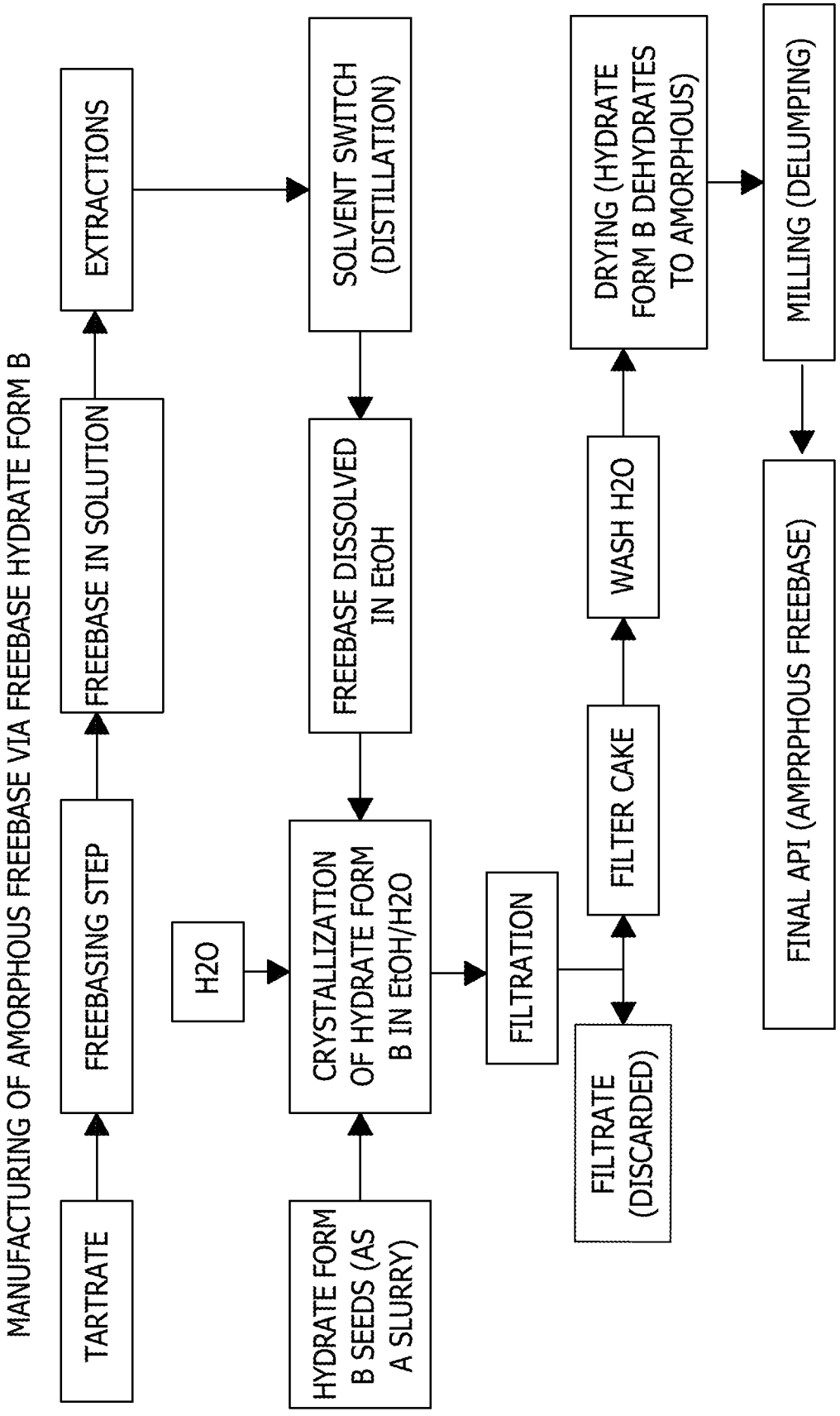
MANUFACTURING OF AMORPHOUS FREEBASE VIA FREEBASE HYDRATE FORM B
TARTRATE
FREEBASING STEP
FREEBASE IN SOLUTION
EXTRACTIONS
SOLVENT SWITCH (DISTILLATION)
FREEBASE DISSOLVED IN EtOH
H2O
HYDRATE FORM B SEEDS (AS A SLURRY)
CRYSTALLIZATION OF HYDRATE FORM B IN EtOH/H2O
FILTRATION
FILTRATE (DISCARDED)
FILTER CAKE
WASH H2O
DRYING (HYDRATE FORM B DEHYDRATES TO AMORPHOUS)
MILLING (DELUMPING)
FINAL API (AMPRPHOUS FREEBASE)

FIG. 1A

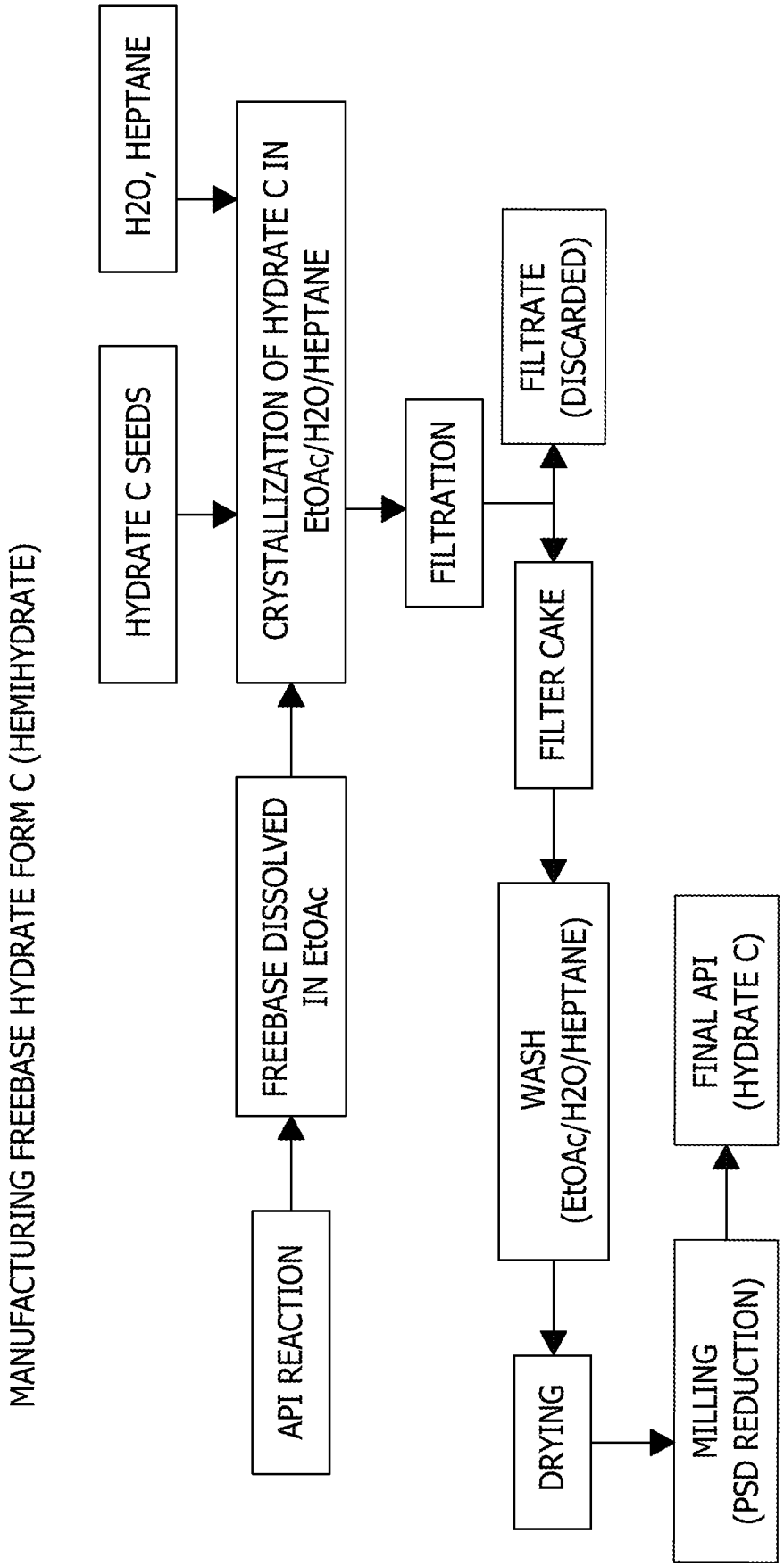
MANUFACTURING FREEBASE HYDRATE FORM C (HEMIHYDRATE)
API REACTION
FREEBASE DISSOLVED IN EtOAc
HYDRATE C SEEDS
H2O, HEPTANE
CRYSTALLIZATION OF HYDRATE C IN EtOAc/H2O/HEPTANE
FILTRATION
FILTRATE (DISCARDED)
FILTER CAKE
WASH (EtOAc/H2O/HEPTANE)
DRYING
MILLING (PSD REDUCTION)
FINAL API (HYDRATE C)

FIG. 1B

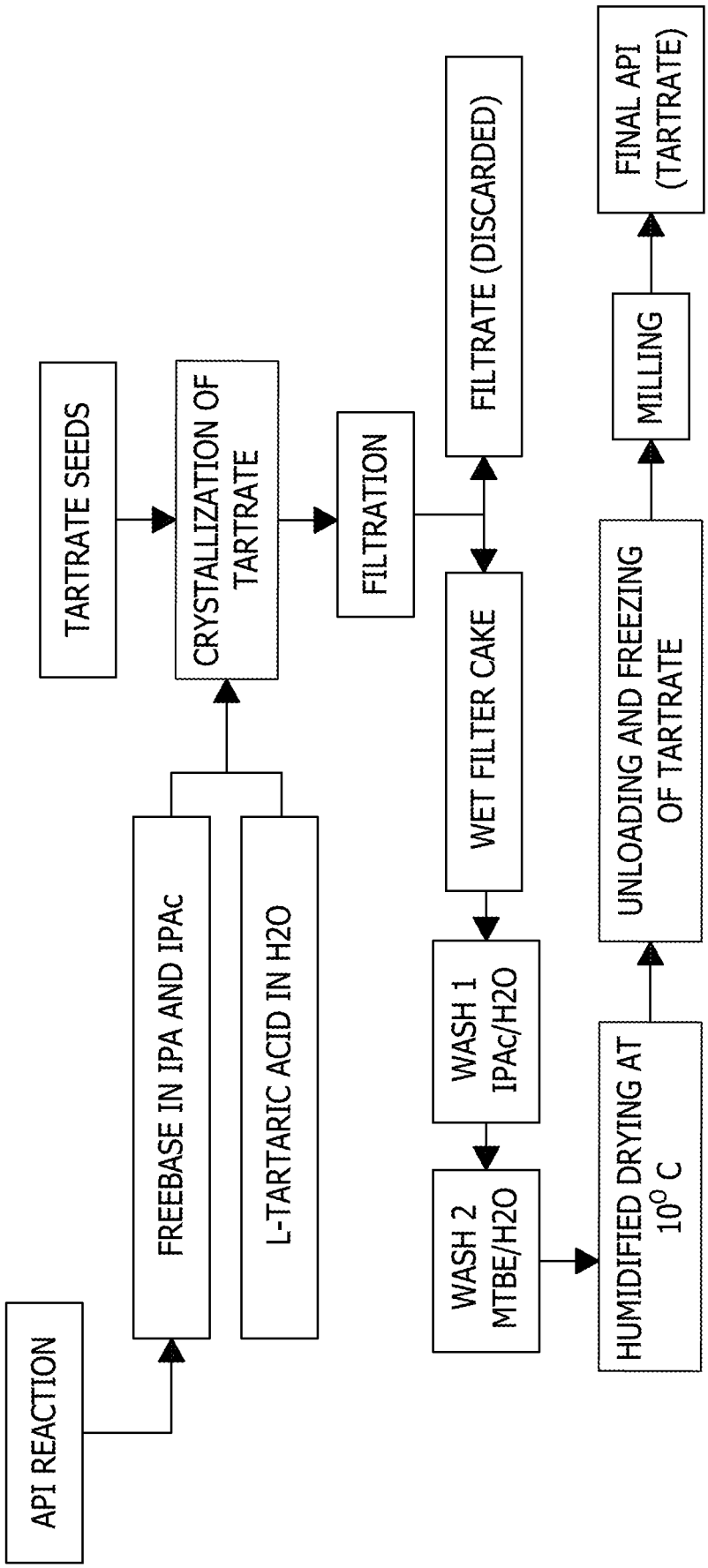
API REACTION
FREEBASE IN IPA AND IPAc
L-TARTARIC ACID IN H2O
TARTRATE SEEDS
CRYSTALLIZATION OF TARTRATE
FILTRATION
FILTRATE (DISCARDED)
WET FILTER CAKE
WASH 1 IPAc/H2O
WASH 2 MTBE/H2O
HUMIDIFIED DRYING AT 10° C
UNLOADING AND FREEZING OF TARTRATE
MILLING
FINAL API (TARTRATE)

FIG. 1C

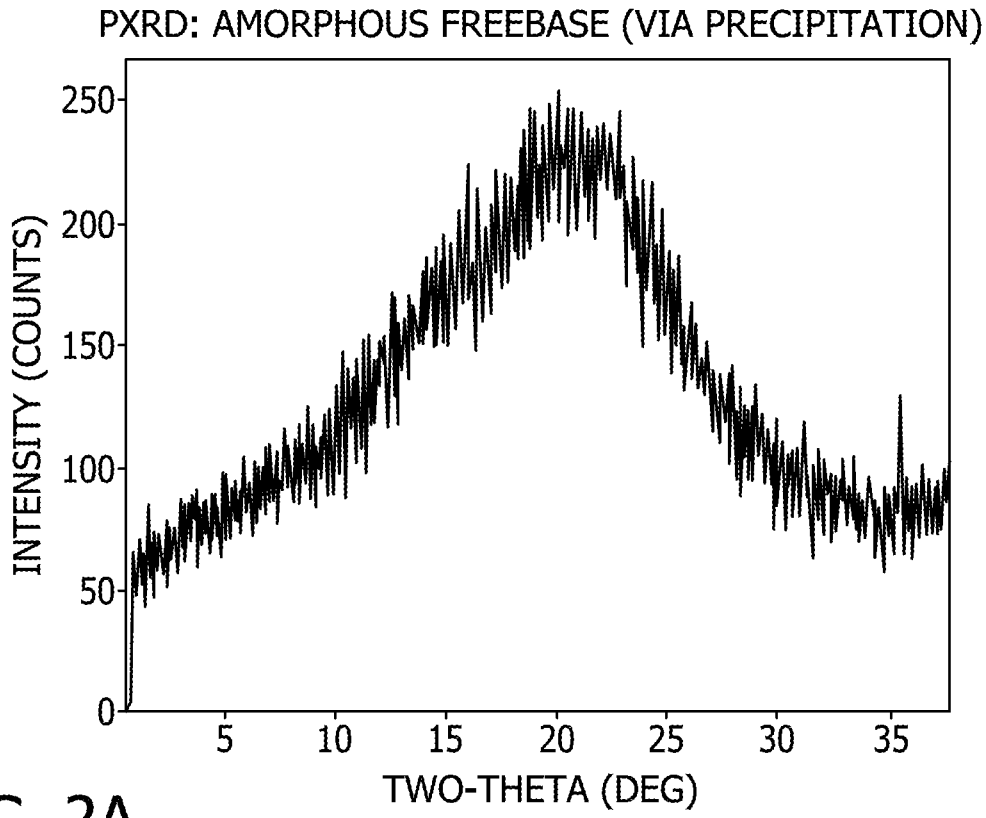
PXRD: AMORPHOUS FREEBASE (VIA PRECIPITATION)
INTENSITY (COUNTS)
0
50
100
150
200
250
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 2A

