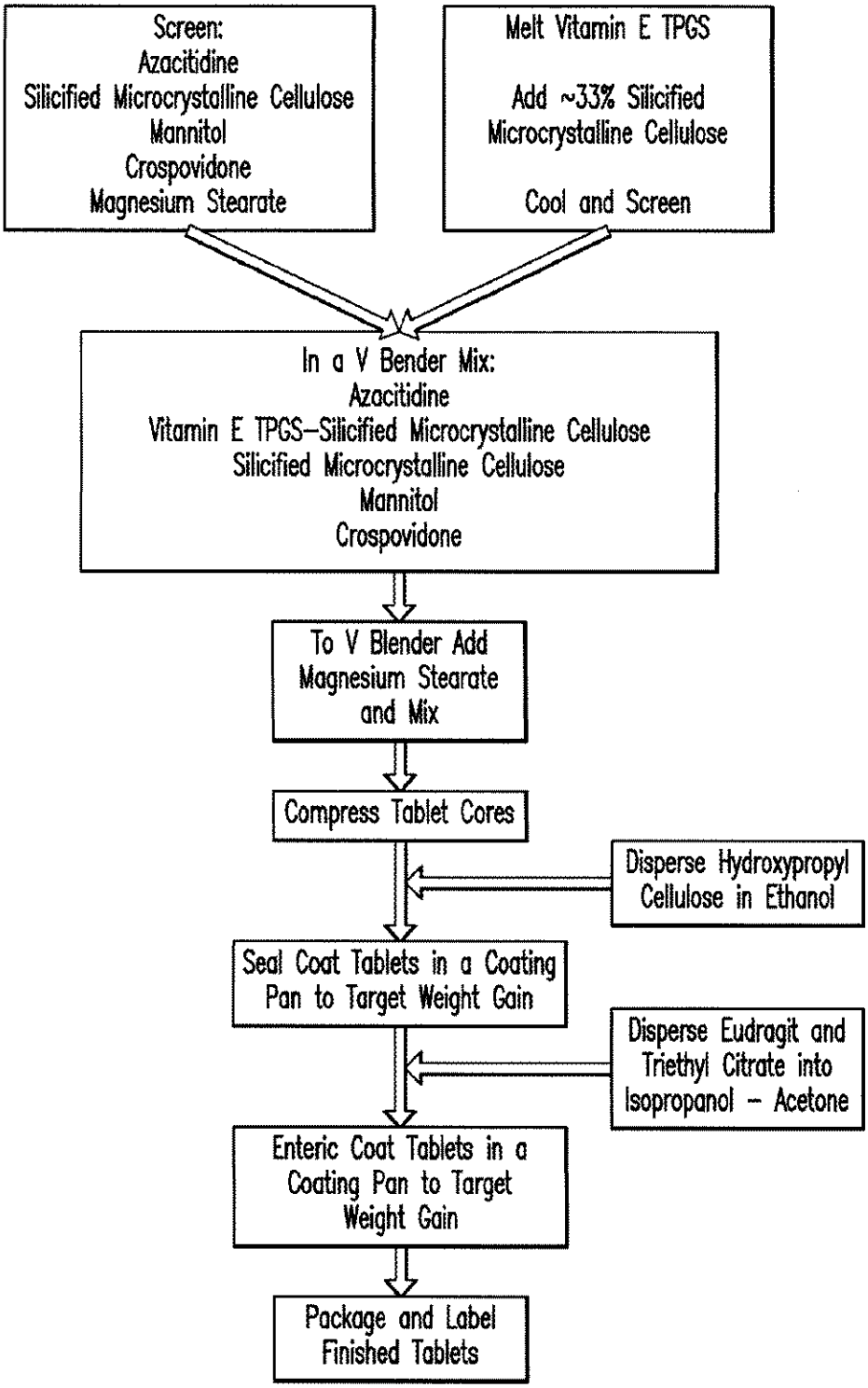

Screen:
Azacitidine
Silicified Microcrystalline Cellulose
Mannitol
Crospovidone
Magnesium Stearate
Melt Vitamin E TPGS
Add ~33% Silicified Microcrystalline Cellulose
Cool and Screen
In a V Bender Mix:
Azacitidine
Vitamin E TPGS–Silicified Microcrystalline Cellulose
Silicified Microcrystalline Cellulose
Mannitol
Crospovidone
To V Blender Add Magnesium Stearate and Mix
Compress Tablet Cores
Disperse Hydroxypropyl Cellulose in Ethanol
Seal Coat Tablets in a Coating Pan to Target Weight Gain
Disperse Eudragit and Triethyl Citrate into Isopropanol – Acetone
Enteric Coat Tablets in a Coating Pan to Target Weight Gain
Package and Label Finished Tablets

FIG.1

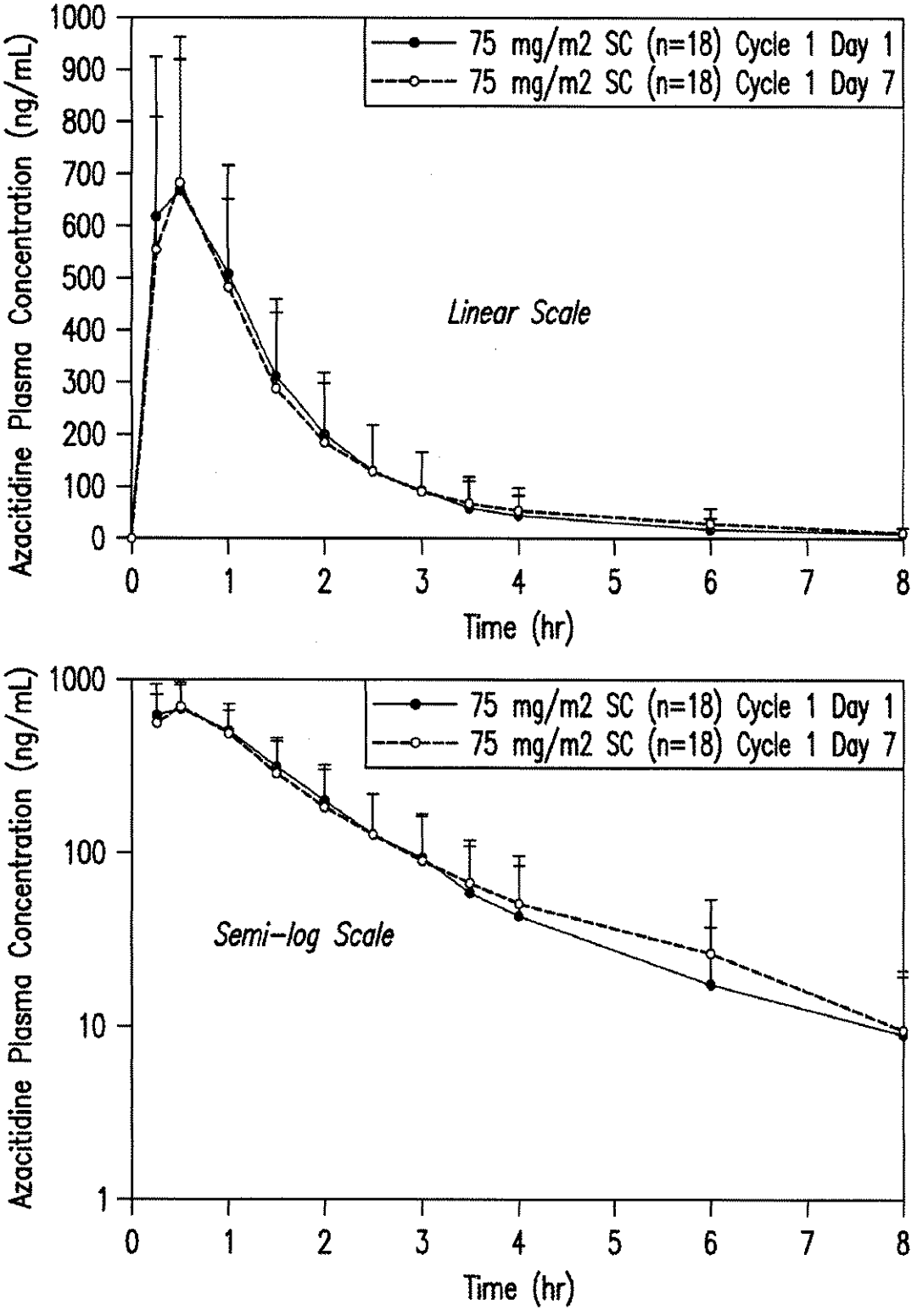

Azacitidine Plasma Concentration (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
75 mg/m2 SC (n=18) Cycle 1 Day 1
75 mg/m2 SC (n=18) Cycle 1 Day 7
Linear Scale
0
1
2
3
4
5
6
7
8
Time (hr)
Azacitidine Plasma Concentration (ng/mL)
1000
100
10
1
75 mg/m2 SC (n=18) Cycle 1 Day 1
75 mg/m2 SC (n=18) Cycle 1 Day 7
Semi-log Scale
0
1
2
3
4
5
6
7
8
Time (hr)

