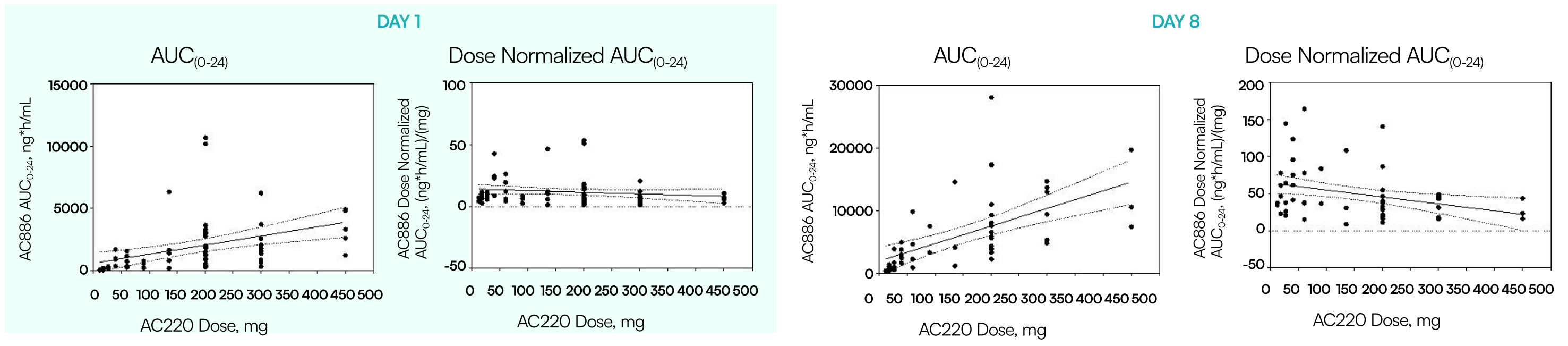


Table 3

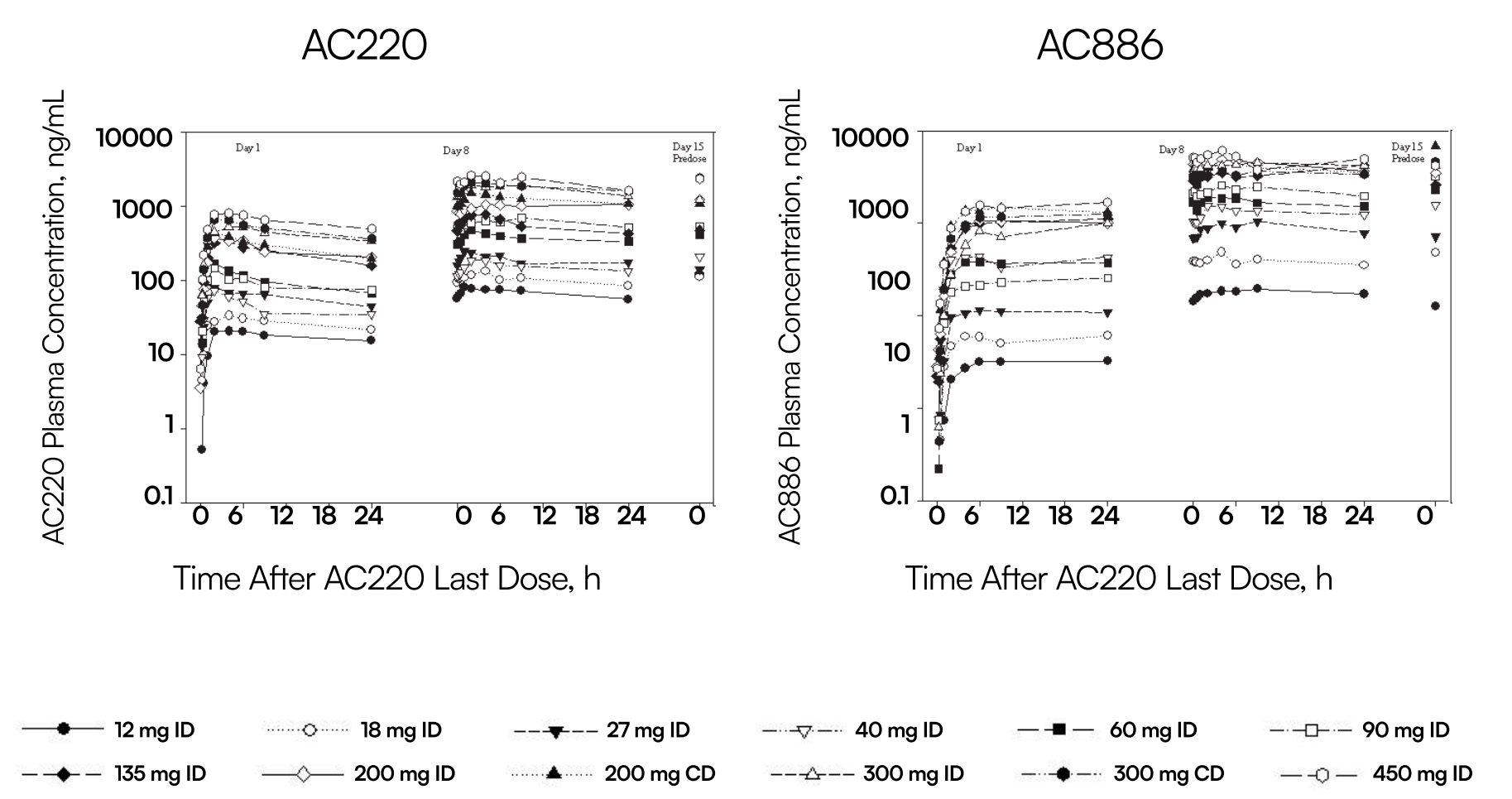
* The p value < 0.05 may be due to the intersubject variability in this data set