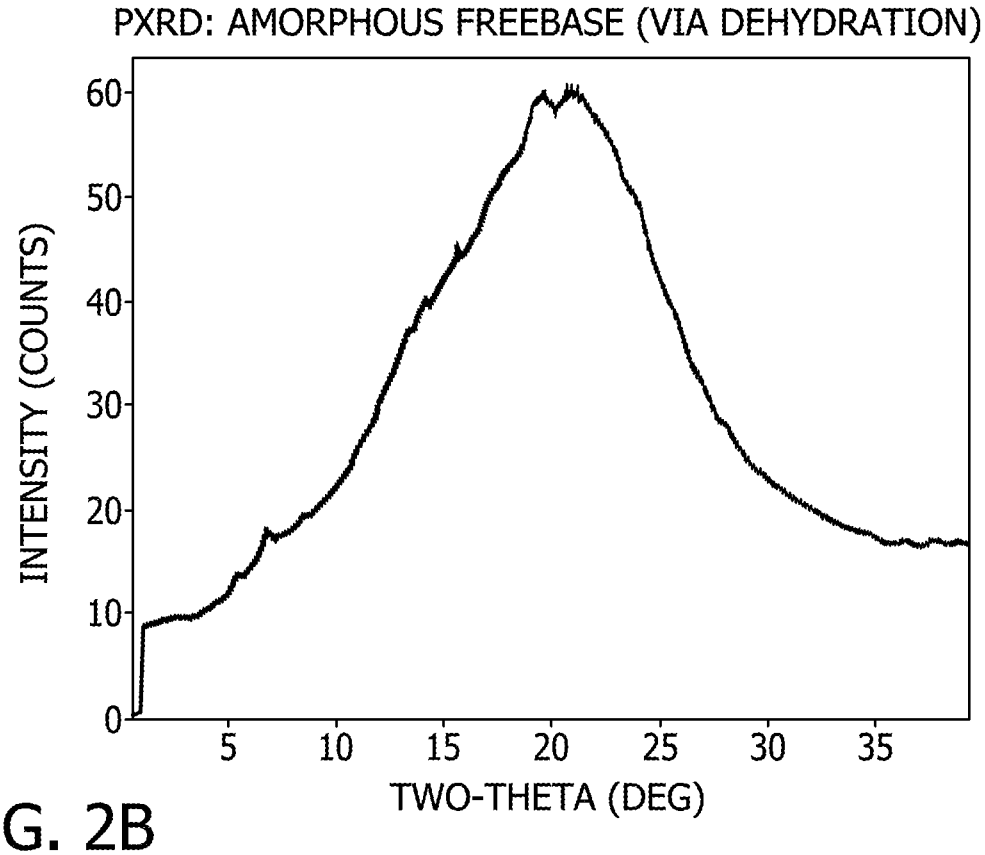
PXRD: AMORPHOUS FREEBASE (VIA DEHYDRATION)
INTENSITY (COUNTS)
0
10
20
30
40
50
60
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 2B

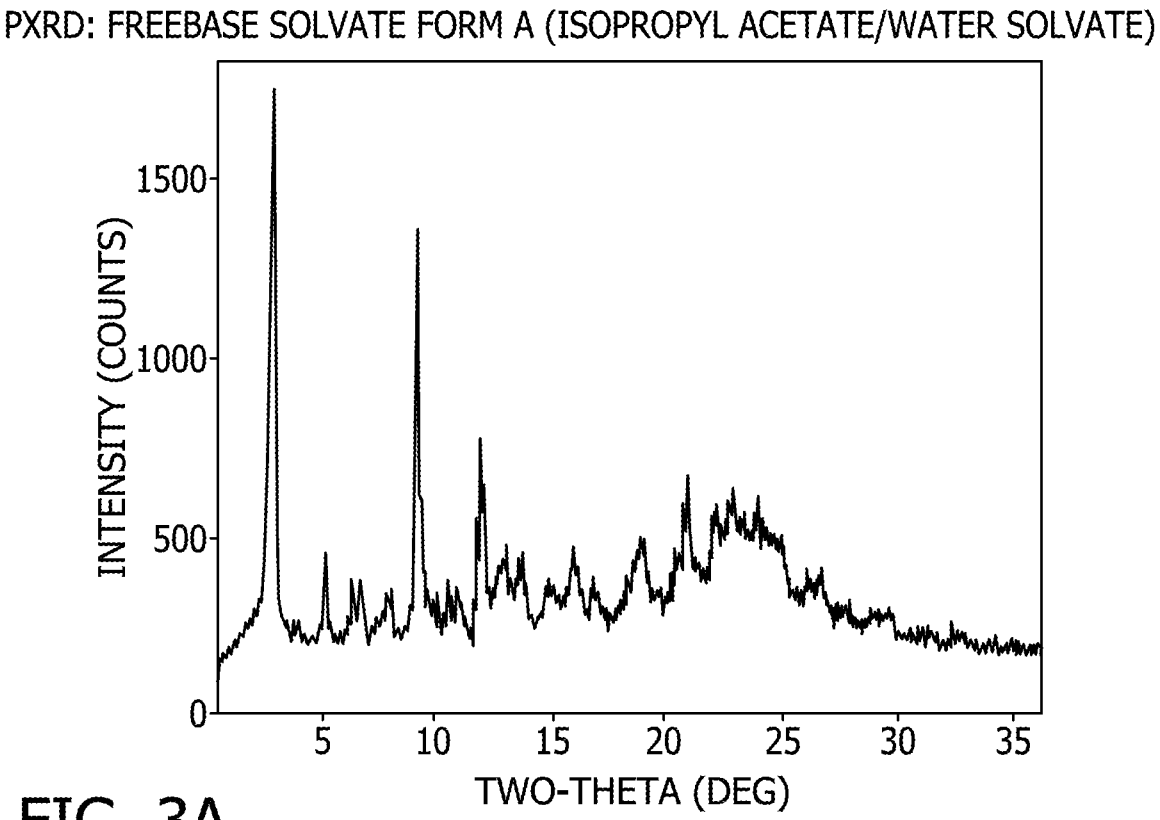
PXRD: FREEBASE SOLVATE FORM A (ISOPROPYL ACETATE/WATER SOLVATE)
INTENSITY (COUNTS)
1500
1000
500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3A

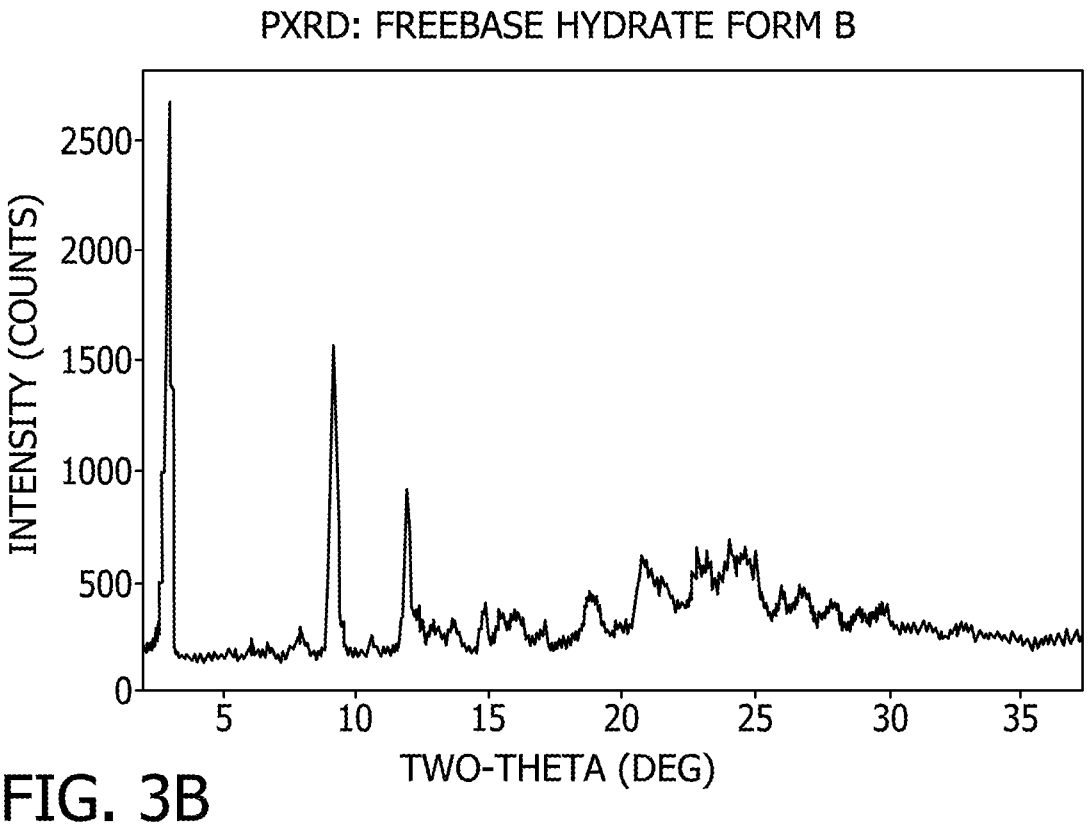
PXRD: FREEBASE HYDRATE FORM B
INTENSITY (COUNTS)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3B

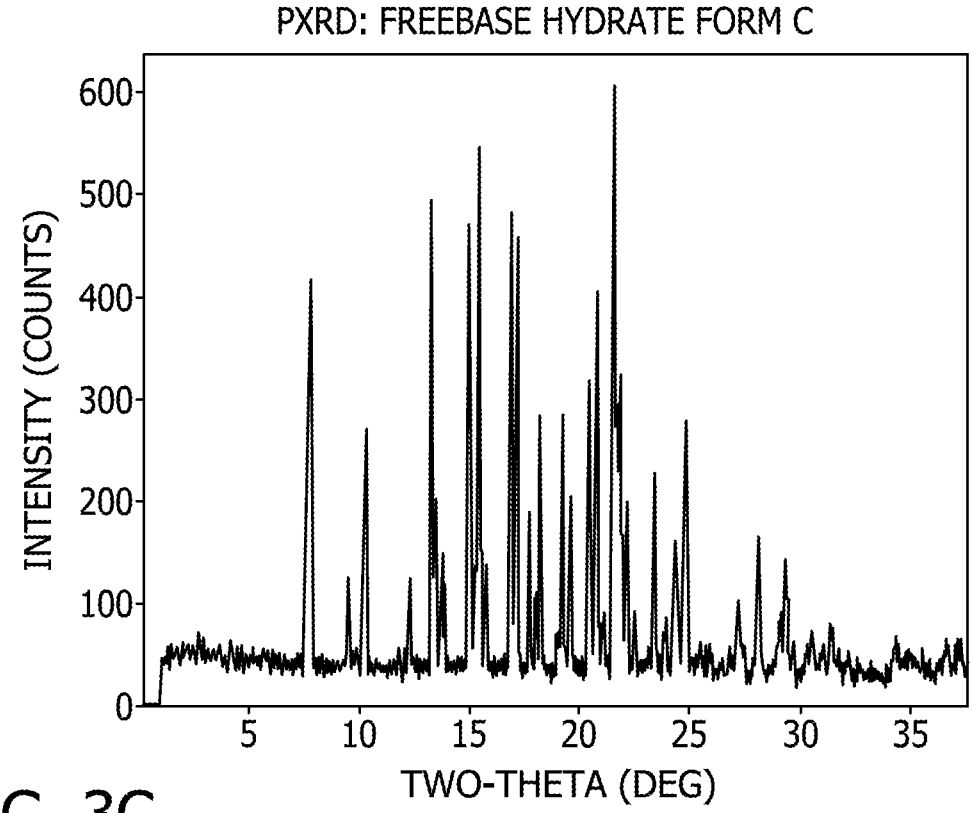
PXRD: FREEBASE HYDRATE FORM C
INTENSITY (COUNTS)
0
100
200
300
400
500
600
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3C

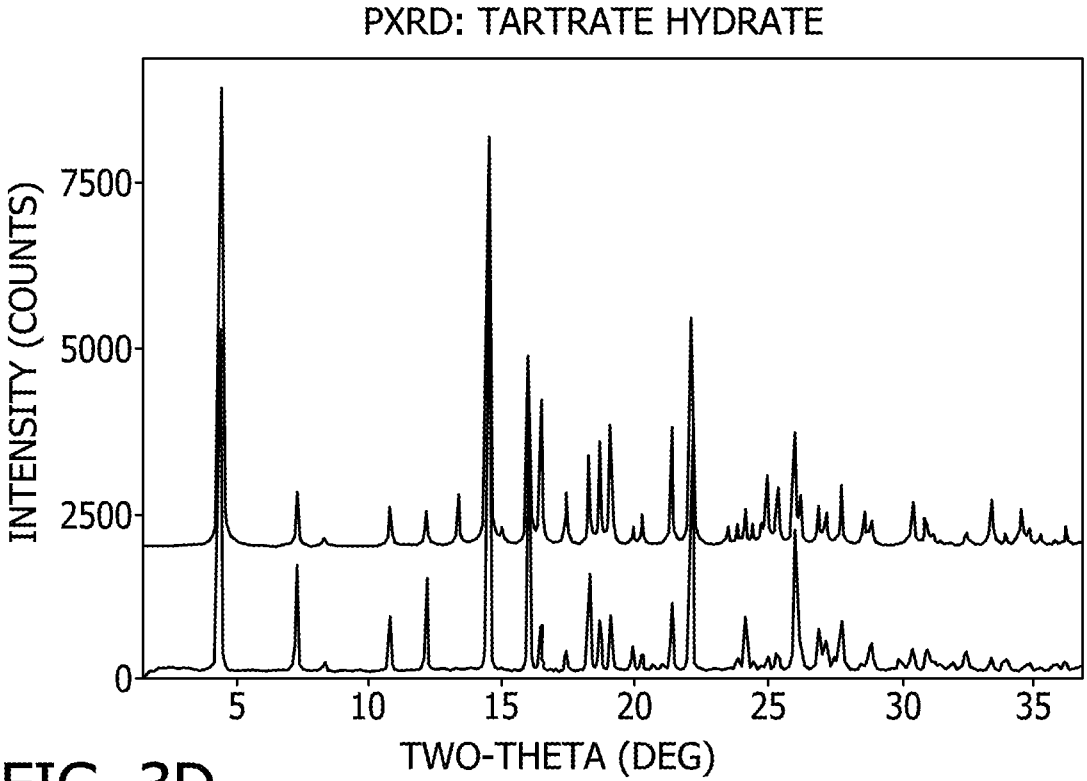
PXRD: TARTRATE HYDRATE
INTENSITY (COUNTS)
0
2500
5000
7500
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3D