FIG.2

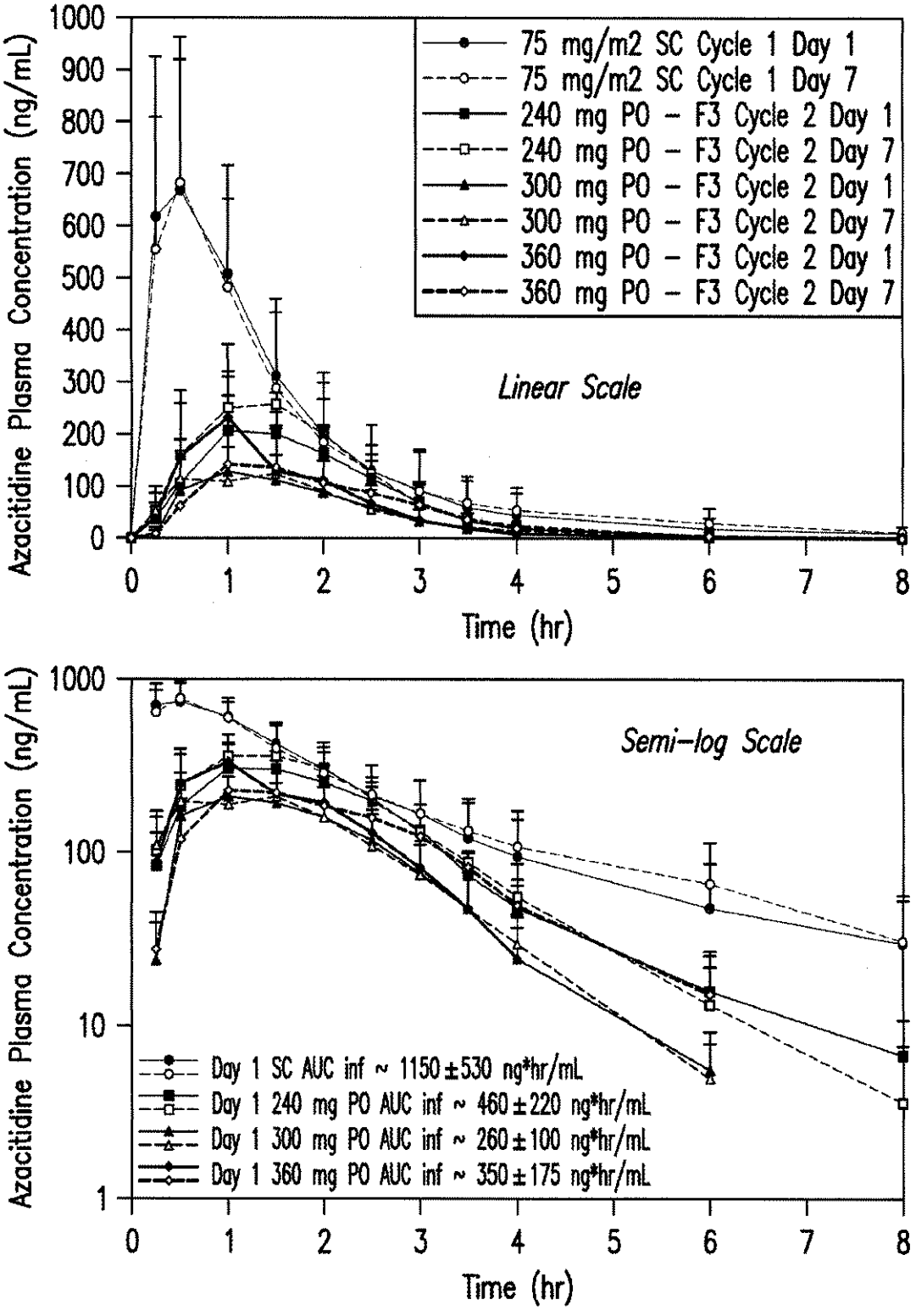
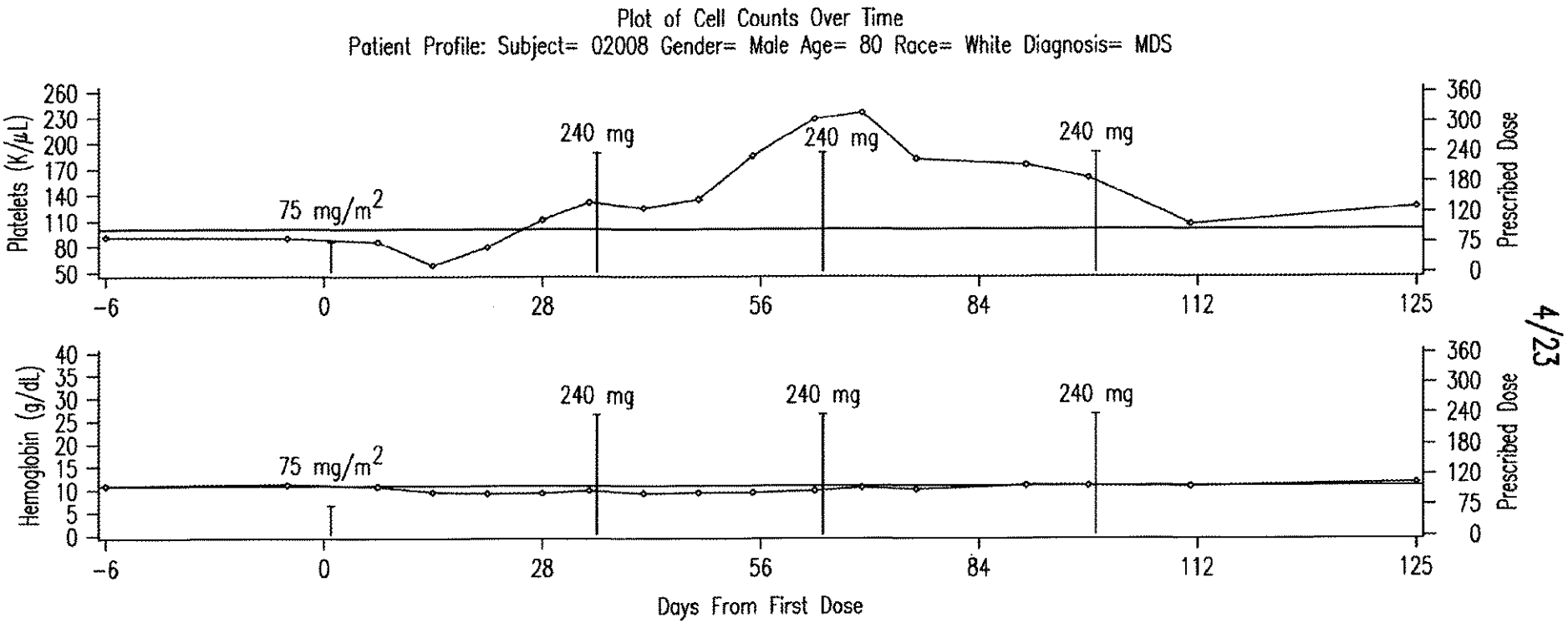
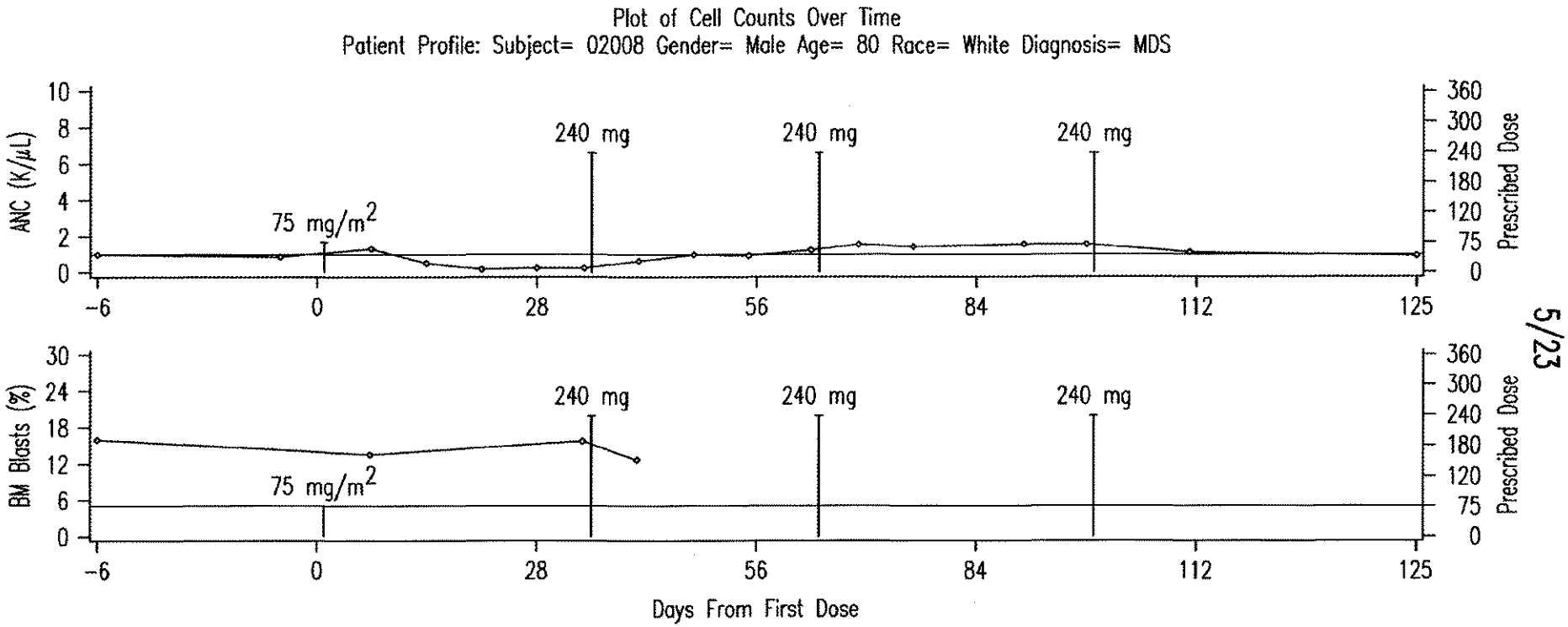

Azacitidine Plasma Concentration (ng/mL)
1000
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
8
Time (hr)
75 mg/m2 SC Cycle 1 Day 1
75 mg/m2 SC Cycle 1 Day 7
240 mg PO – F3 Cycle 2 Day 1
240 mg PO – F3 Cycle 2 Day 7
300 mg PO – F3 Cycle 2 Day 1
300 mg PO – F3 Cycle 2 Day 7
360 mg PO – F3 Cycle 2 Day 1
360 mg PO – F3 Cycle 2 Day 7
Linear Scale
Azacitidine Plasma Concentration (ng/mL)
1000
100
10
1
0
1
2
3
4
5
6
7
8
Time (hr)
Semi-log Scale
Day 1 SC AUC inf ~ 1150±530 ng*hr/mL
Day 1 240 mg PO AUC inf ~ 460±220 ng*hr/mL
Day 1 300 mg PO AUC inf ~ 260±100 ng*hr/mL
Day 1 360 mg PO AUC inf ~ 350±175 ng*hr/mL