Summary Statistics for the Assessment of Dose Proportionality of AC220 and AC886 in Human Subjects on Days 1 and 8 Following Escalating AC220 Oral Doses

Analyte	Parameter	Linear Regression Model						ANOVA Model
		Slope (SE)	95% CI	P-value (Slope≠0)	Intercept (SE)	95% CI	P-value (Intercept=0)	P-value (among means)
AC220								
	Day 1							
	C_{max}	1.980 (0.1615)	1.657 to 2.303	< 0.0001	25.81 (34.33)	-42.84 to 94.46	0.4550	0.3667
	$AUC_{(0-24)}$	33.41 (2.277)	28.89 to 37.92	< 0.0001	41.30 (479.6)	-918.0 to 1001	0.9317	0.0807
	Day 8							
	C_{max}	6.645 (0.6540)	5.348 to 7.942	< 0.0001	64.75 (125.6)	-188.6 to 317.6	0.5086	0.3667
	$AUC_{(0-24)}$	120.3 (12.05)	96.05 to 144.6	<0.0001	720.8 (2350)	-4008 to 5450	0.7603	0.6680
AC220								
	Day 1							
	C_{max}	0.4046 (0.1003)	0.2039 to 0.6053	0.0001	28.84 (20.92)	-13.81 to 71.50	0.1813	0.1553
	$AUC_{(0-24)}$	7.198 (1.996)	3.206 to 11.19	0.0006	619.5 (424.2)	-229.1 to 1468	0.1494	0.362
	Day 8							
	C_{max}	1.317 (0.2633)	0.7874 to 1.847	<0.0001	113.2 (51.32)	9.920 to 216.5	0.0322*	0.2331
	$AUC_{(0-24)}$	27.96 (5.588)	16.72 to 39.21	< 0.0001	1969 (1089)	-222.8 to 4161	0.0769	0.5525

Figure 1

Mean Plasma Concentration-Time Profiles of AC220 and AC886 in Human Subjects on Days 1, 8 and 15 Following Escalating Oral Doses of AC220



Conclusions

AC220 and its active metabolite, AC886, exhibited favorable PK in humans with systemic exposure that supports once daily dosing. AC220 was fairly rapidly absorbed, and was dose proportional. AC886 was rapidly produced and measurable in plasma following AC220 dosing and was also dose proportional.

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