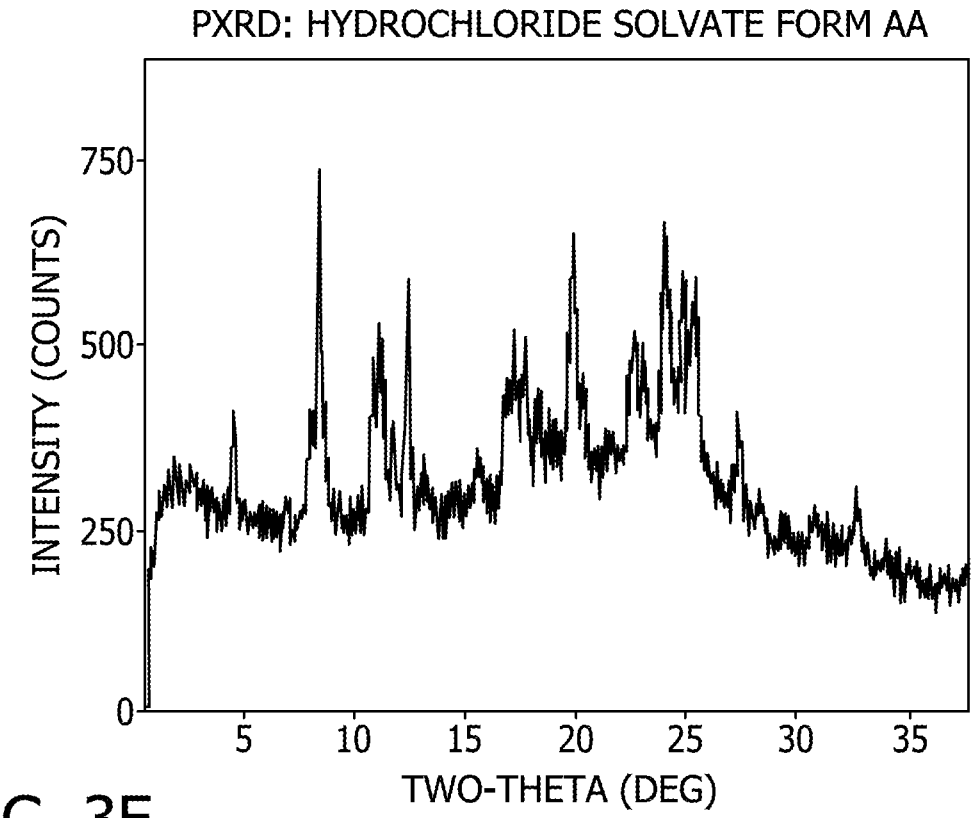
PXRD: HYDROCHLORIDE SOLVATE FORM AA
INTENSITY (COUNTS)
0
250
500
750
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3E

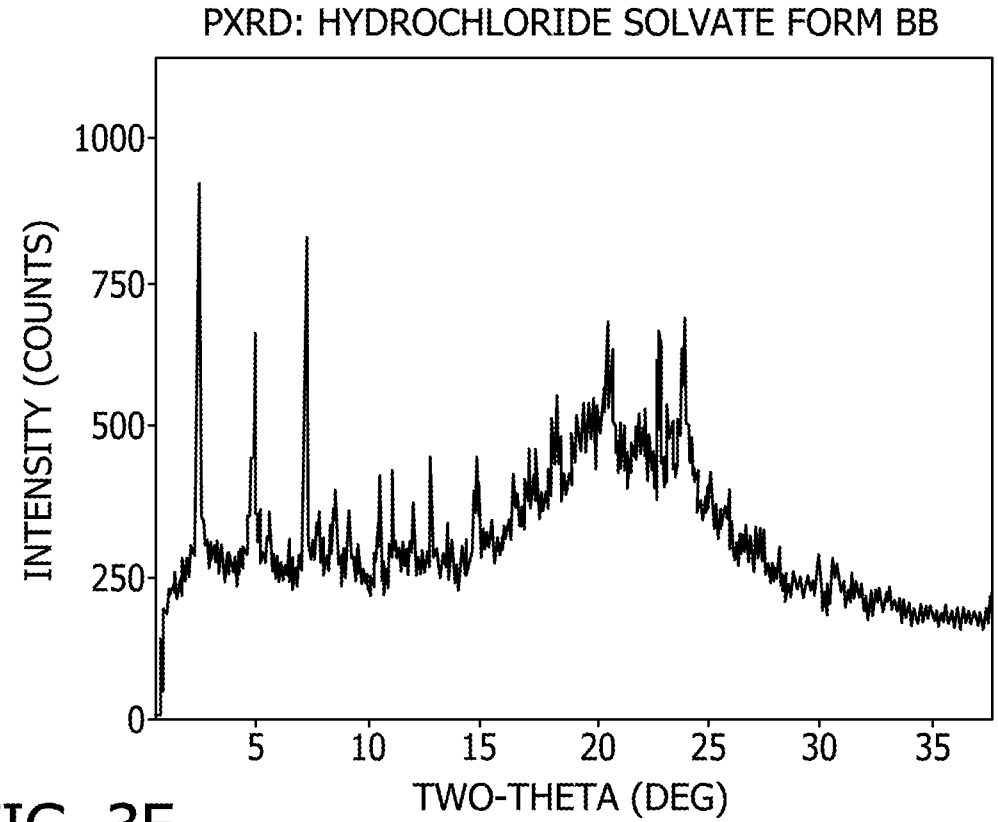
PXRD: HYDROCHLORIDE SOLVATE FORM BB
INTENSITY (COUNTS)
0
250
500
750
1000
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3F

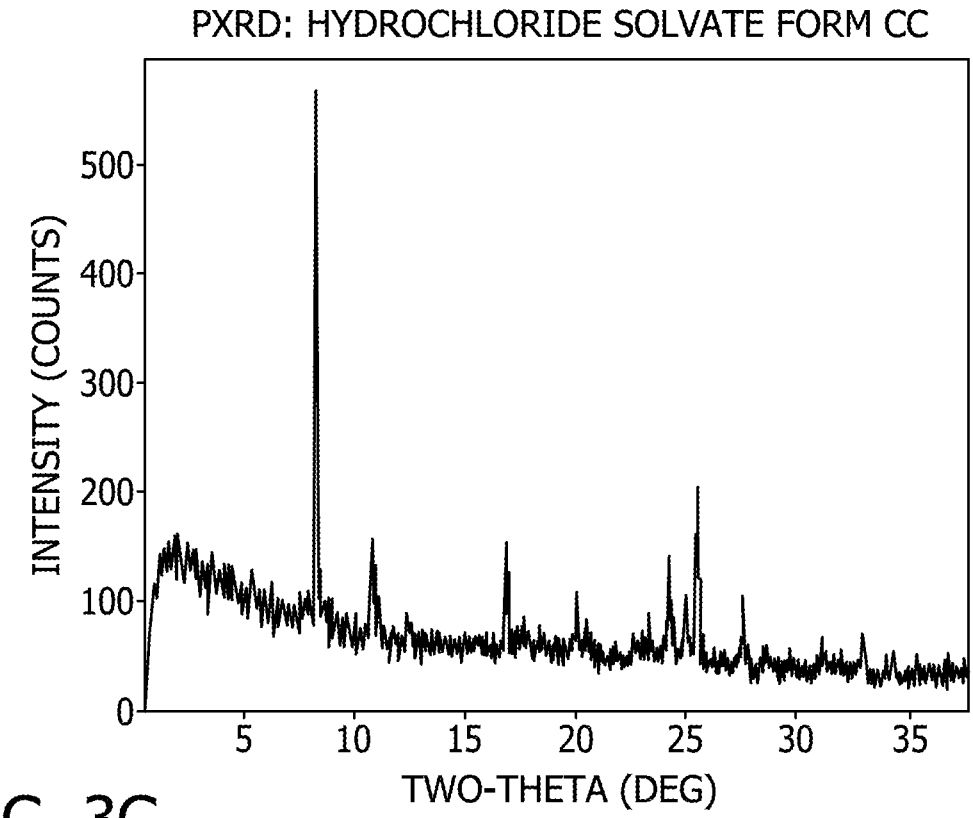
PXRD: HYDROCHLORIDE SOLVATE FORM CC
INTENSITY (COUNTS)
0
100
200
300
400
500
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3G

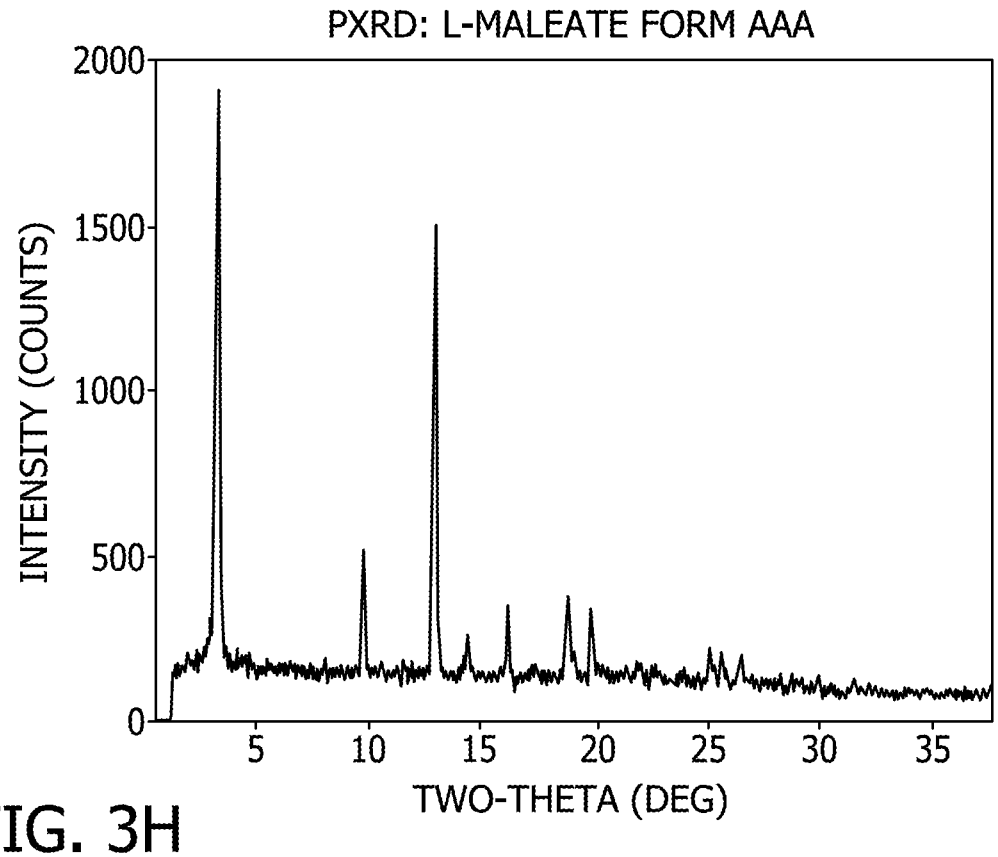
PXRD: L-MALEATE FORM AAA
INTENSITY (COUNTS)
0
500
1000
1500
2000
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3H

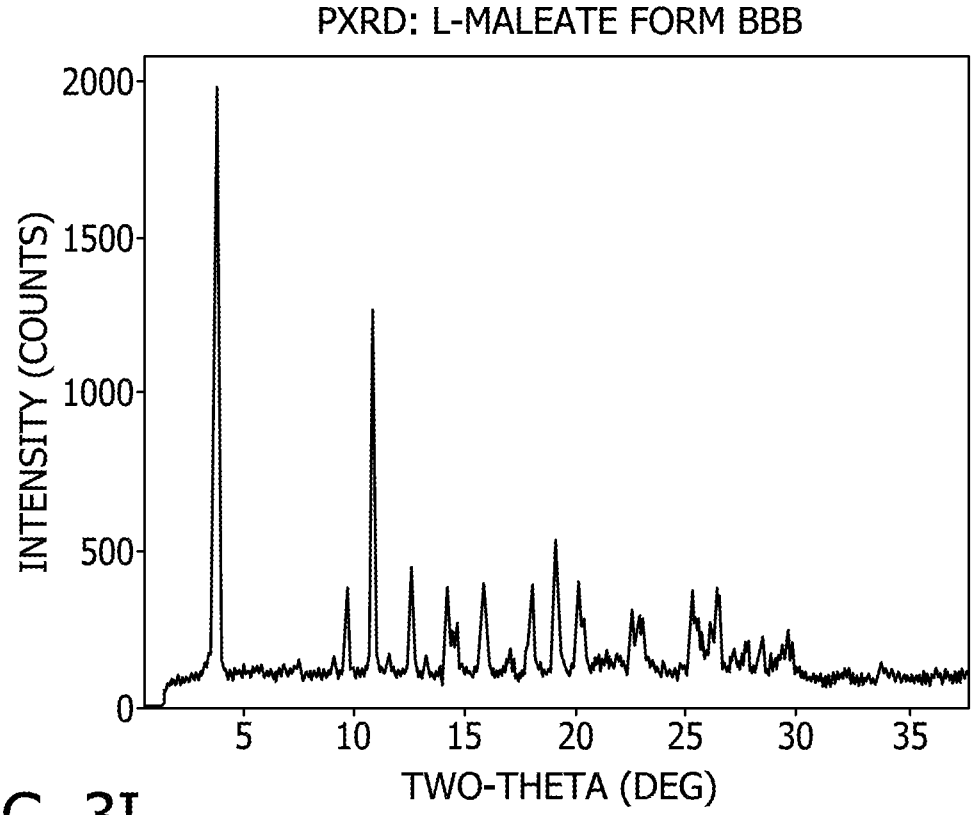
PXRD: L-MALEATE FORM BBB
INTENSITY (COUNTS)
2000
1500
1000
500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3I