FIG.3



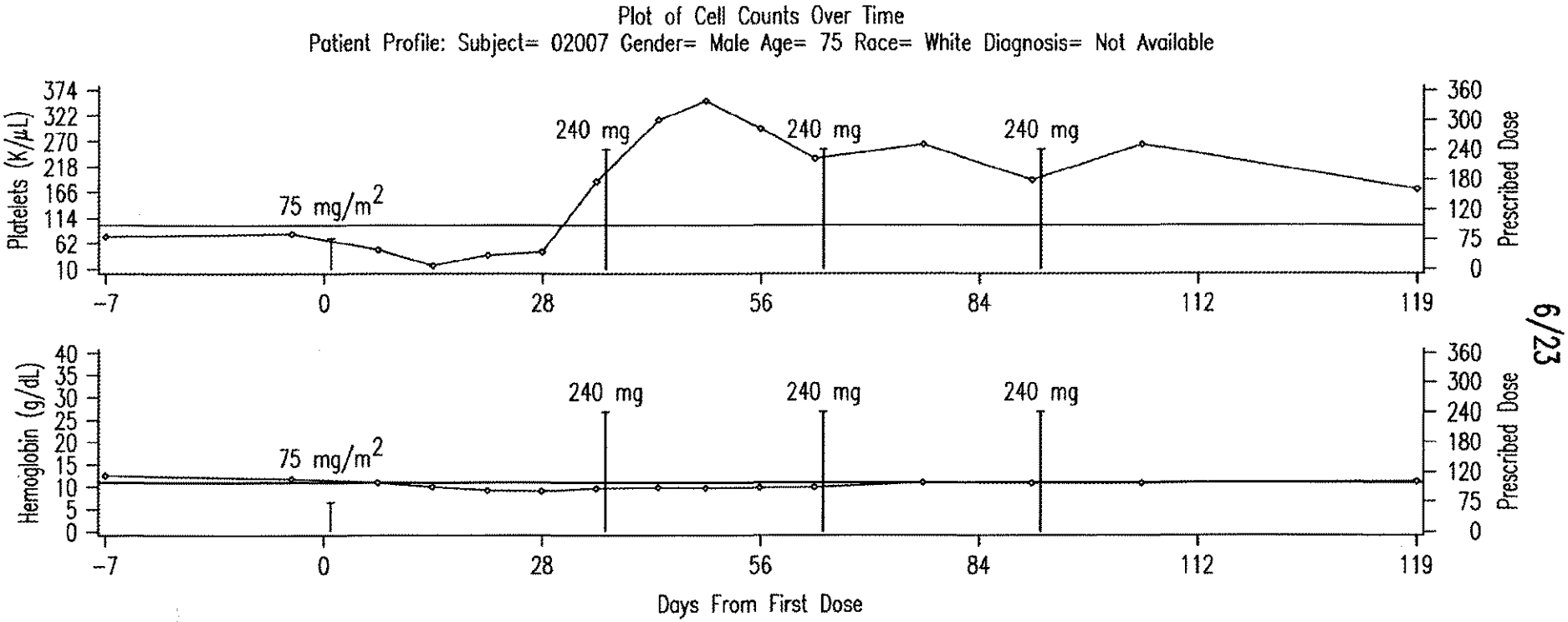
Note(s): P= Platelet transfusion, R= RBC transfusion. Verticle lines represent start of treatment cycles. 1K/μL = 1 k/cmm.

FIG.4A



Note(s): P= Platelet transfusion, R= RBC transfusion. Verticle lines represent start of treatment cycles. 1K/μL = 1 k/cmm.

FIG.4B



Note(s): P= Platelet transfusion, R= RBC transfusion. Verticle lines represent start of treatment cycles. 1K/μL = 1 k/cmm.

FIG.5A

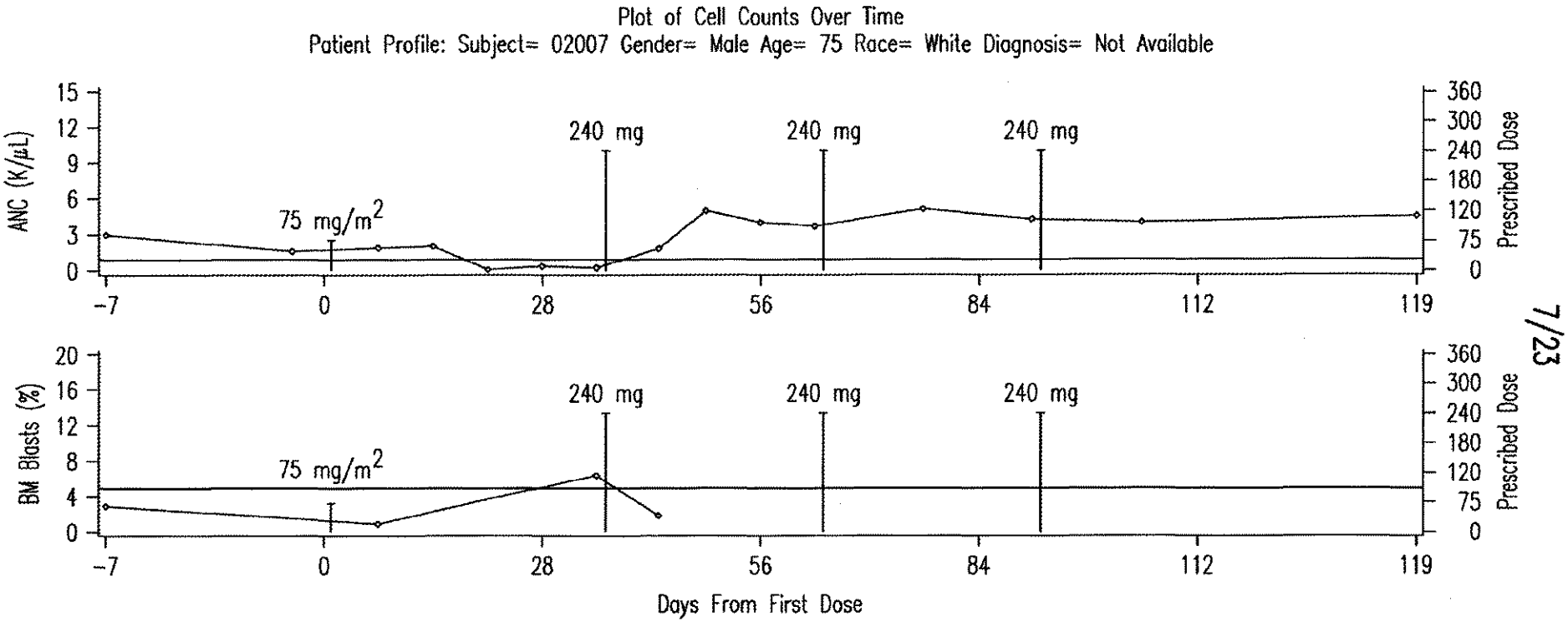
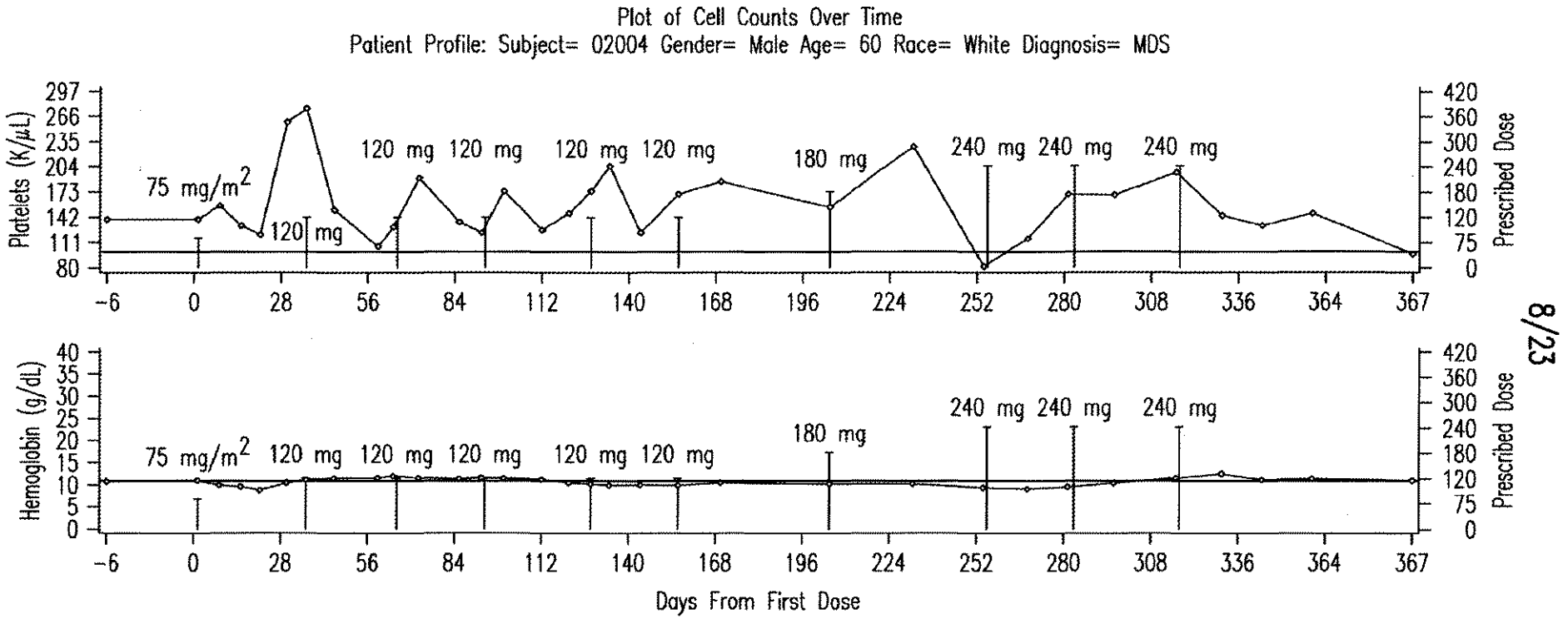
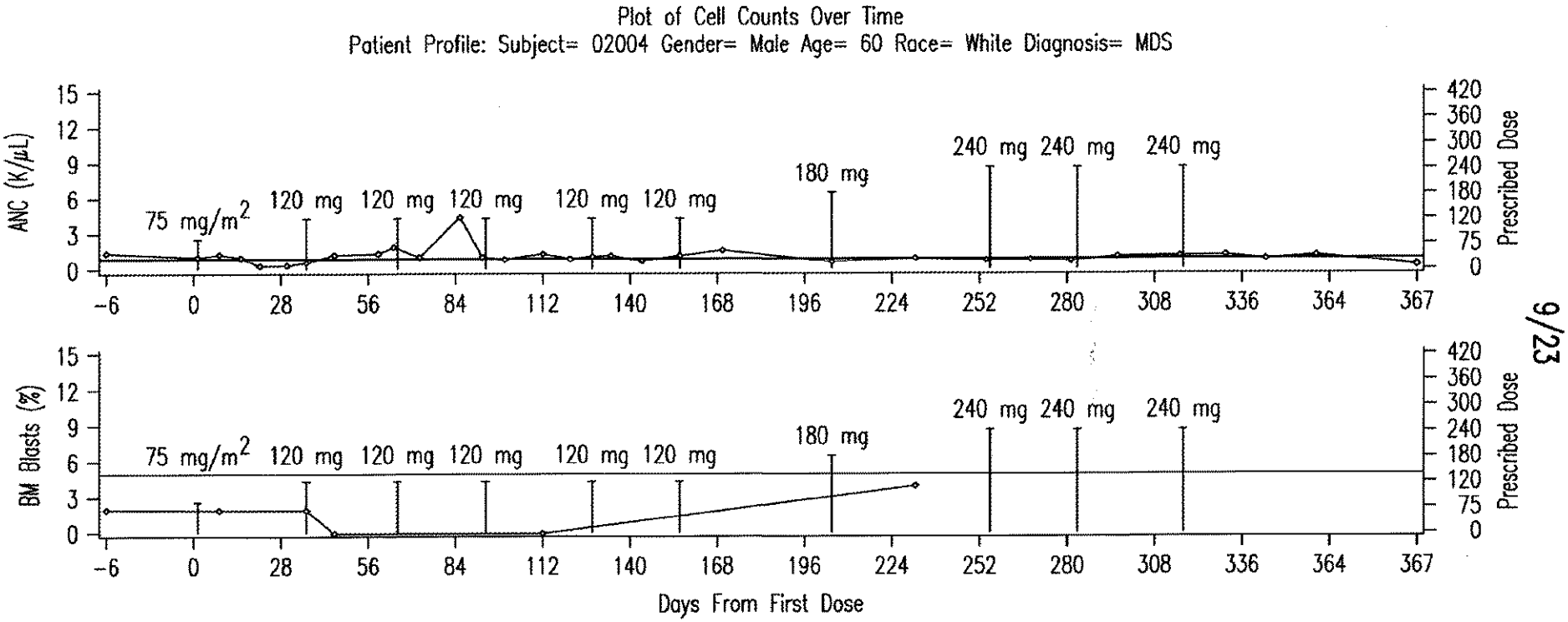

Plot of Cell Counts Over Time
Patient Profile: Subject= 02007 Gender= Male Age= 75 Race= White Diagnosis= Not Available
ANC (K/µL)
BM Blasts (%)
75 mg/m2
240 mg
240 mg
240 mg
Prescribed Dose
Days From First Dose
Note(s): P= Platelet transfusion, R= RBC transfusion. Verticle lines represent start of treatment cycles. 1K/µL = 1 k/cmm.

FIG.5B



Note(s): P= Platelet transfusion, R= RBC transfusion. Verticle lines represent start of treatment cycles. 1K/μL = 1 k/cmm.

FIG.6A



Note(s): P= Platelet transfusion, R= RBC transfusion. Verticle lines represent start of treatment cycles. 1K/μL = 1 k/cmm.

FIG.6B

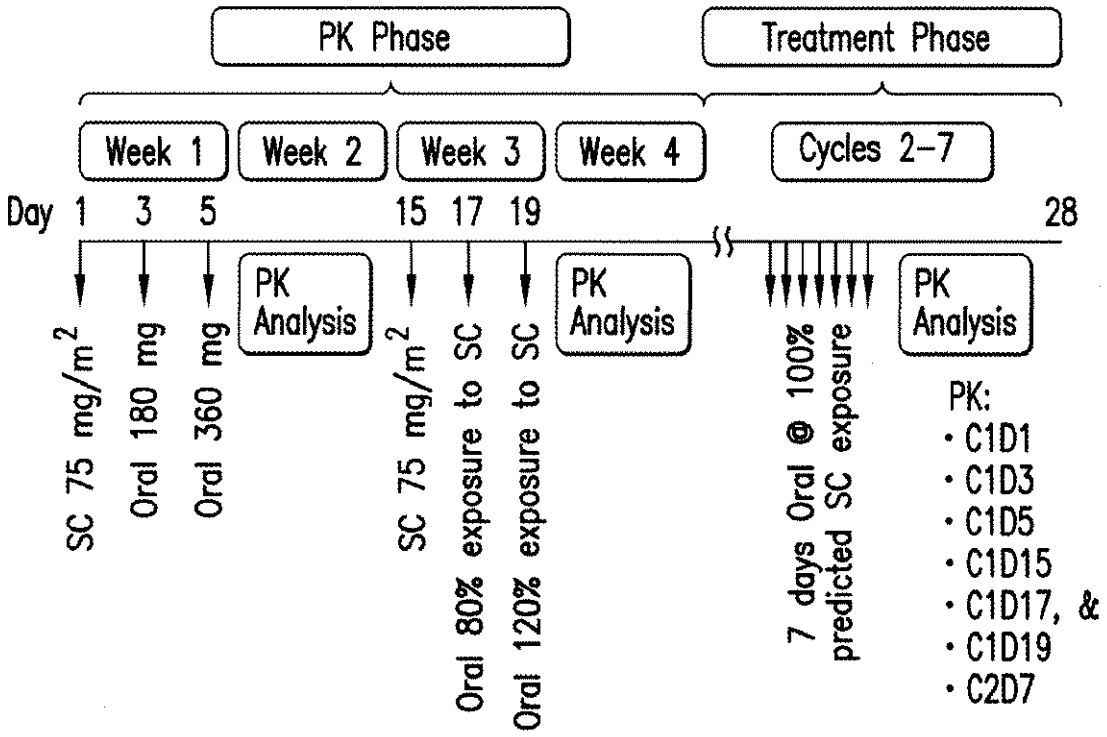

PK Phase
Treatment Phase
Week 1
Week 2
Week 3
Week 4
Cycles 2–7
Day 1 3 5 15 17 19 28
SC 75 mg/m2
Oral 180 mg
Oral 360 mg
PK Analysis
SC 75 mg/m2
Oral 80% exposure to SC
Oral 120% exposure to SC
PK Analysis
7 days Oral @ 100% predicted SC exposure
PK Analysis
PK:
• C1D1
• C1D3
• C1D5
• C1D15
• C1D17, &
• C1D19
• C2D7

FIG.7

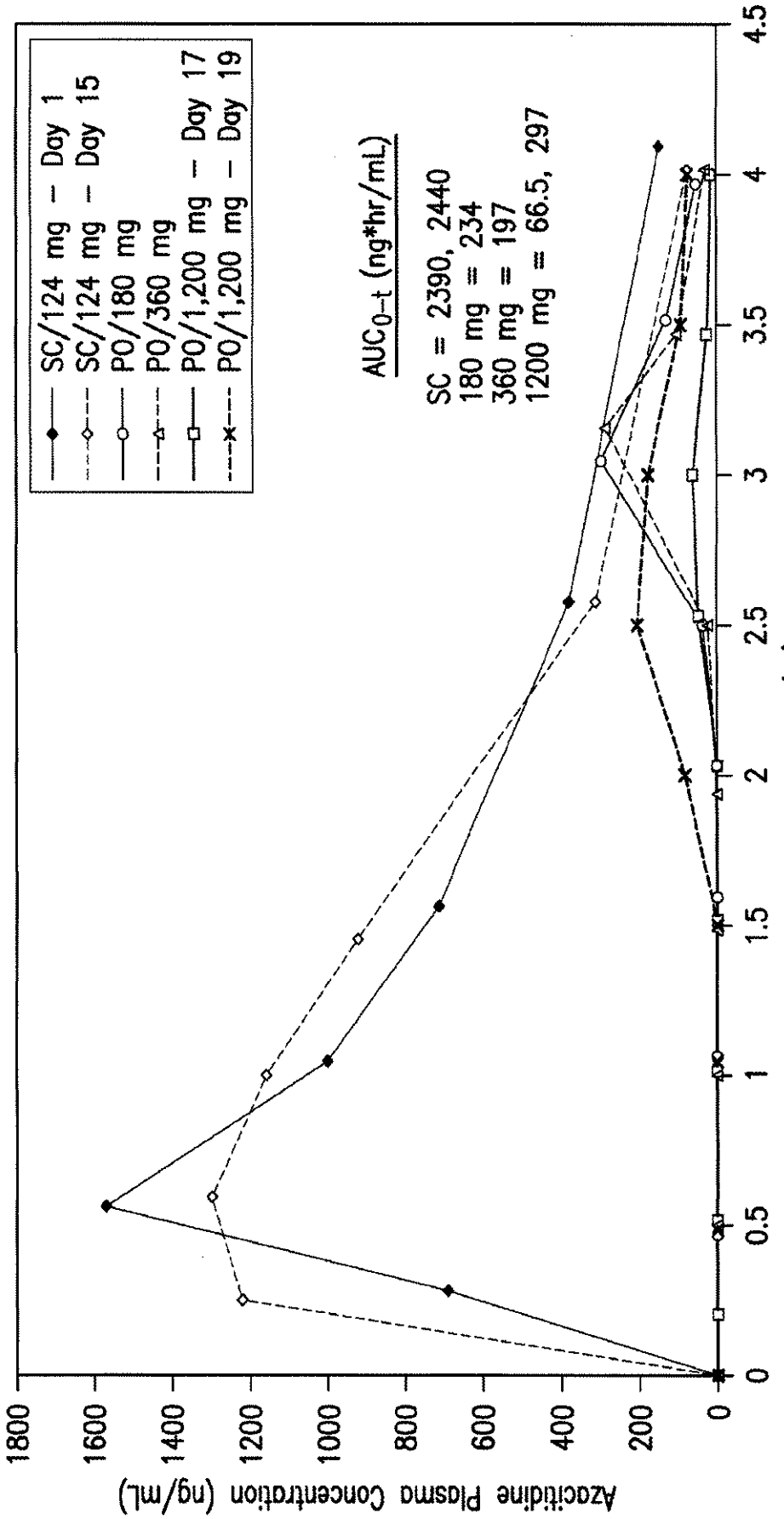

SC/124 mg – Day 1
SC/124 mg – Day 15
PO/180 mg
PO/360 mg
PO/1,200 mg – Day 17
PO/1,200 mg – Day 19
AUC0–t (ng*hr/mL)
SC = 2390, 2440
180 mg = 234
360 mg = 197
1200 mg = 66.5, 297
Azacitidine Plasma Concentration (ng/mL)
Time (hr)
0
200
400
600
800
1000
1200
1400
1600
1800
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5