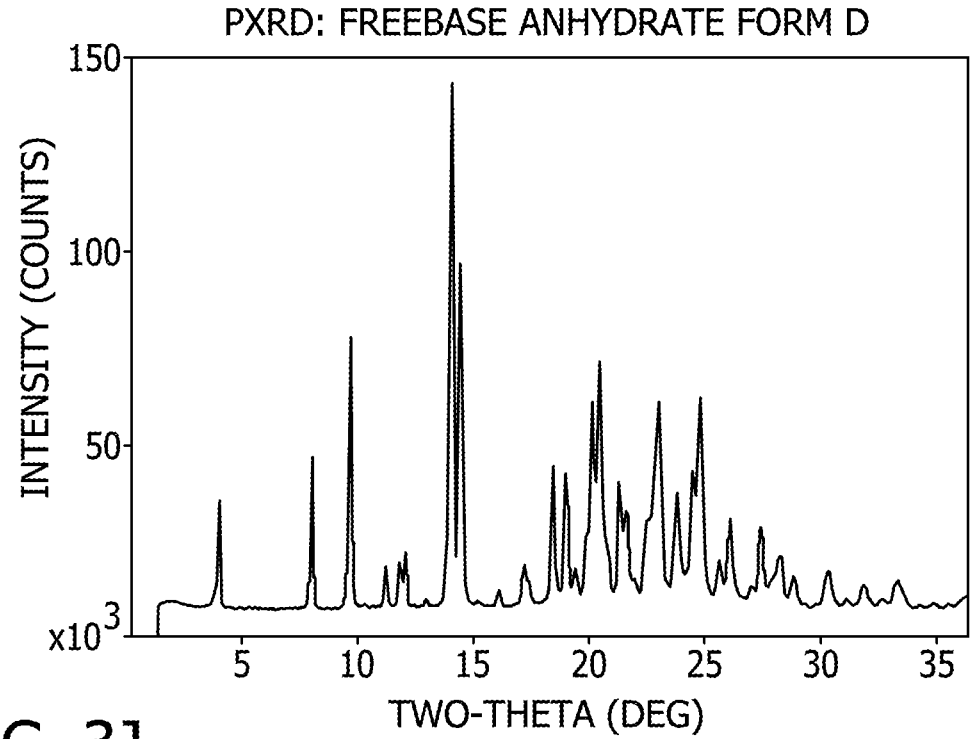
PXRD: FREEBASE ANHYDRATE FORM D
INTENSITY (COUNTS)
150
100
50
x10^3
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3J

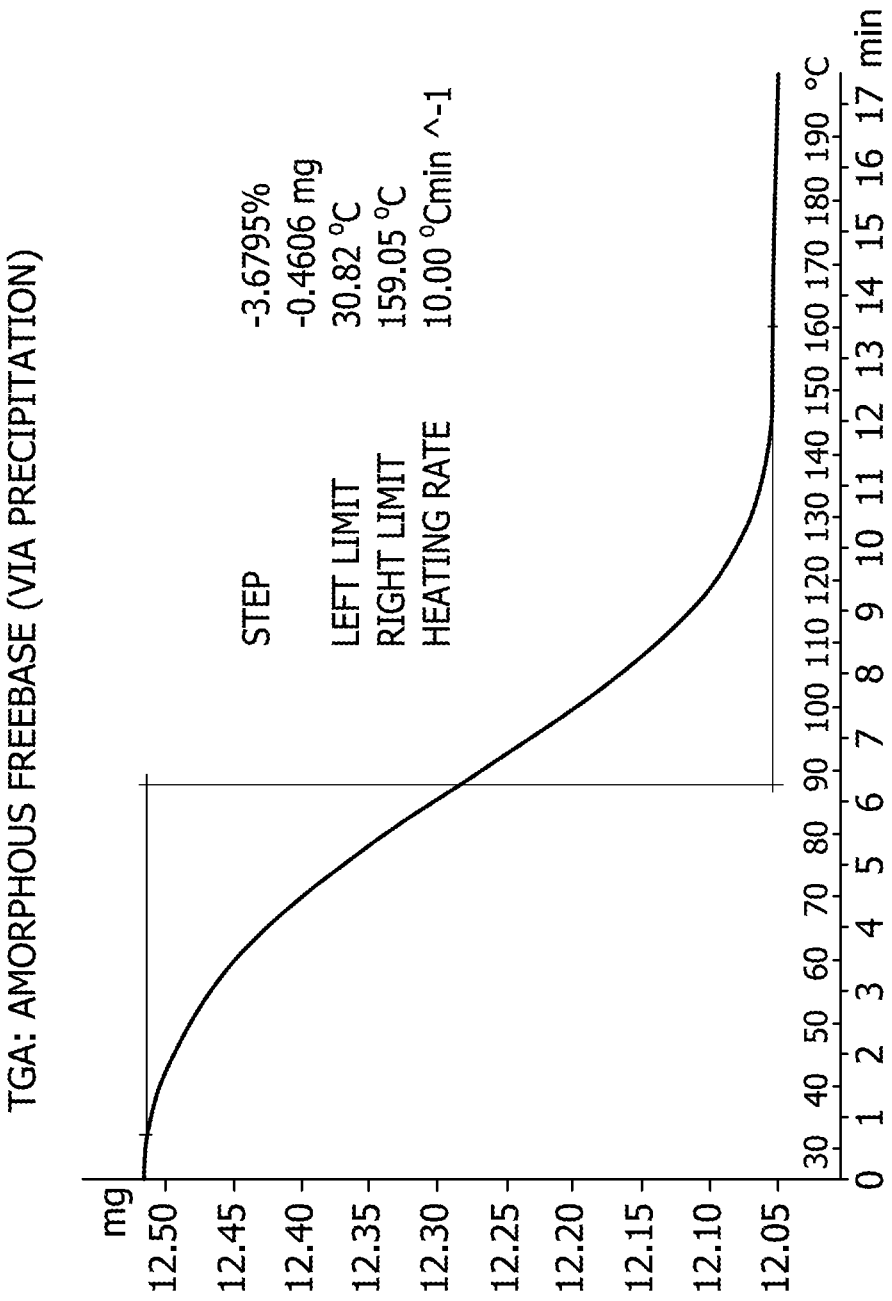
TGA: AMORPHOUS FREEBASE (VIA PRECIPITATION)
STEP -3.6795%
-0.4606 mg
LEFT LIMIT 30.82 °C
RIGHT LIMIT 159.05 °C
HEATING RATE 10.00 °Cmin ^-1
mg
12.50
12.45
12.40
12.35
12.30
12.25
12.20
12.15
12.10
12.05
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min

FIG. 4A

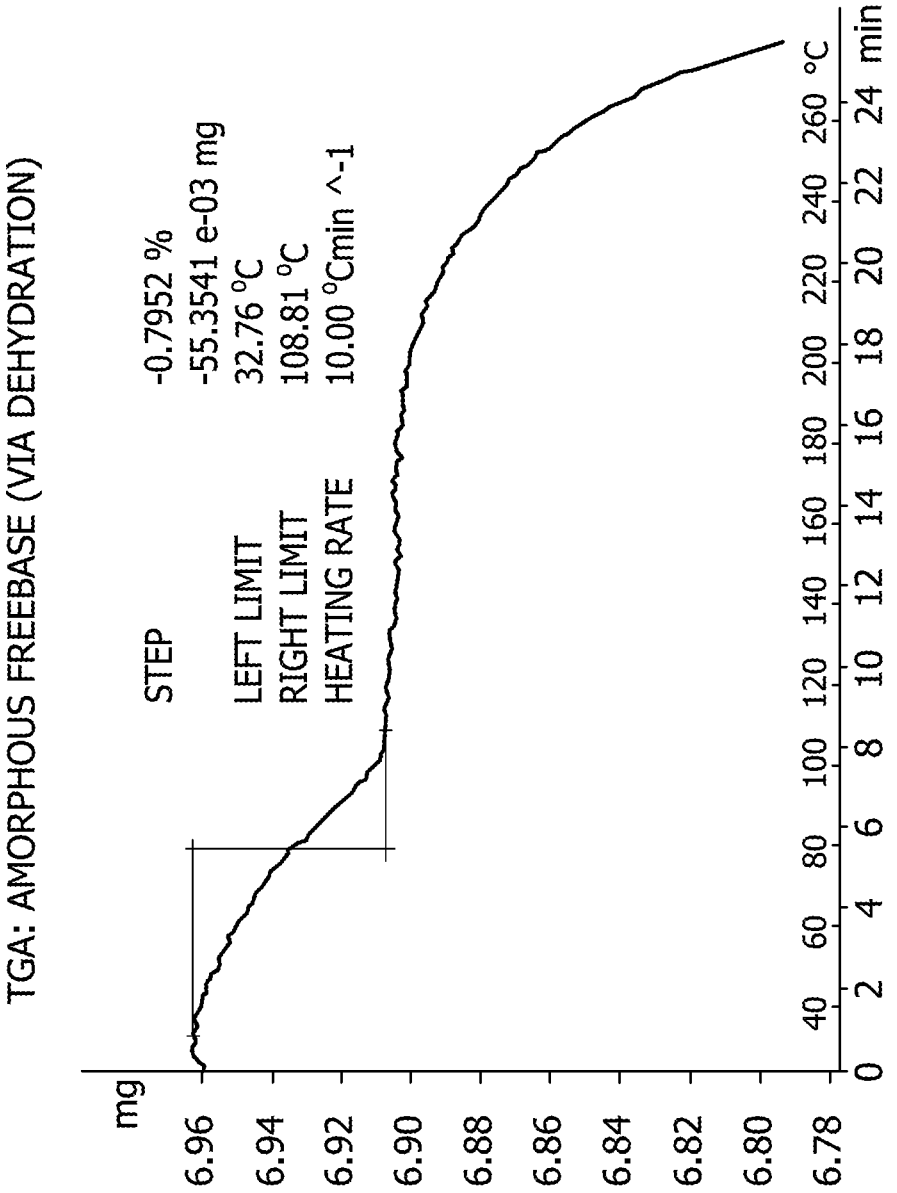
TGA: AMORPHOUS FREEBASE (VIA DEHYDRATION)
STEP
-0.7952 %
-55.3541 e-03 mg
LEFT LIMIT
32.76 °C
RIGHT LIMIT
108.81 °C
HEATING RATE
10.00 °Cmin ^-1
mg
6.96
6.94
6.92
6.90
6.88
6.86
6.84
6.82
6.80
6.78
0 2 4 6 8 10 12 14 16 18 20 22 24 min
40 60 80 100 120 140 160 180 200 220 240 260 °C

FIG. 4B

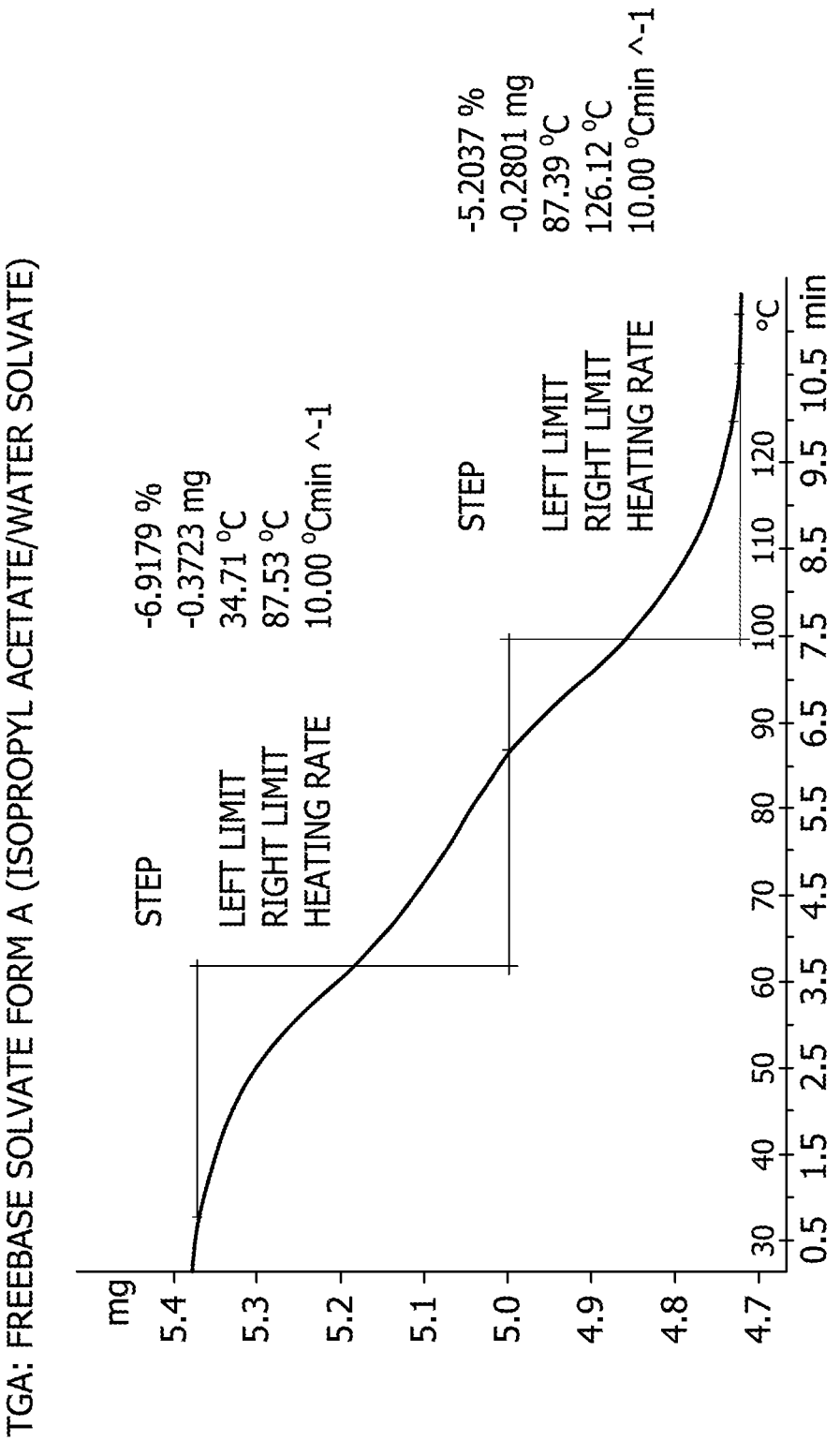
TGA: FREEBASE SOLVATE FORM A (ISOPROPYL ACETATE/WATER SOLVATE)
STEP
-6.9179 %
-0.3723 mg
LEFT LIMIT 34.71 °C
RIGHT LIMIT 87.53 °C
HEATING RATE 10.00 °Cmin ^-1
STEP
-5.2037 %
-0.2801 mg
LEFT LIMIT 87.39 °C
RIGHT LIMIT 126.12 °C
HEATING RATE 10.00 °Cmin ^-1
mg
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
30 40 50 60 70 80 90 100 110 120 °C
0.5 1.5 2.5 3.5 4.5 5.5 6.5 7.5 8.5 9.5 10.5 min