FIG.8

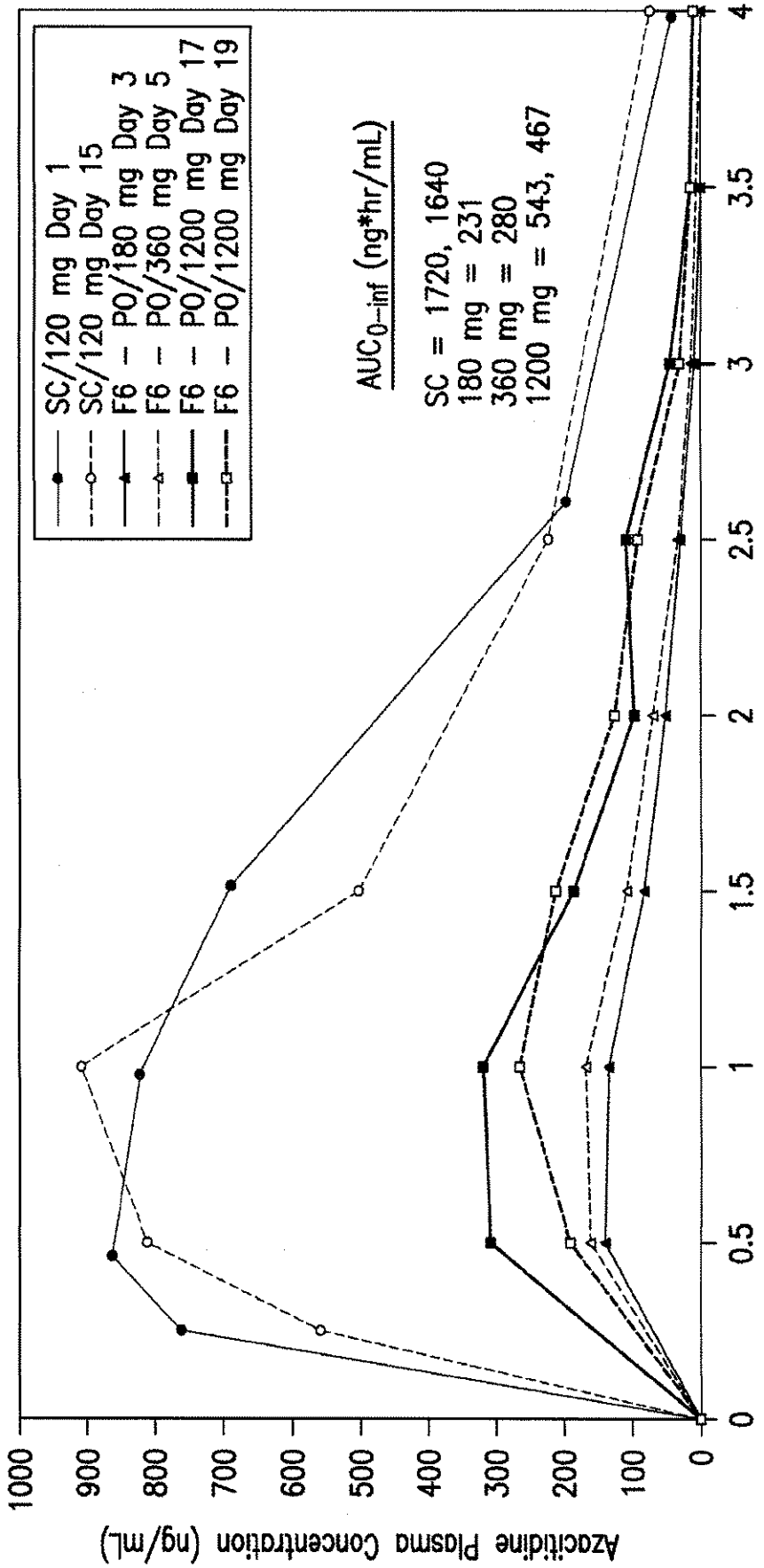

SC/120 mg Day 1
SC/120 mg Day 15
F6 – PO/180 mg Day 3
F6 – PO/360 mg Day 5
F6 – PO/1200 mg Day 17
F6 – PO/1200 mg Day 19
AUC0–inf (ng*hr/mL)
SC = 1720, 1640
180 mg = 231
360 mg = 280
1200 mg = 543, 467
Azacitidine Plasma Concentration (ng/mL)
Time (hr)
0
100
200
300
400
500
600
700
800
900
1000
0.5
1
1.5
2
2.5
3
3.5
4

FIG.9

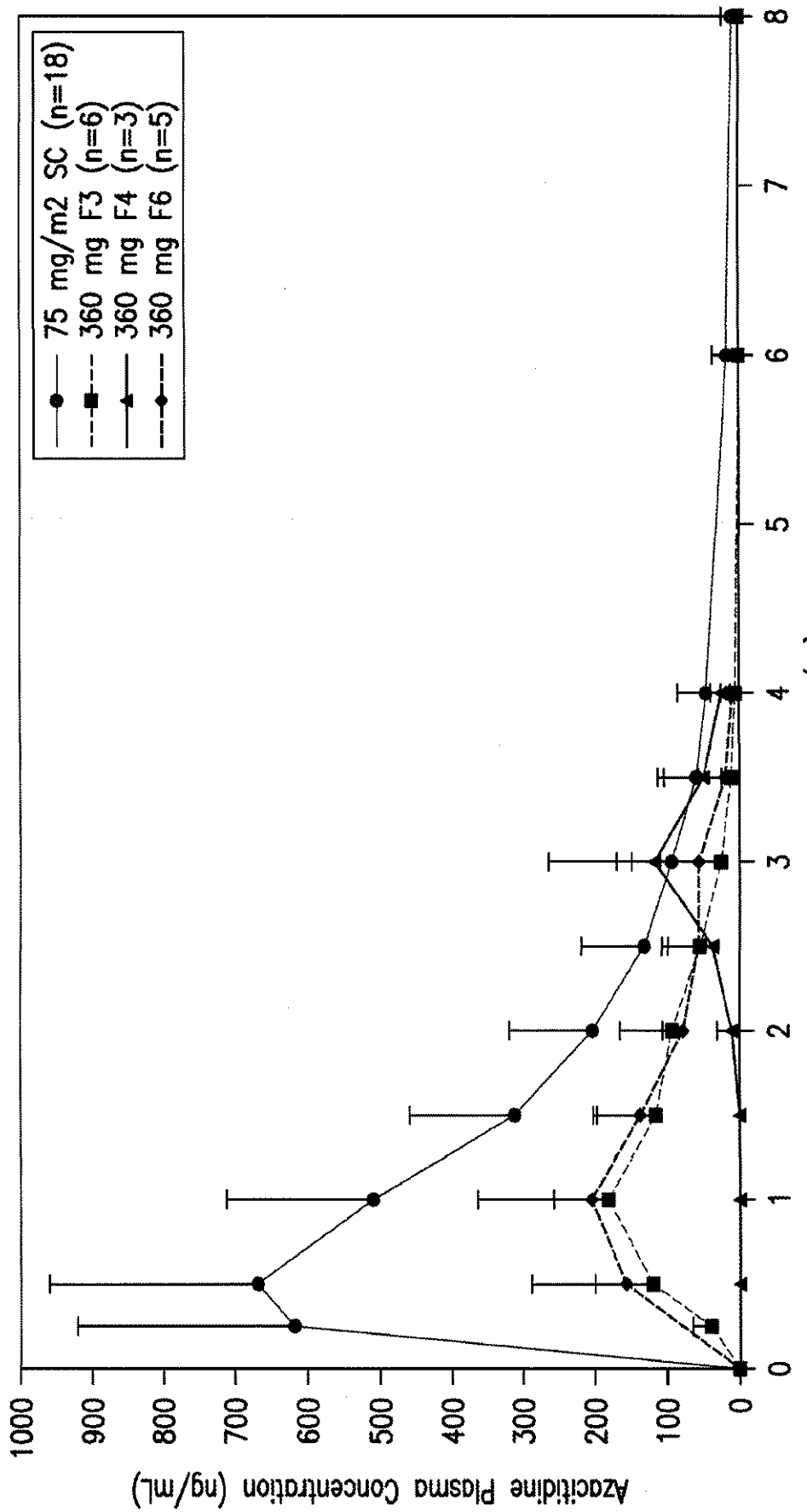

75 mg/m2 SC (n=18)
360 mg F3 (n=6)
360 mg F4 (n=3)
360 mg F6 (n=5)
Azacitidine Plasma Concentration (ng/mL)
Time (hr)
0
100
200
300
400
500
600
700
800
900
1000
0
1
2
3
4
5
6
7
8

FIG. 10

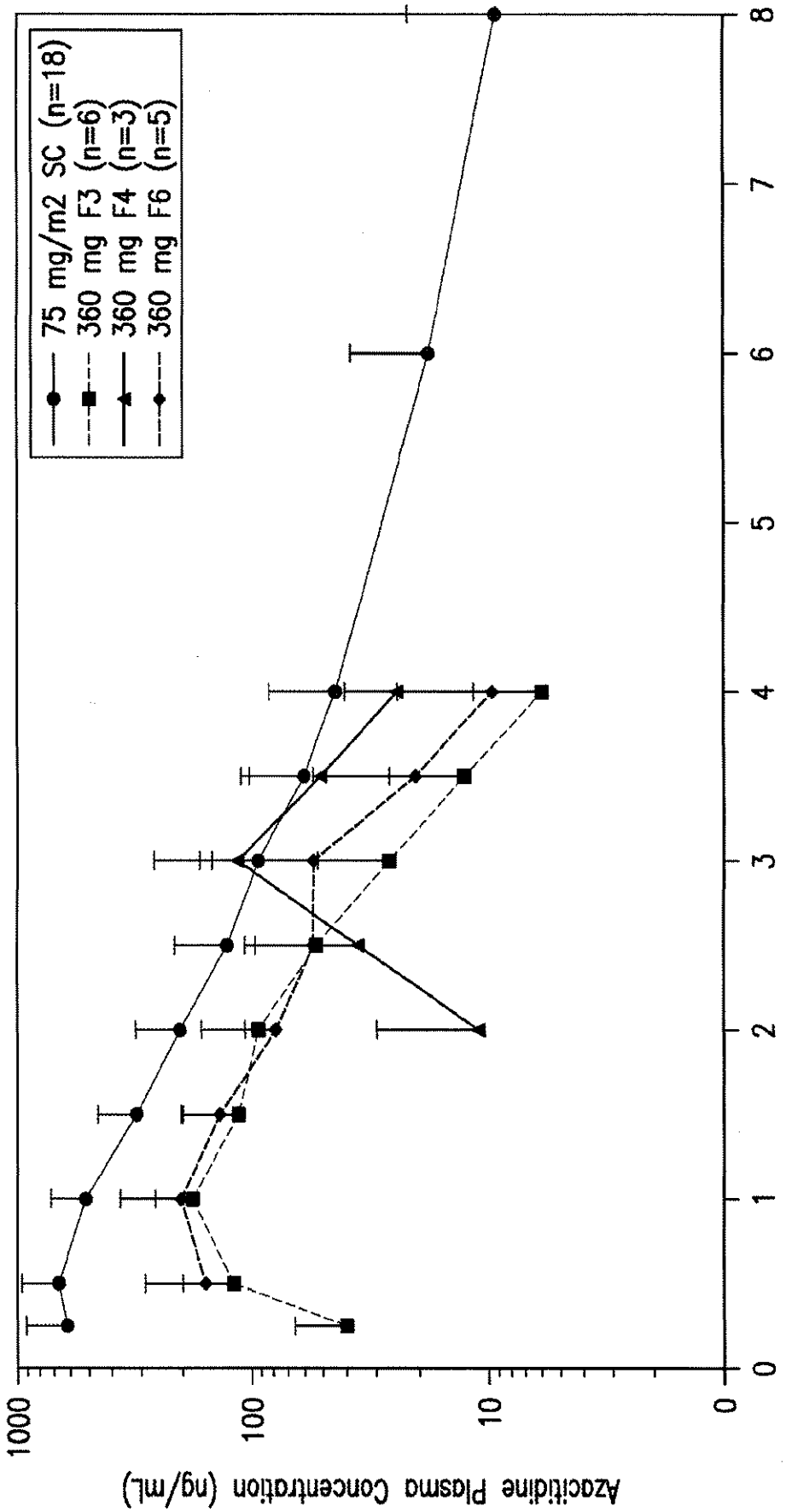

75 mg/m2 SC (n=18)
360 mg F3 (n=6)
360 mg F4 (n=3)
360 mg F6 (n=5)
Azacitidine Plasma Concentration (ng/mL)
1000
100
10
0
0
1
2
3
4
5
6
7
8
Time (hr)