FIG. 4C

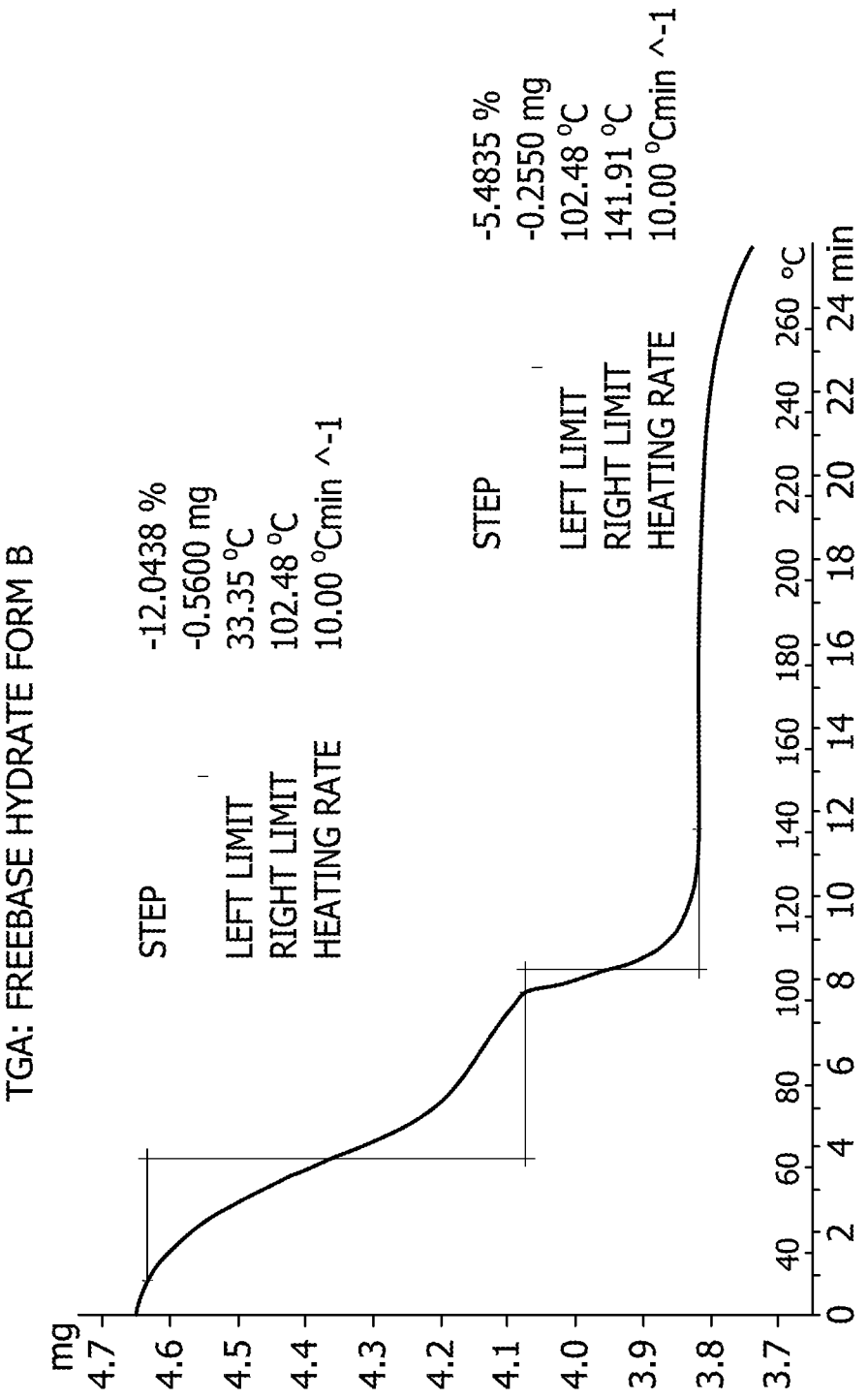
TGA: FREEBASE HYDRATE FORM B
STEP
-12.0438 %
-0.5600 mg
LEFT LIMIT
33.35 °C
RIGHT LIMIT
102.48 °C
HEATING RATE
10.00 °Cmin ^-1
STEP
-5.4835 %
-0.2550 mg
LEFT LIMIT
102.48 °C
RIGHT LIMIT
141.91 °C
HEATING RATE
10.00 °Cmin ^-1
mg
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
0
2
4
6
8
10
12
14
16
18
20
22
24 min
40
60
80
100
120
140
160
180
200
220
240
260 °C

FIG. 4D

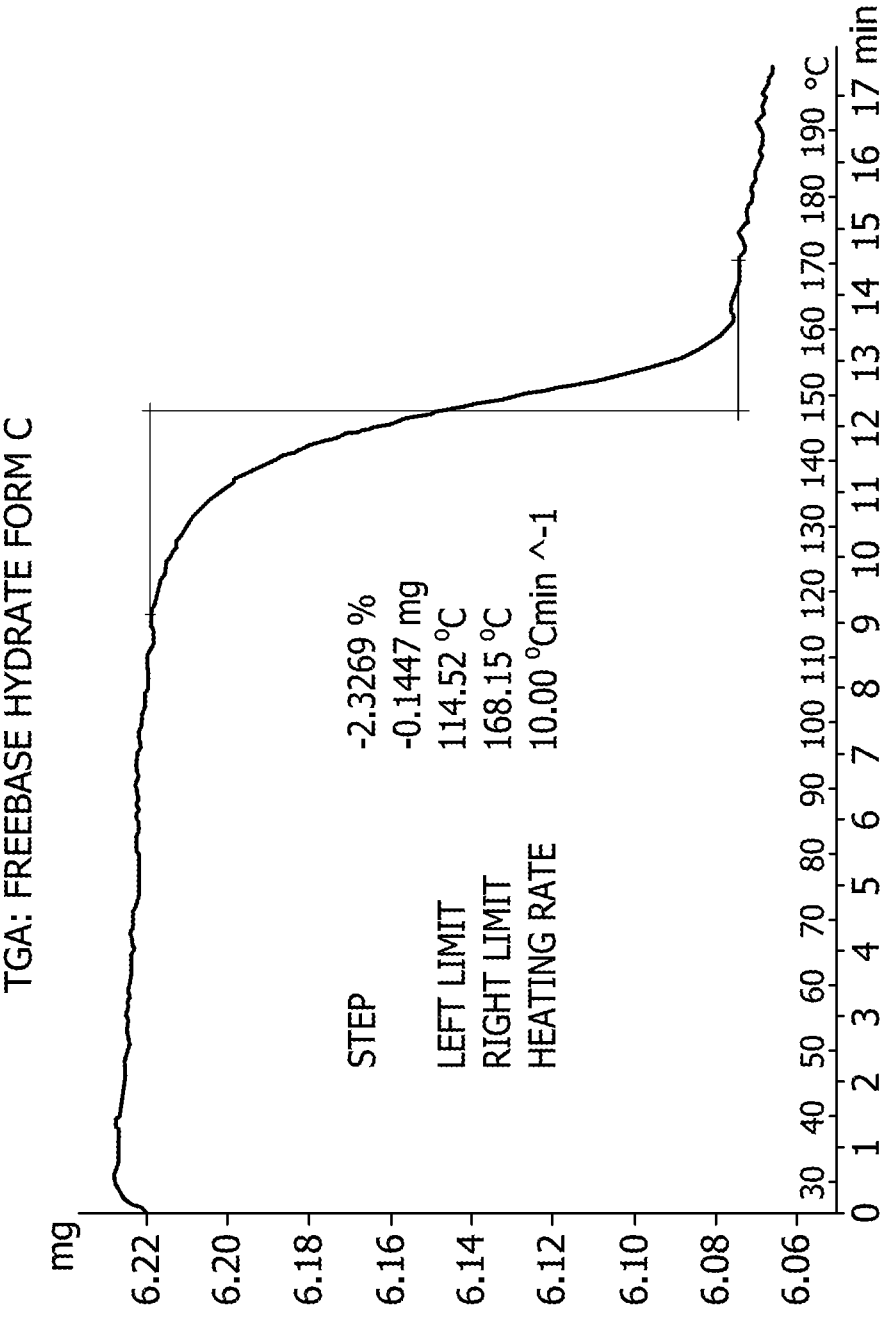
TGA: FREEBASE HYDRATE FORM C
mg
6.22
6.20
6.18
6.16
6.14
6.12
6.10
6.08
6.06
STEP
-2.3269 %
-0.1447 mg
LEFT LIMIT
114.52 °C
RIGHT LIMIT
168.15 °C
HEATING RATE
10.00 °Cmin ^-1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C

FIG. 4E

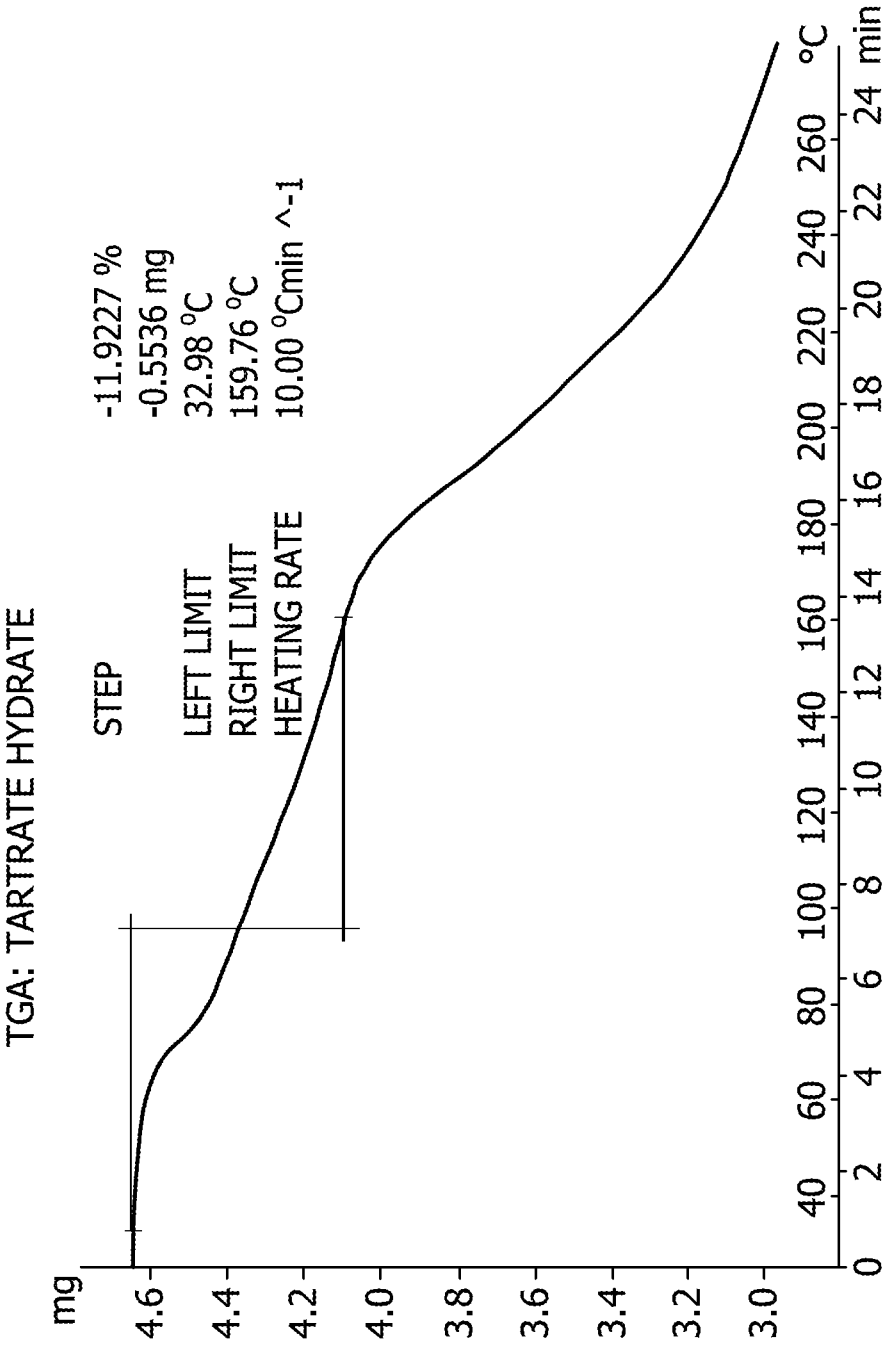
TGA: TARTRATE HYDRATE
STEP
LEFT LIMIT
RIGHT LIMIT
HEATING RATE
-11.9227 %
-0.5536 mg
32.98 °C
159.76 °C
10.00 °Cmin ^-1
mg
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
40 60 80 100 120 140 160 180 200 220 240 260 °C
0 2 4 6 8 10 12 14 16 18 20 22 24 min

FIG. 4F

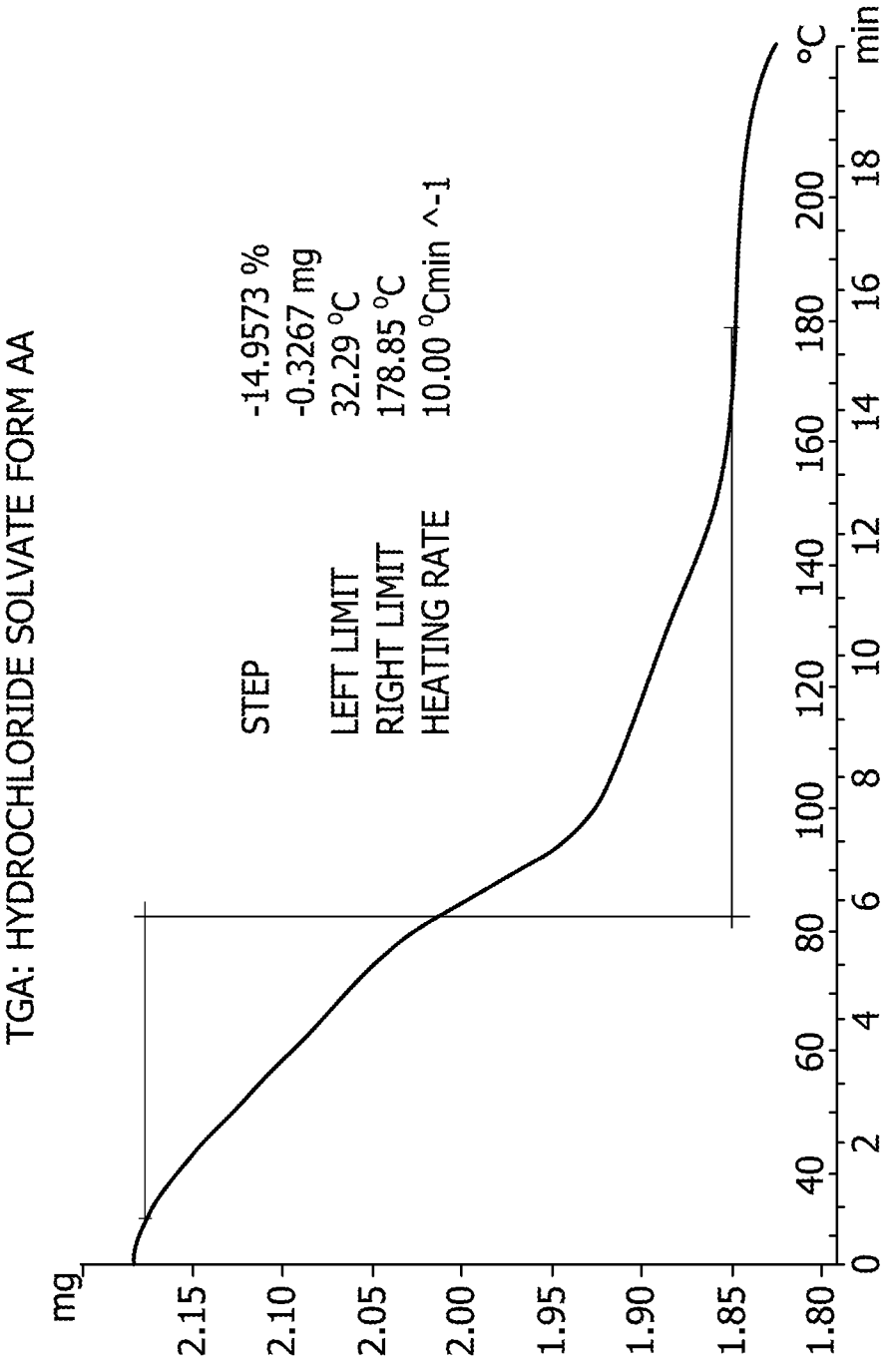
TGA: HYDROCHLORIDE SOLVATE FORM AA
STEP
-14.9573 %
-0.3267 mg
LEFT LIMIT
32.29 °C
RIGHT LIMIT
178.85 °C
HEATING RATE
10.00 °Cmin ^-1
mg
2.15
2.10
2.05
2.00
1.95
1.90
1.85
1.80
0
40
2
60
4
80
6
100
8
120
10
140
12
160
14
180
16
200
18
°C
min