FIG.11

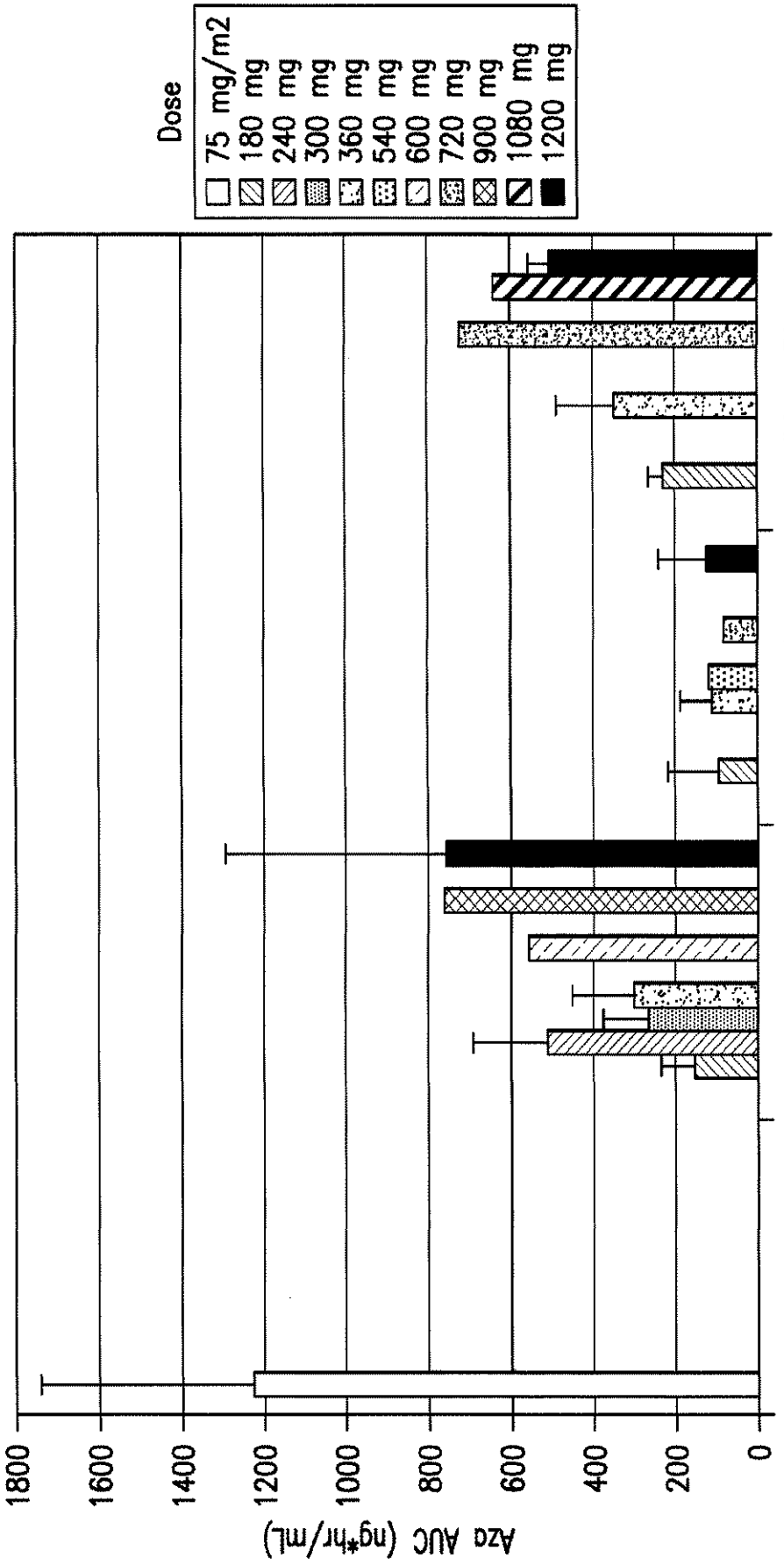

Dose
75 mg/m2
180 mg
240 mg
300 mg
360 mg
540 mg
600 mg
720 mg
900 mg
1080 mg
1200 mg
Aza AUC (ng*hr/mL)
0
200
400
600
800
1000
1200
1400
1600
1800
SC
PO – F3
PO – F4
PO – F6
Formulation

FIG.12


Dose
75 mg/m2
180 mg
240 mg
300 mg
360 mg
540 mg
600 mg
720 mg
900 mg
1080 mg
1200 mg
Aza Cmax (ng*hr/mL)
0
200
400
600
800
1000
1200
SC
PO – F3
PO – F4
PO – F6
Formulation

FIG.13

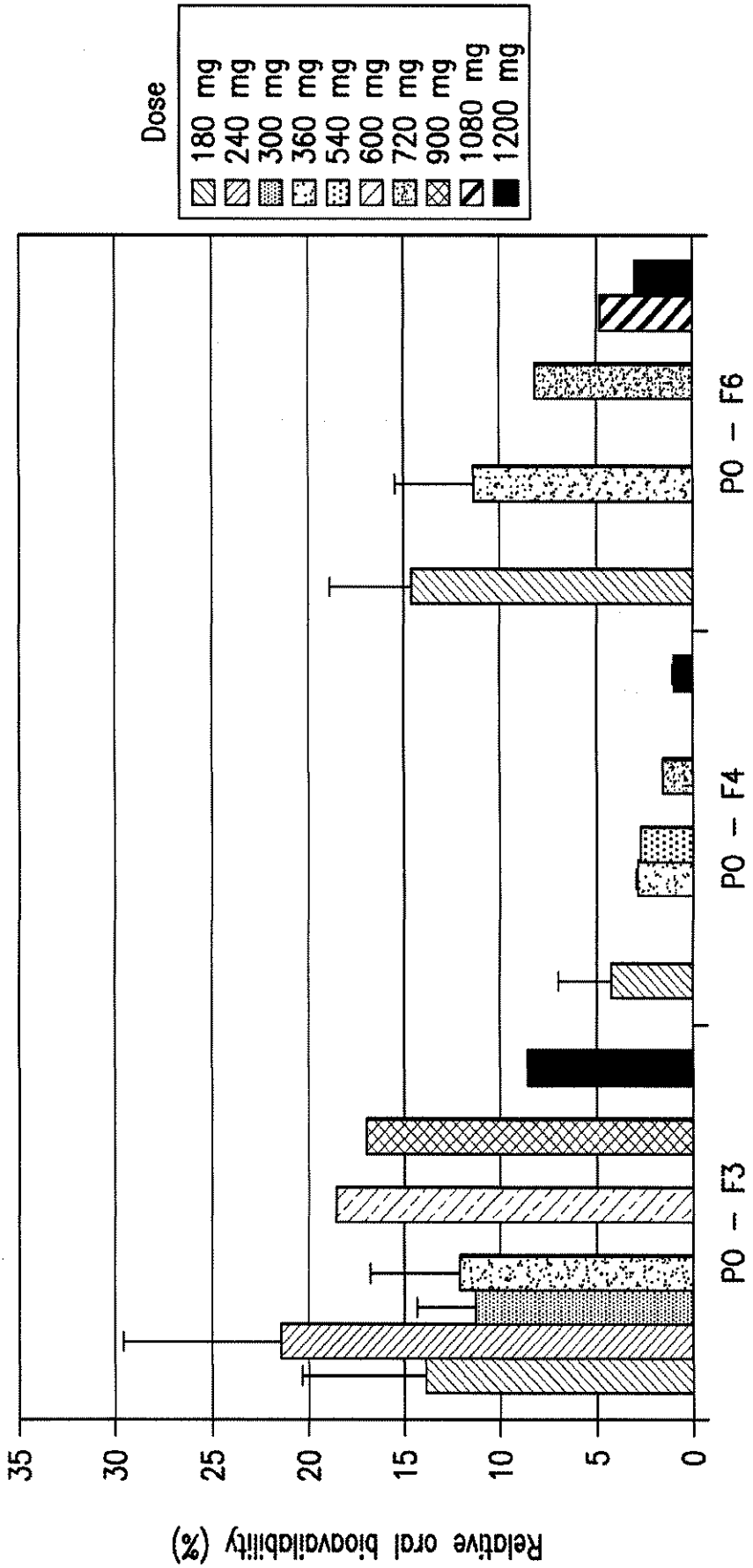

Dose
180 mg
240 mg
300 mg
360 mg
540 mg
600 mg
720 mg
900 mg
1080 mg
1200 mg
Relative oral bioavailability (%)
35
30
25
20
15
10
5
0
PO – F3
PO – F4
PO – F6
Formulation

FIG. 14

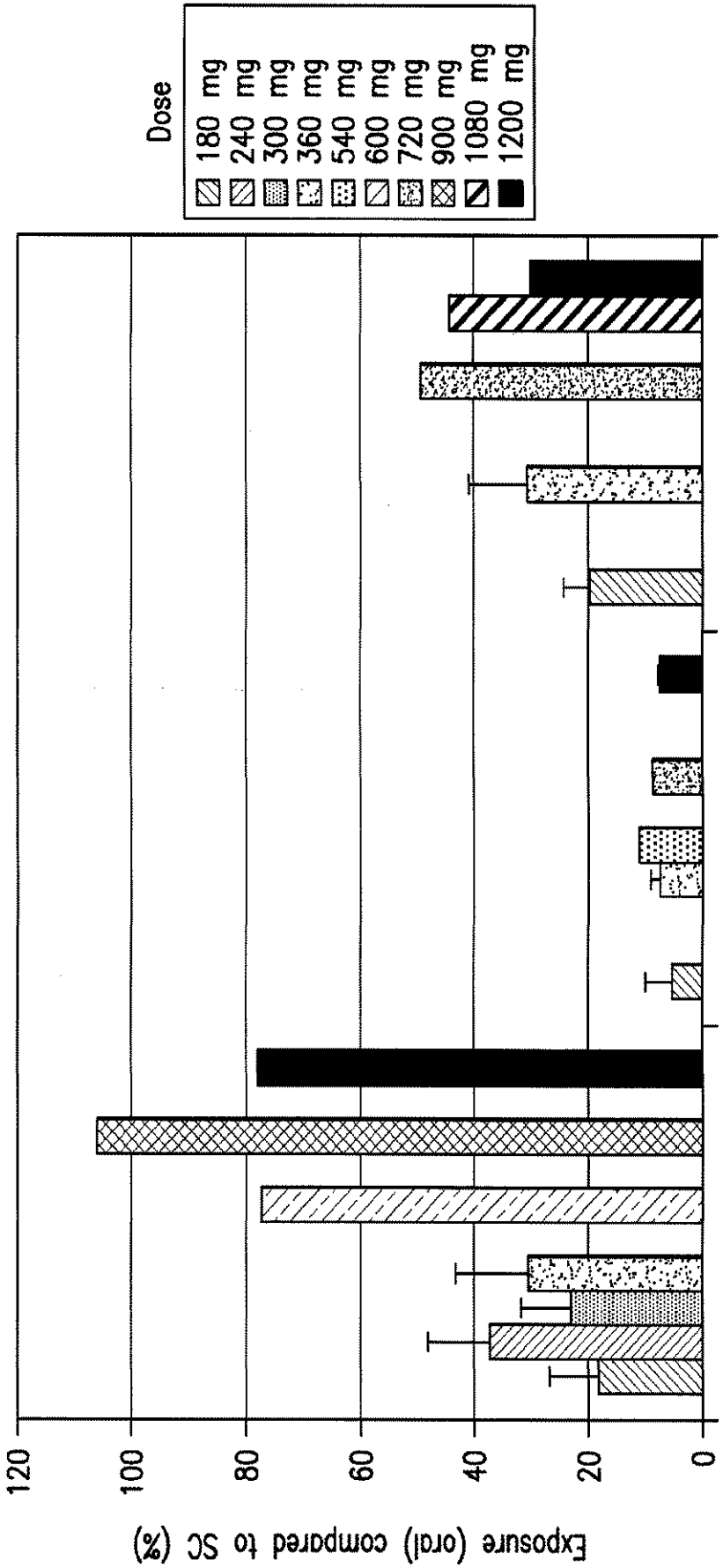

Dose
180 mg
240 mg
300 mg
360 mg
540 mg
600 mg
720 mg
900 mg
1080 mg
1200 mg
120
100
80
60
40
20
0
Exposure (oral) compared to SC (%)
PO – F3
PO – F4
PO – F6
Formulation