FIG. 4G

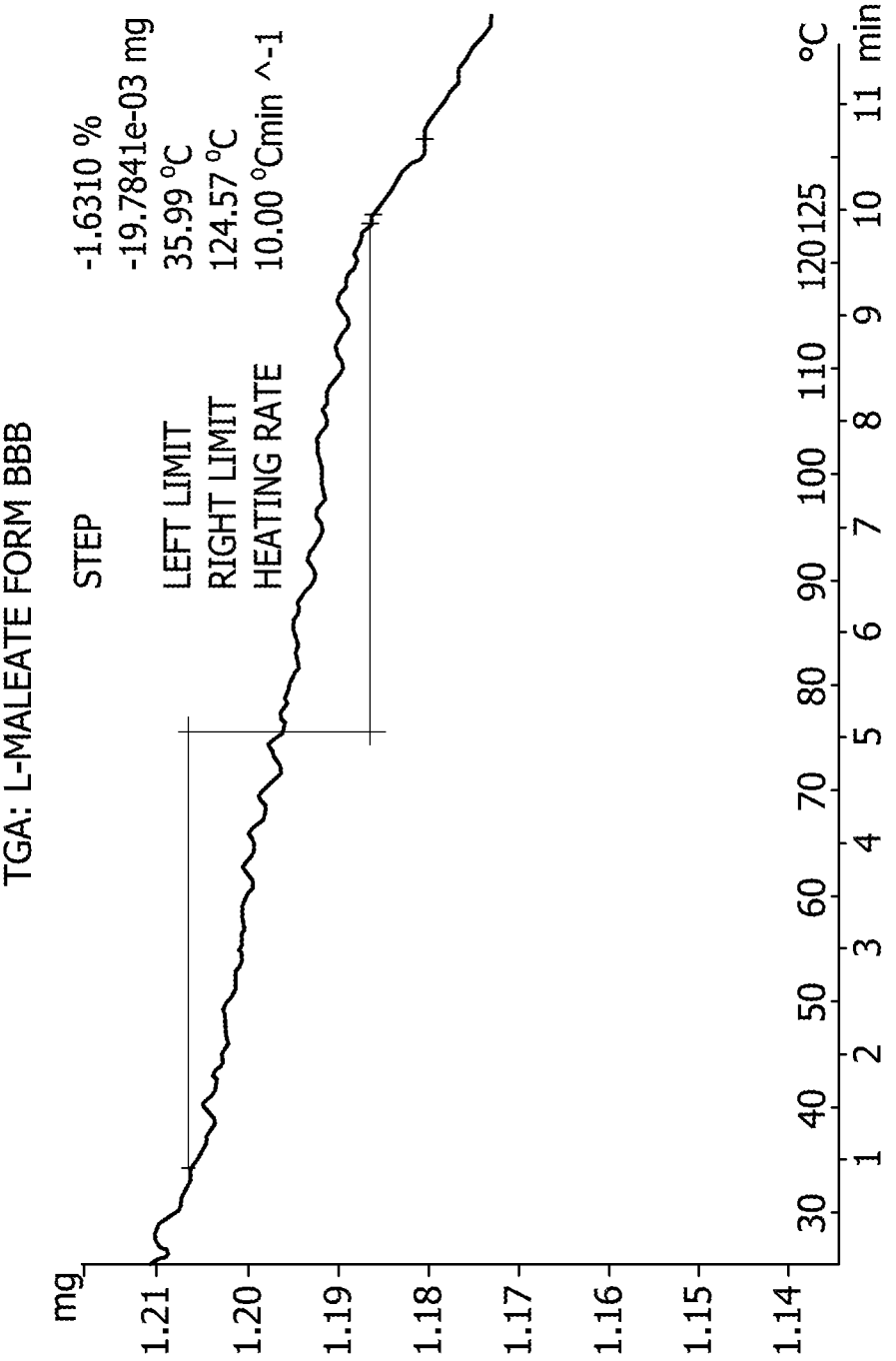
TGA: L-MALEATE FORM BBB
STEP
LEFT LIMIT
RIGHT LIMIT
HEATING RATE
-1.6310 %
-19.7841e-03 mg
35.99 °C
124.57 °C
10.00 °Cmin ^-1
mg
1.21
1.20
1.19
1.18
1.17
1.16
1.15
1.14
30
40
50
60
70
80
90
100
110
120
125
°C
1
2
3
4
5
6
7
8
9
10
11
min

FIG. 4H

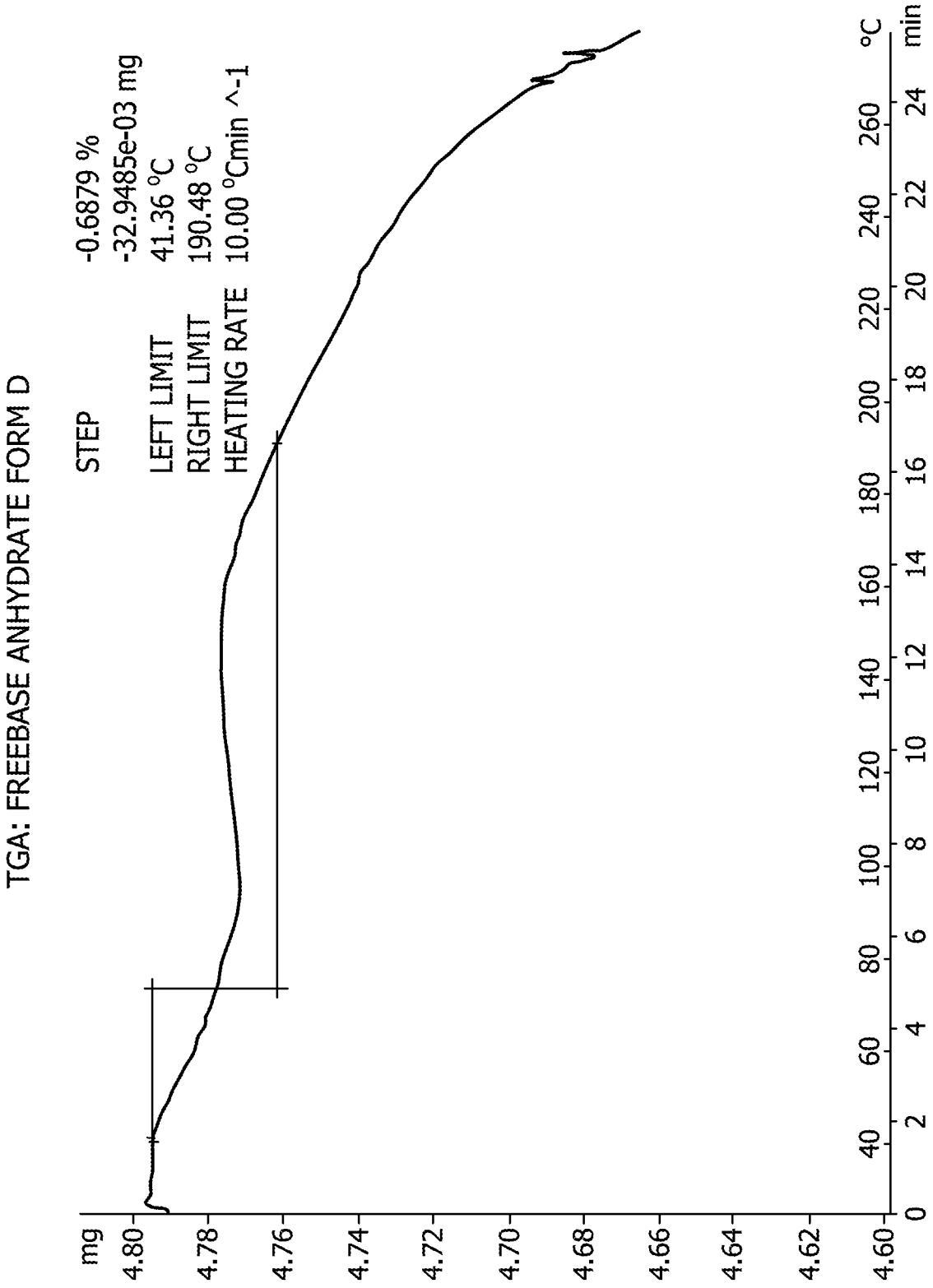
TGA: FREEBASE ANHYDRATE FORM D
STEP
-0.6879 %
-32.9485e-03 mg
LEFT LIMIT
41.36 °C
RIGHT LIMIT
190.48 °C
HEATING RATE
10.00 °Cmin ^-1
mg
4.80
4.78
4.76
4.74
4.72
4.70
4.68
4.66
4.64
4.62
4.60
0
2
4
6
8
10
12
14
16
18
20
22
24
min
40
60
80
100
120
140
160
180
200
220
240
260
°C

FIG. 4I

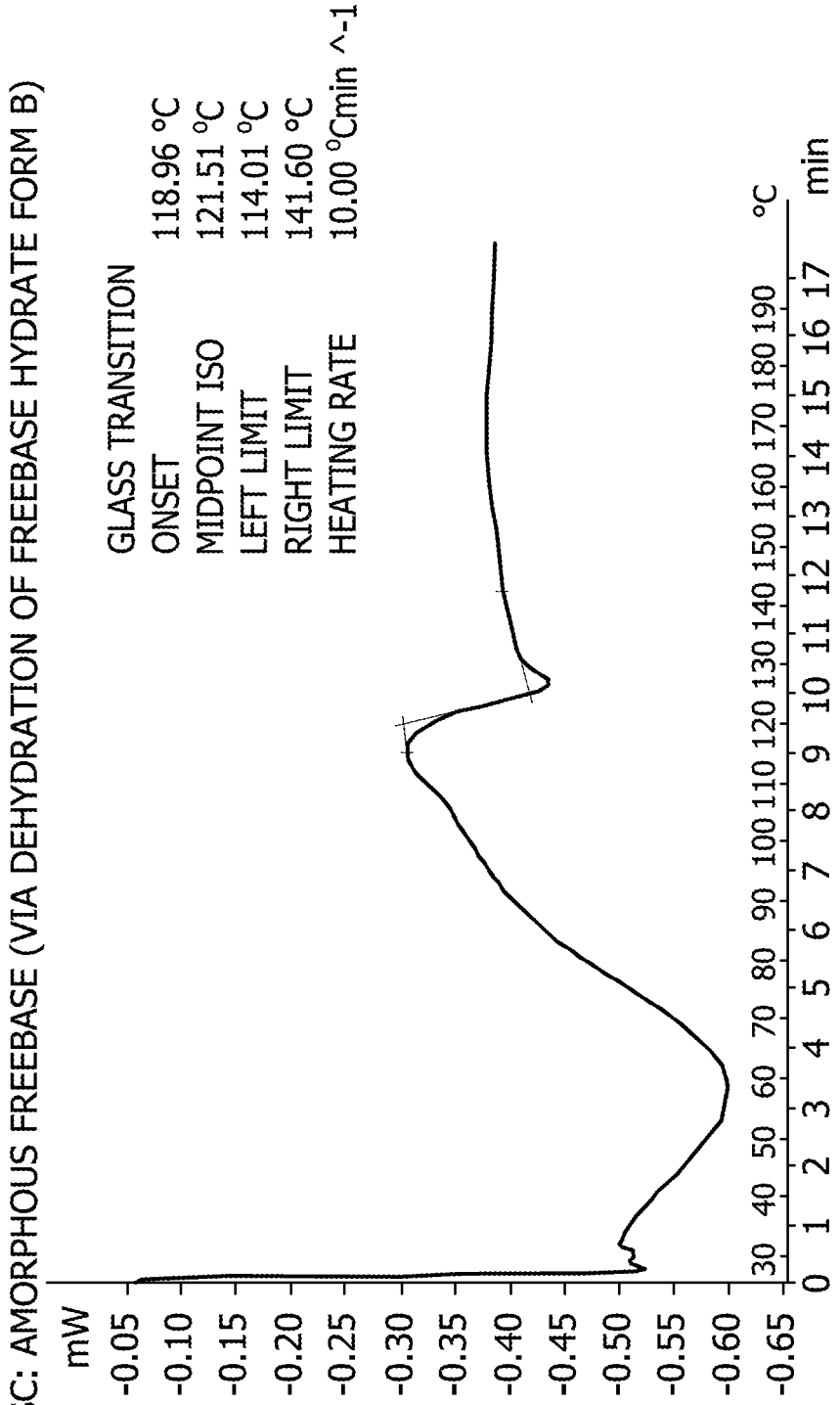
DSC: AMORPHOUS FREEBASE (VIA DEHYDRATION OF FREEBASE HYDRATE FORM B)
GLASS TRANSITION
ONSET 118.96 °C
MIDPOINT ISO 121.51 °C
LEFT LIMIT 114.01 °C
RIGHT LIMIT 141.60 °C
HEATING RATE 10.00 °Cmin ^-1
mW
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
-0.35
-0.40
-0.45
-0.50
-0.55
-0.60
-0.65
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min

FIG. 5A

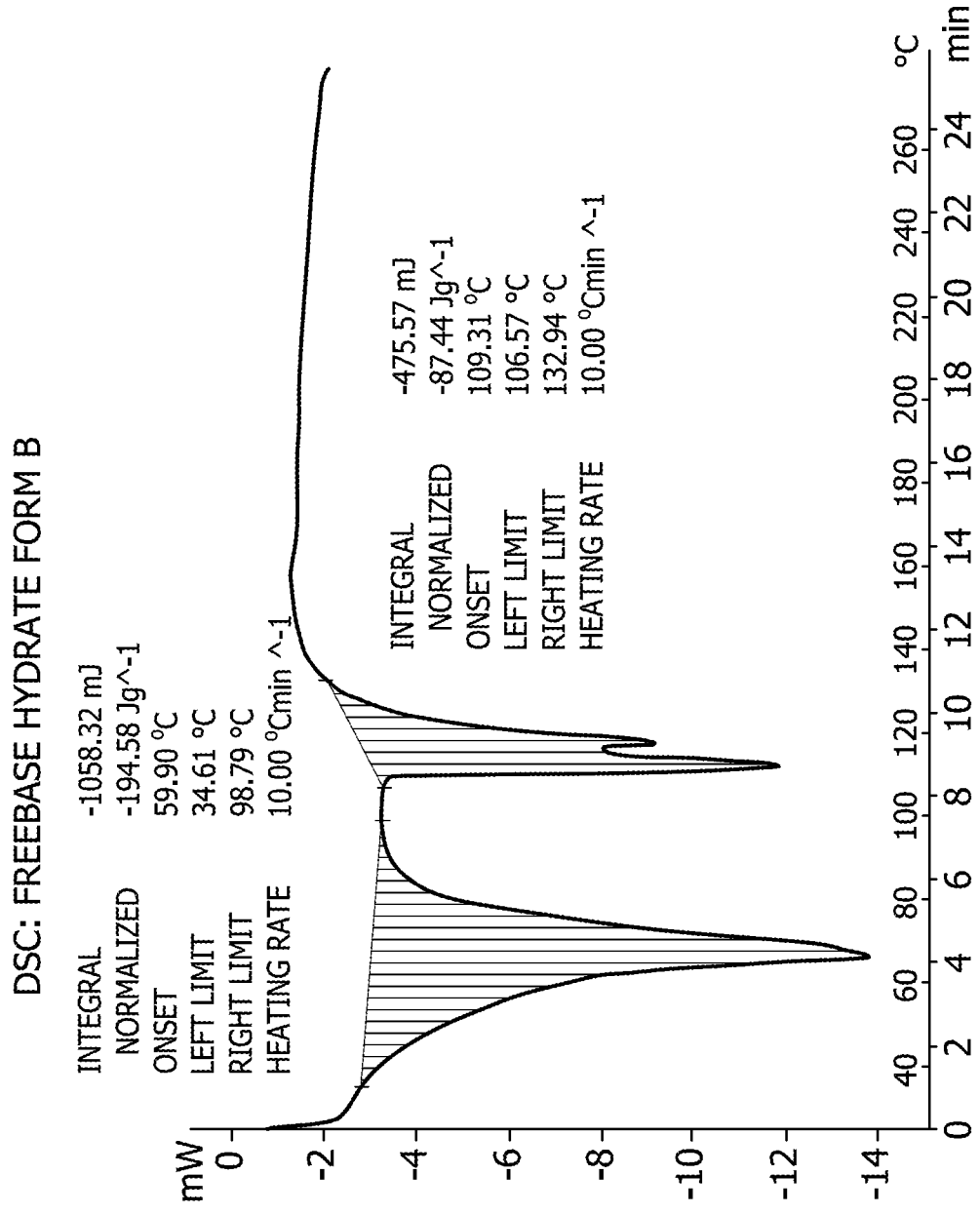
DSC: FREEBASE HYDRATE FORM B
INTEGRAL -1058.32 mJ
NORMALIZED -194.58 Jg^-1
ONSET 59.90 °C
LEFT LIMIT 34.61 °C
RIGHT LIMIT 98.79 °C
HEATING RATE 10.00 °Cmin ^-1
INTEGRAL -475.57 mJ
NORMALIZED -87.44 Jg^-1
ONSET 109.31 °C
LEFT LIMIT 106.57 °C
RIGHT LIMIT 132.94 °C
HEATING RATE 10.00 °Cmin ^-1
mW
0
-2
-4
-6
-8
-10
-12
-14
0 2 4 6 8 10 12 14 16 18 20 22 24 min
40 60 80 100 120 140 160 180 200 220 240 260 °C

FIG. 5B

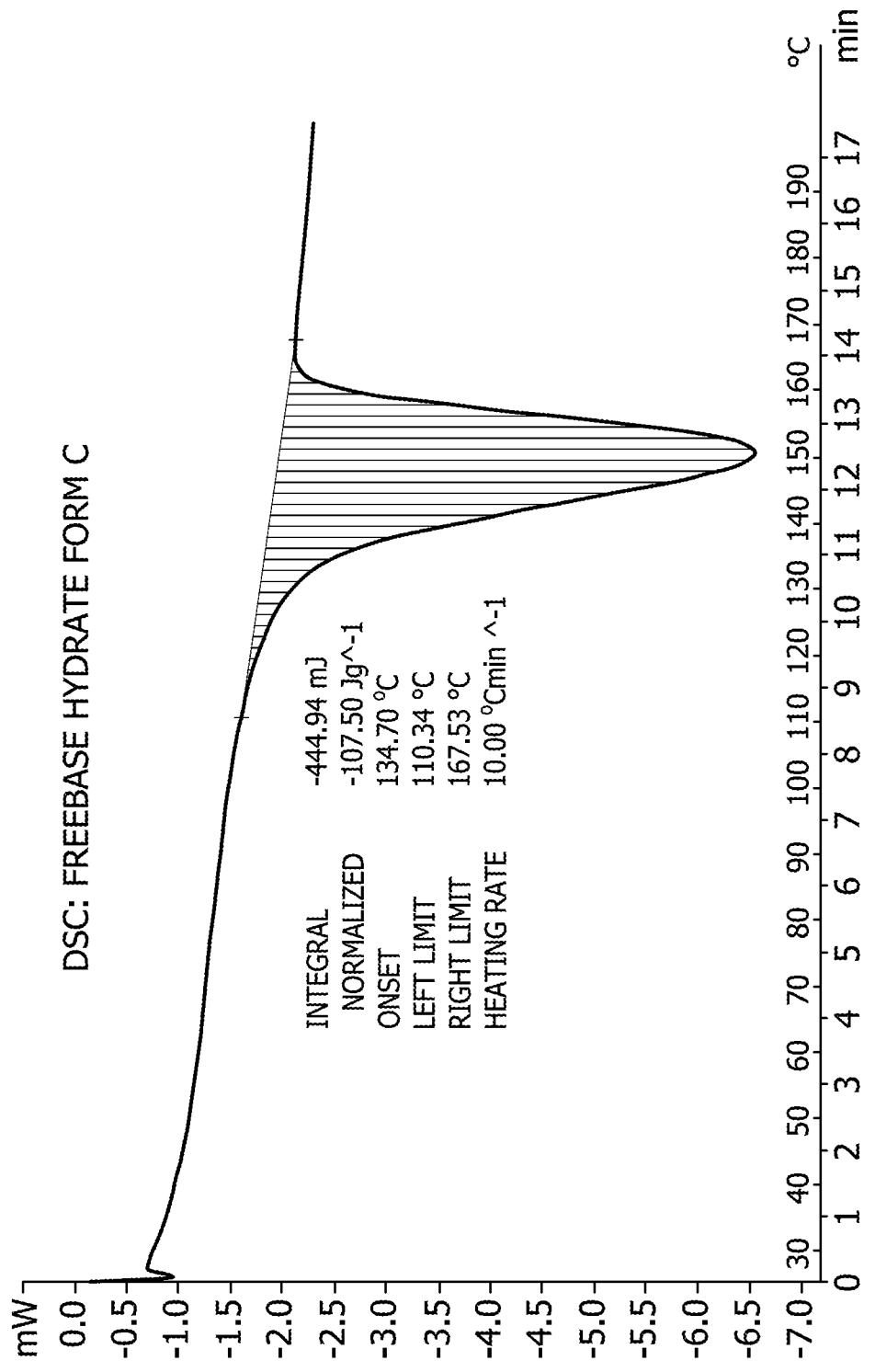
DSC: FREEBASE HYDRATE FORM C
INTEGRAL -444.94 mJ
NORMALIZED -107.50 Jg^-1
ONSET 134.70 °C
LEFT LIMIT 110.34 °C
RIGHT LIMIT 167.53 °C
HEATING RATE 10.00 °Cmin ^-1
mW
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min

FIG. 5C

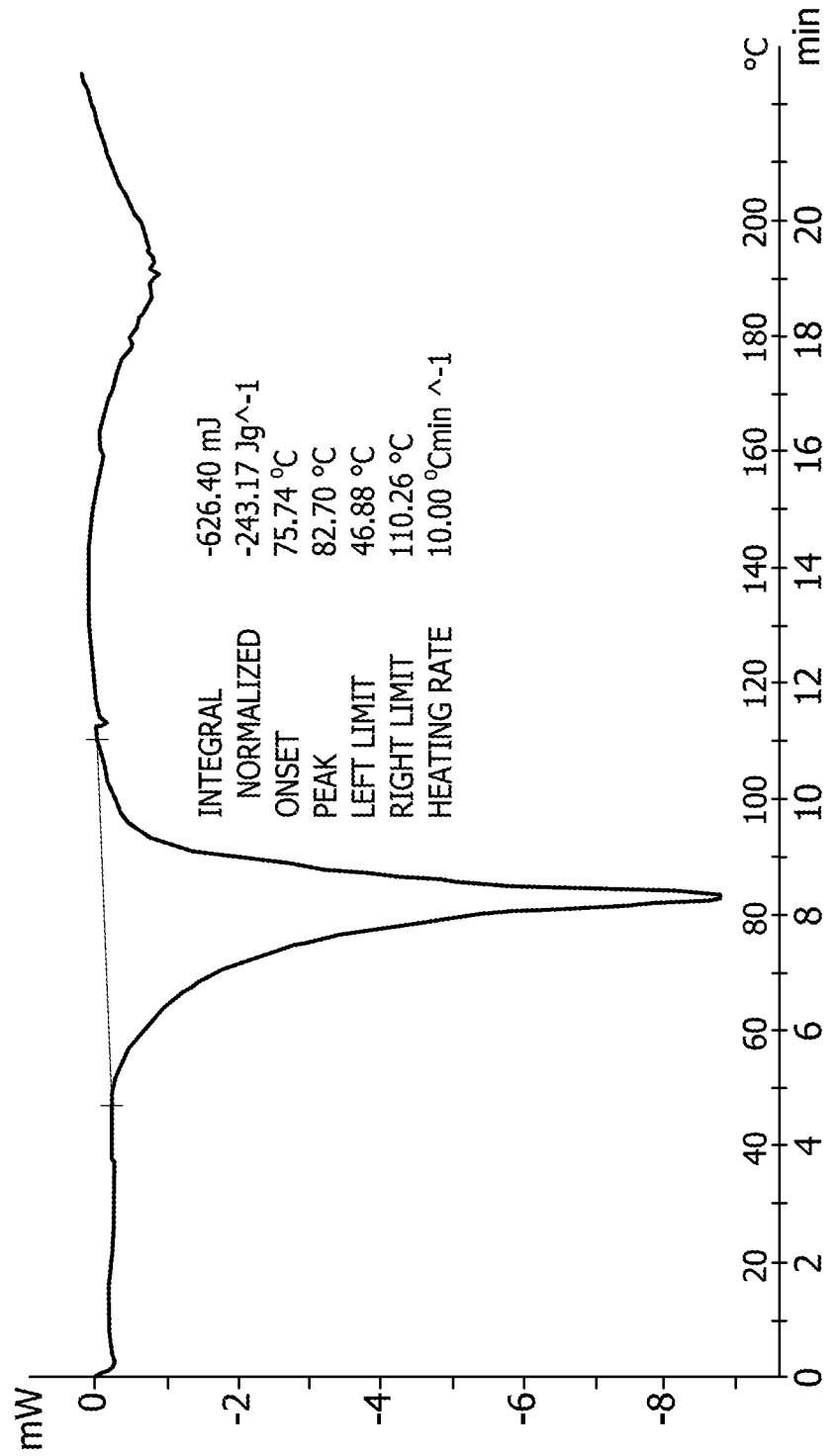
DSC: TARTRATE HYDRATE
INTEGRAL -626.40 mJ
NORMALIZED -243.17 Jg^-1
ONSET 75.74 °C
PEAK 82.70 °C
LEFT LIMIT 46.88 °C
RIGHT LIMIT 110.26 °C
HEATING RATE 10.00 °Cmin ^-1
mW
0
-2
-4
-6
-8
°C
min
0
20
40
60
80
100
120
140
160
180
200
2
4
6
8
10
12
14
16
18
20