FIG. 15

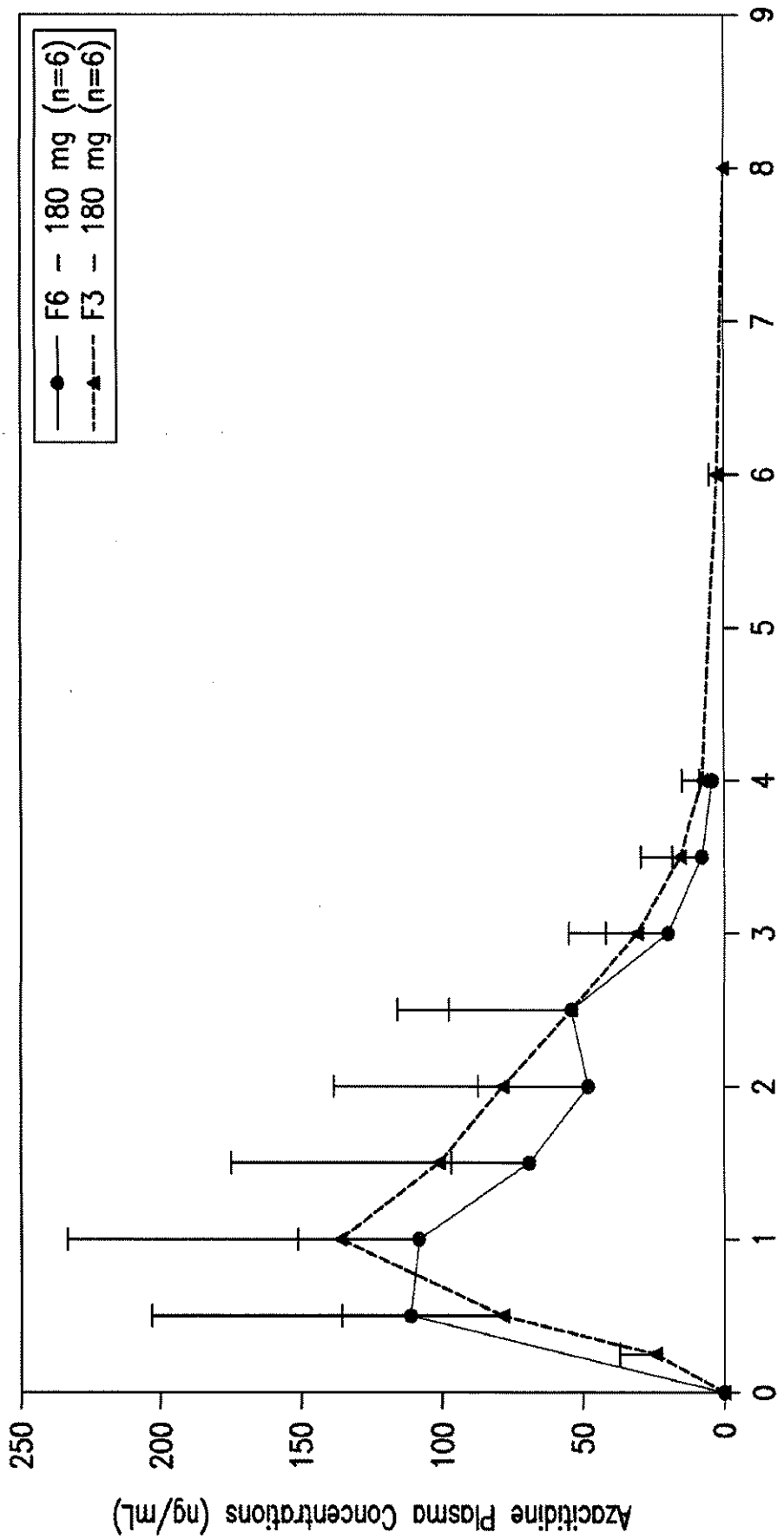

F6 – 180 mg (n=6)
F3 – 180 mg (n=6)
Azacitidine Plasma Concentrations (ng/mL)
250
200
150
100
50
0
0
1
2
3
4
5
6
7
8
9
Time (hr)

FIG.16

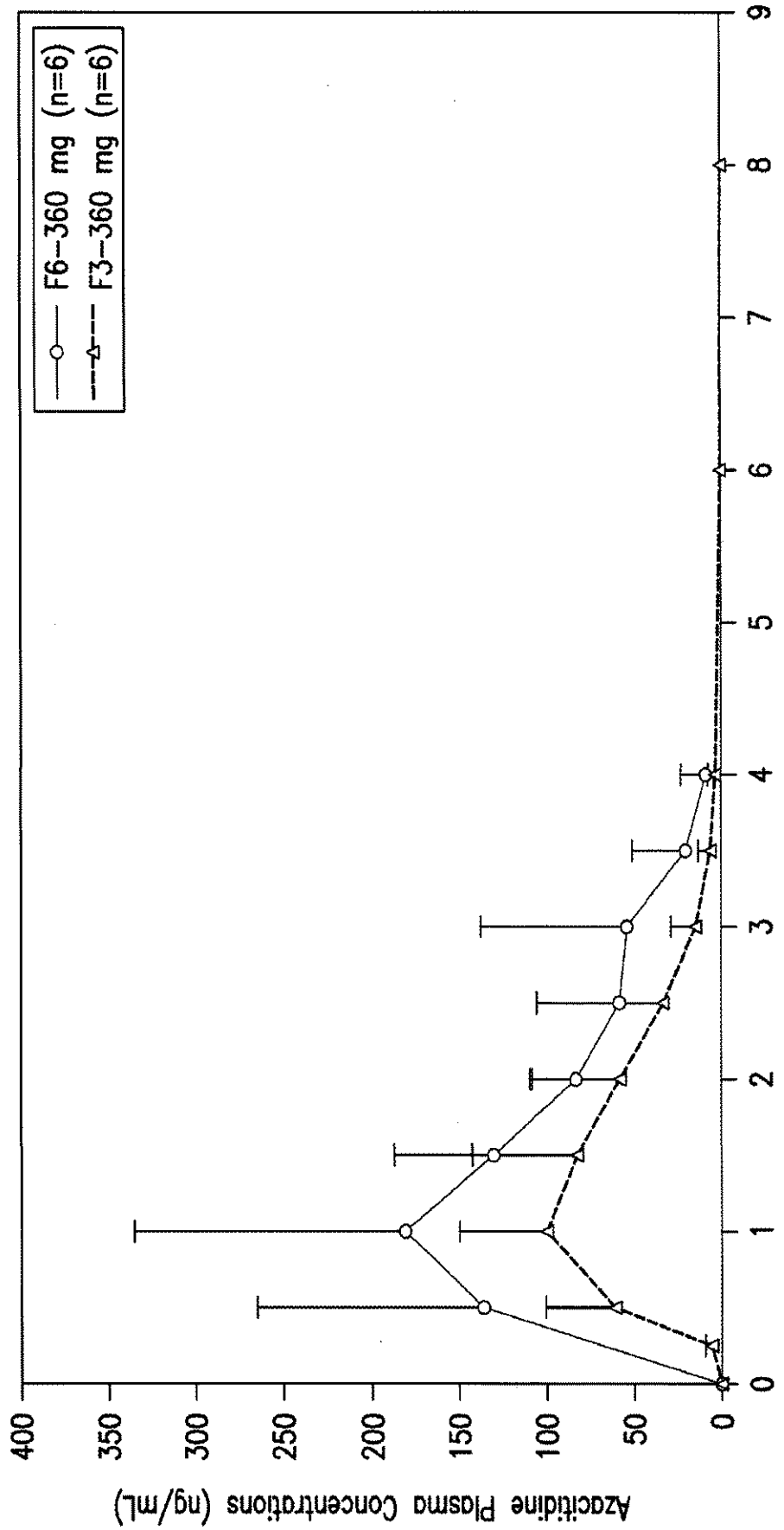

F6-360 mg (n=6)
F3-360 mg (n=6)
Azacitidine Plasma Concentrations (ng/mL)
Time (hr)
0
50
100
150
200
250
300
350
400
0
1
2
3
4
5
6
7
8
9

FIG. 17

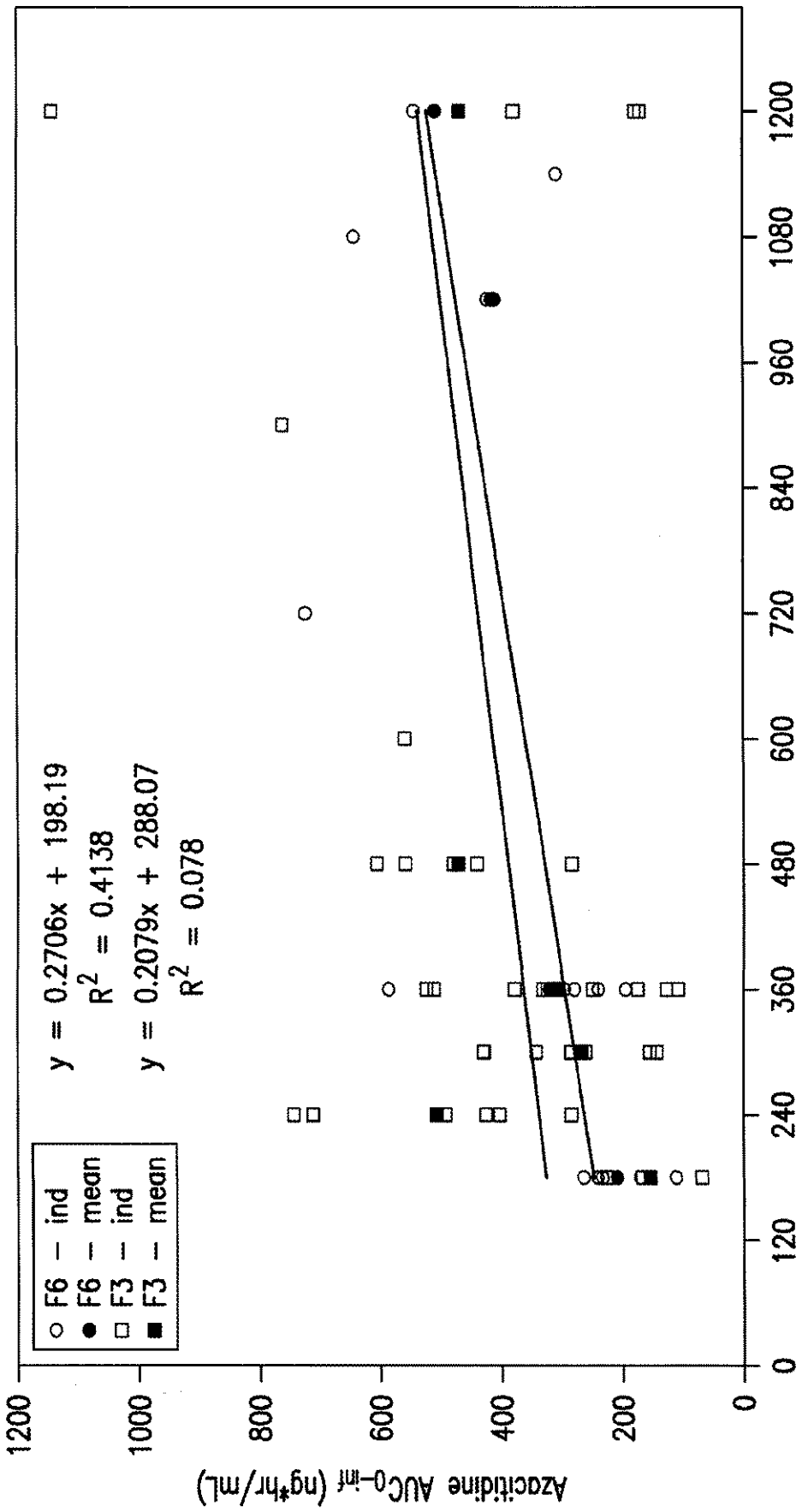

Azacitidine AUC0–inf (ng*hr/mL)
1200
1000
800
600
400
200
0
0
120
240
360
480
600
720
840
960
1080
1200
Dose (mg)
F6 – ind
F6 – mean
F3 – ind
F3 – mean
y = 0.2706x + 198.19
R2 = 0.4138
y = 0.2079x + 288.07
R2 = 0.078

FIG. 18

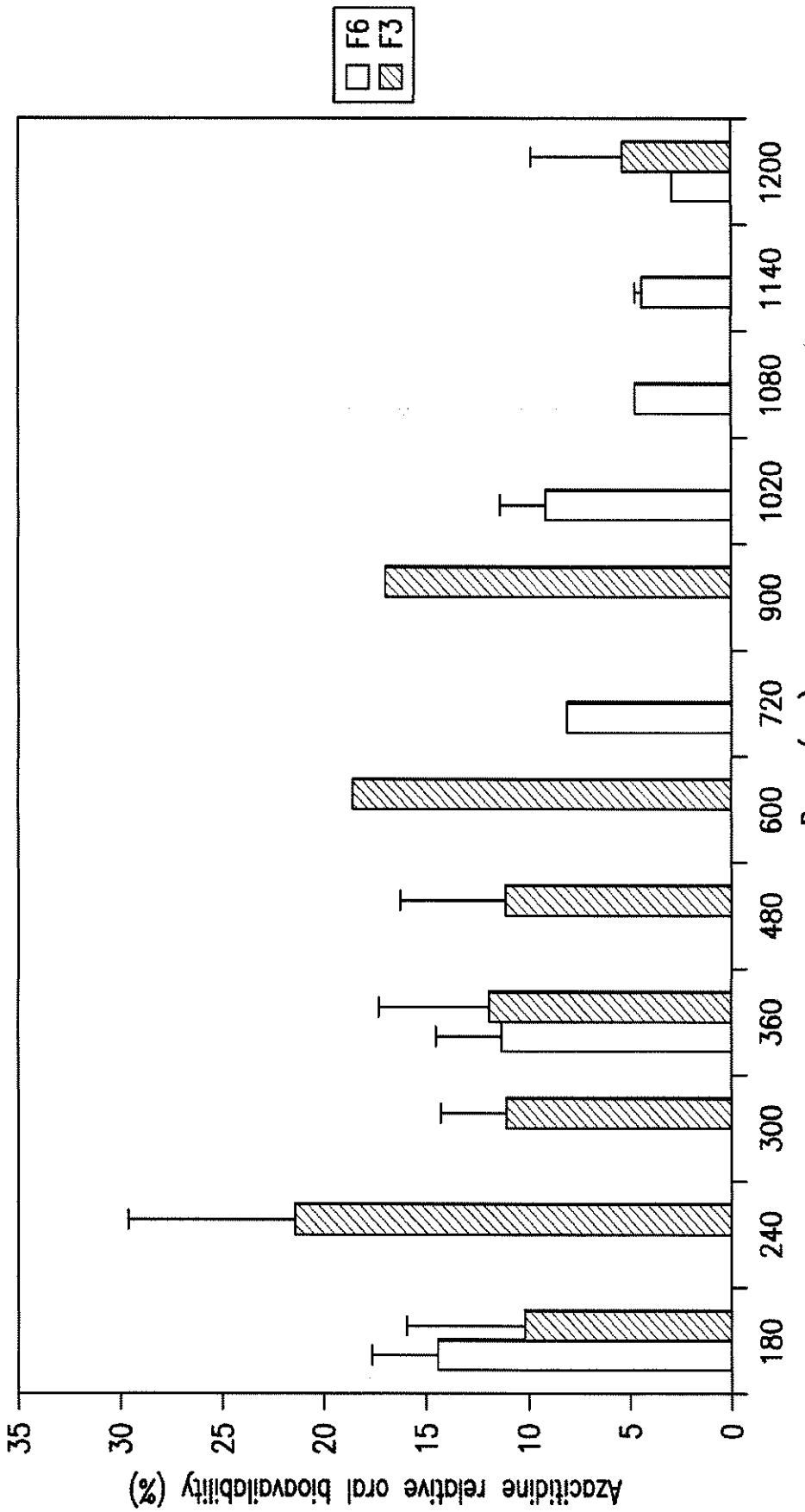

F6
F3
Azacitidine relative oral bioavailability (%)
0
5
10
15
20
25
30
35
180
240
300
360
480
600
720
900
1020
1080
1140
1200
Dose (mg)

FIG.19

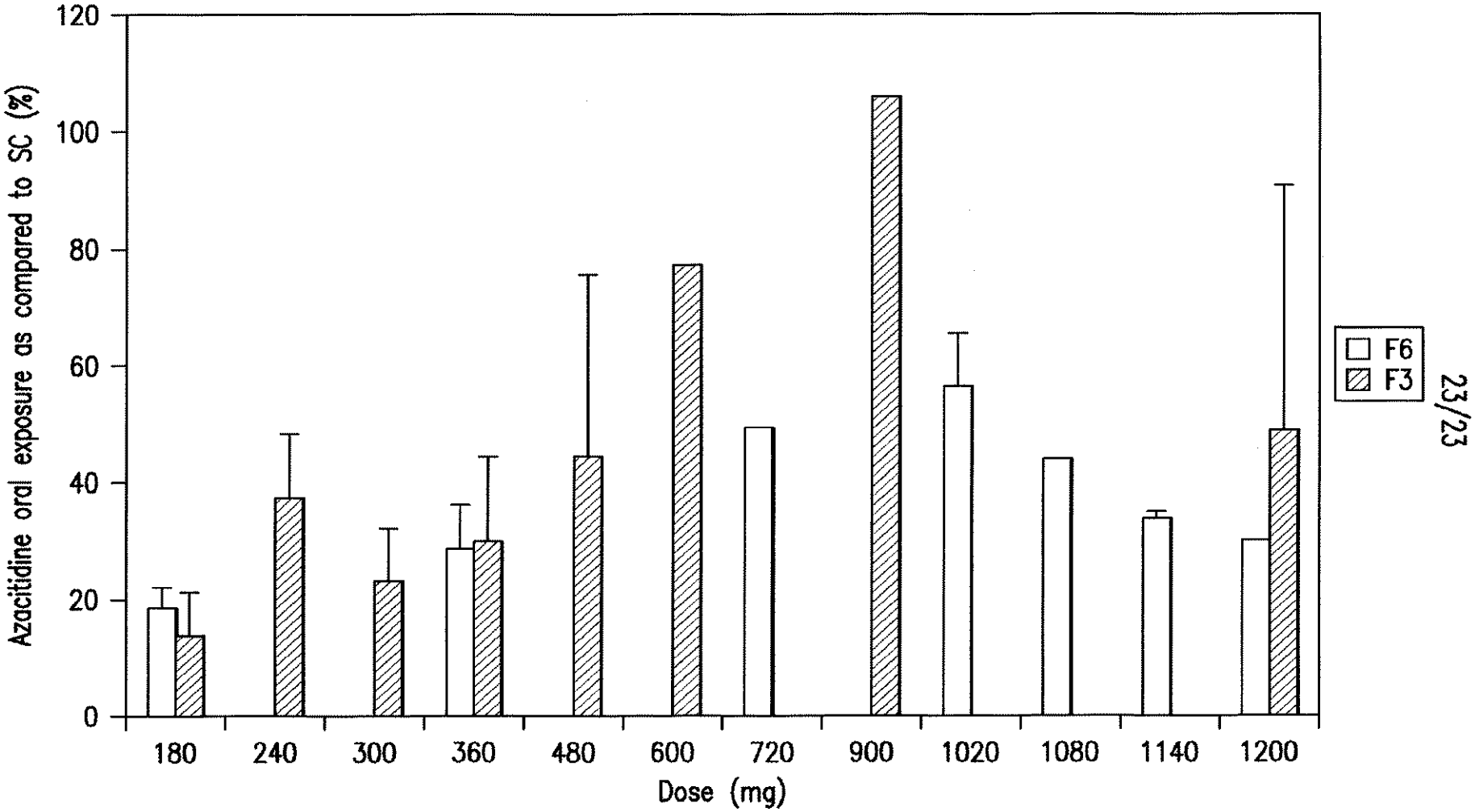

120
100
80
60
40
20
0
Azacitidine oral exposure as compared to SC (%)
180
240
300
360
480
600
720
900
1020
1080
1140
1200
Dose (mg)
F6
F3

FIG.20