FIG. 5D

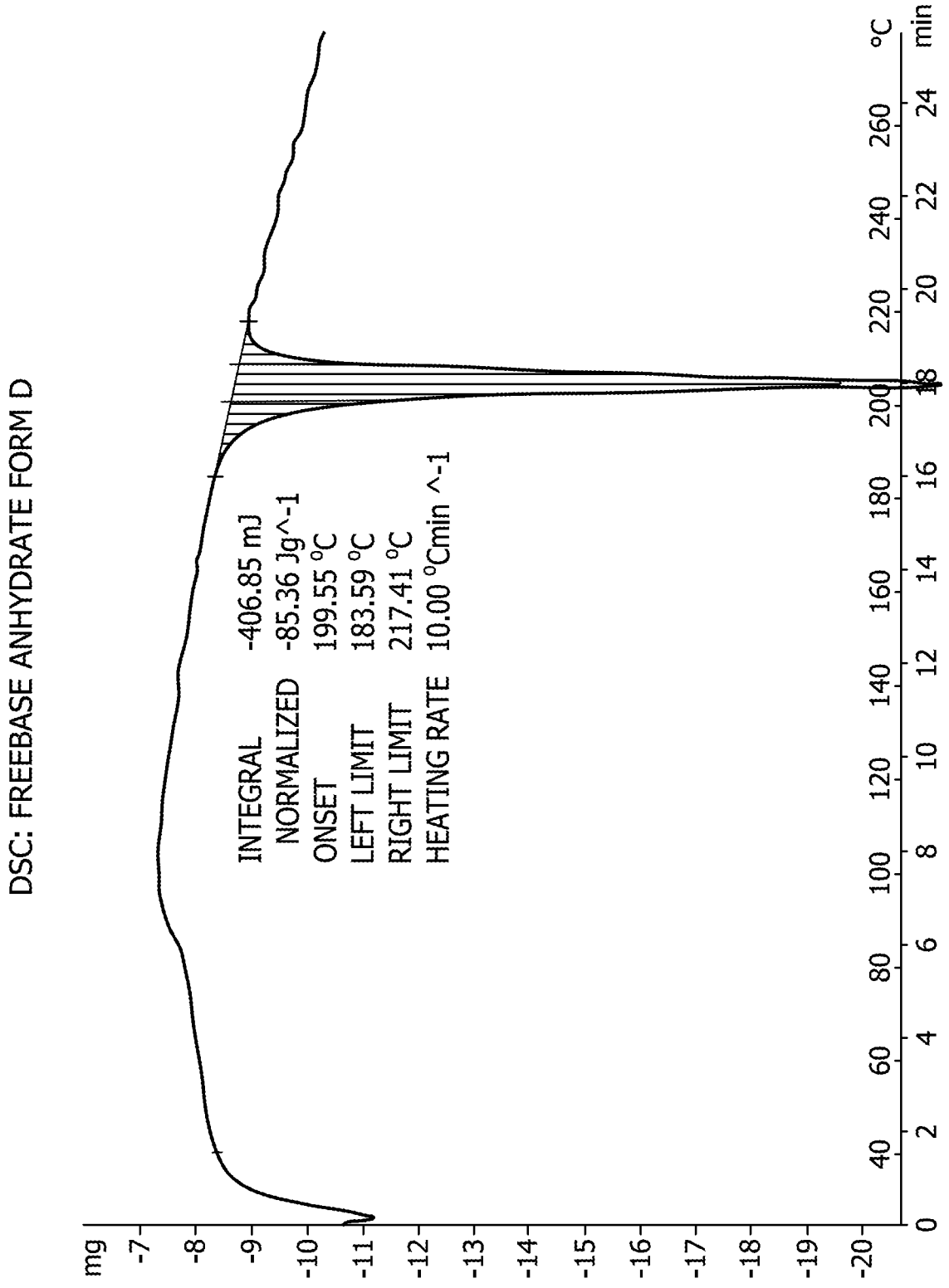
DSC: FREEBASE ANHYDRATE FORM D
INTEGRAL -406.85 mJ
NORMALIZED -85.36 Jg^-1
ONSET 199.55 °C
LEFT LIMIT 183.59 °C
RIGHT LIMIT 217.41 °C
HEATING RATE 10.00 °Cmin ^-1
mg
-7
-8
-9
-10
-11
-12
-13
-14
-15
-16
-17
-18
-19
-20
0
2
4
6
8
10
12
14
16
18
20
22
24
min
40
60
80
100
120
140
160
180
200
220
240
260
°C

FIG. 5E

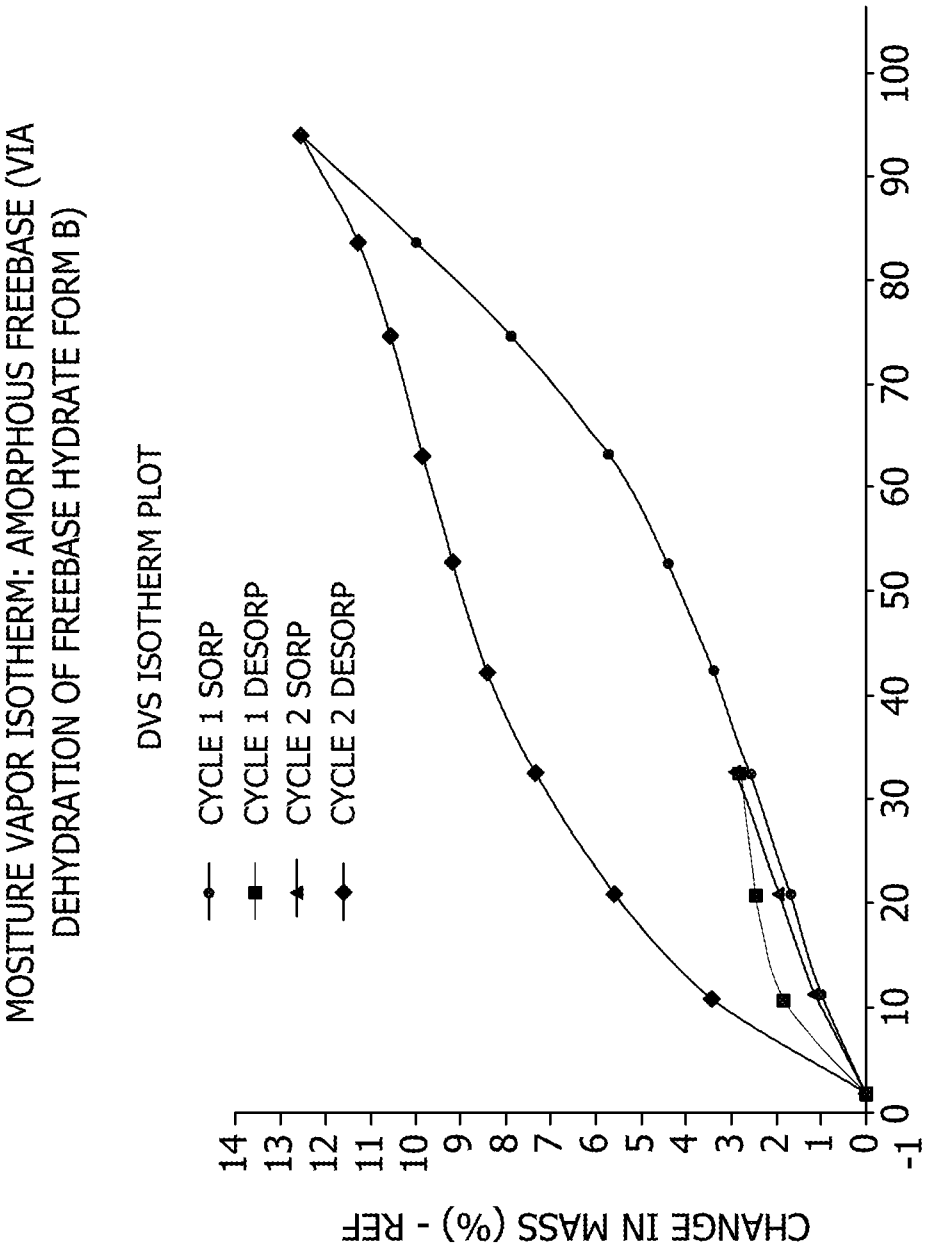
MOSITURE VAPOR ISOTHERM: AMORPHOUS FREEBASE (VIA DEHYDRATION OF FREEBASE HYDRATE FORM B)
DVS ISOTHERM PLOT
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
SAMPLE % P/Po
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
0
10
20
30
40
50
60
70
80
90
100

FIG. 6A

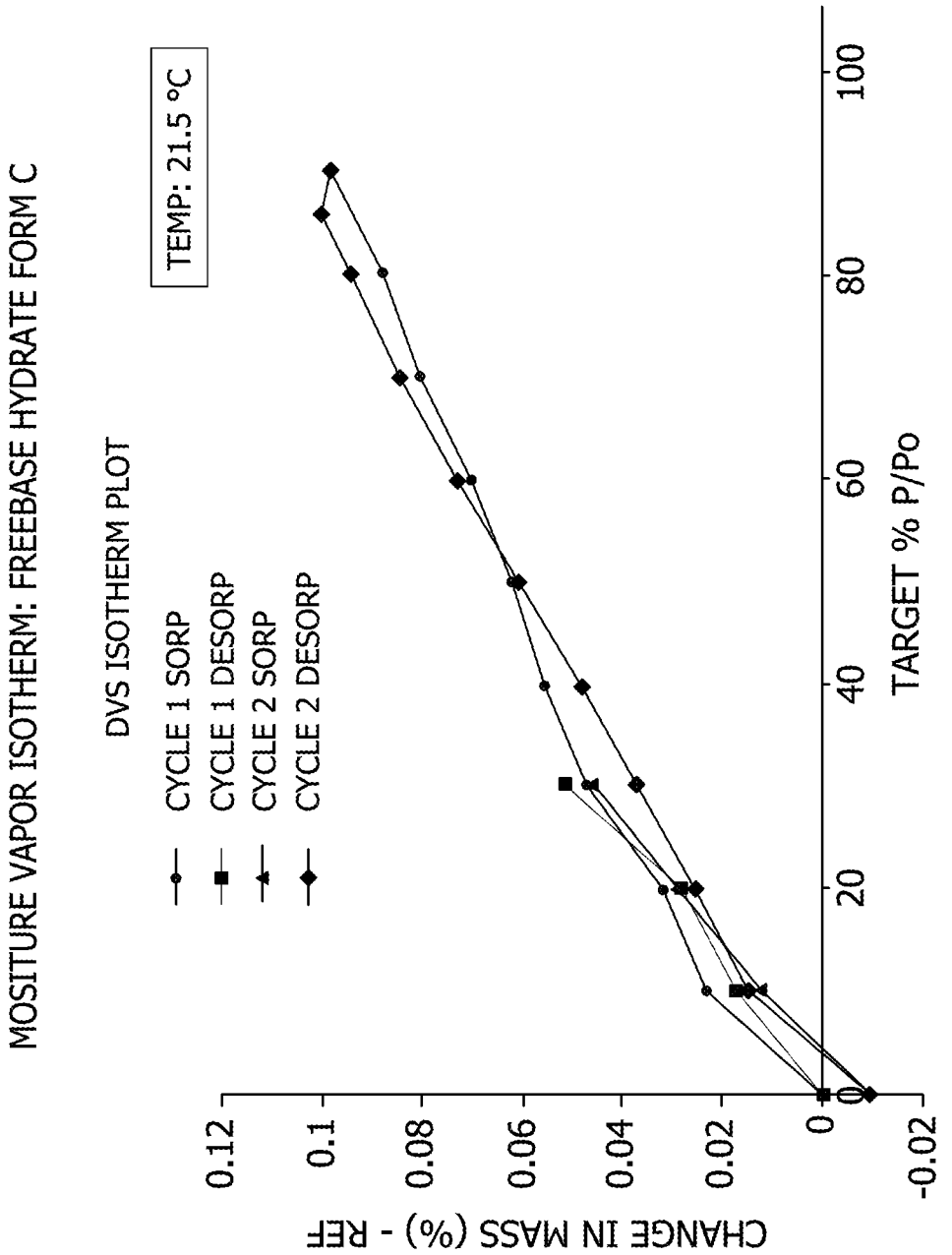
MOSITURE VAPOR ISOTHERM: FREEBASE HYDRATE FORM C
DVS ISOTHERM PLOT
TEMP: 21.5 °C
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
0
20
40
60
80
100
TARGET % P/Po

FIG. 6B

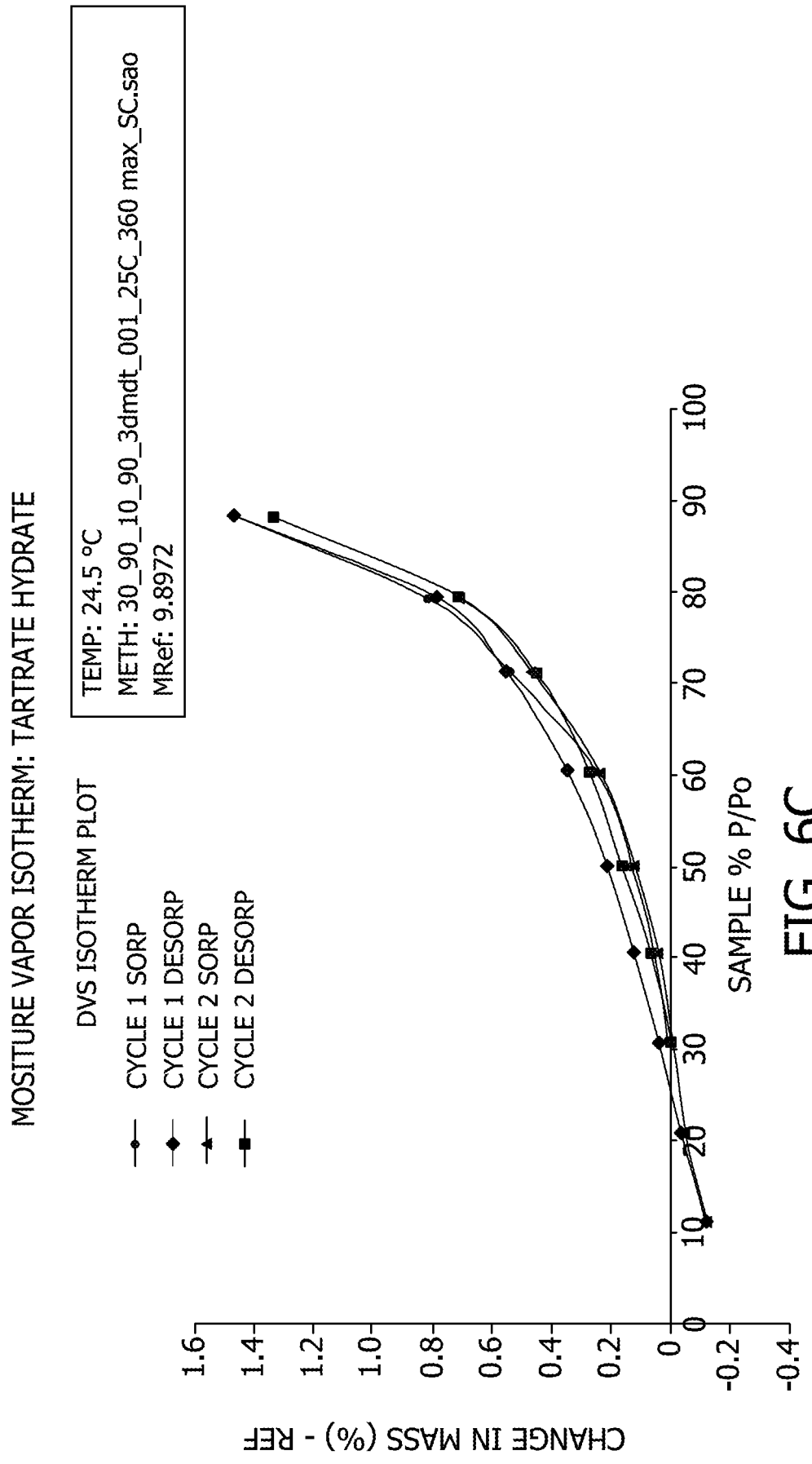
MOSITURE VAPOR ISOTHERM: TARTRATE HYDRATE
TEMP: 24.5 °C
METH: 30_90_10_90_3dmdt_001_25C_360 max_SC.sao
MRef: 9.8972
DVS ISOTHERM PLOT
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
SAMPLE % P/Po
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0
10
20
30
40
50
60
70
80
90
100

FIG. 6C

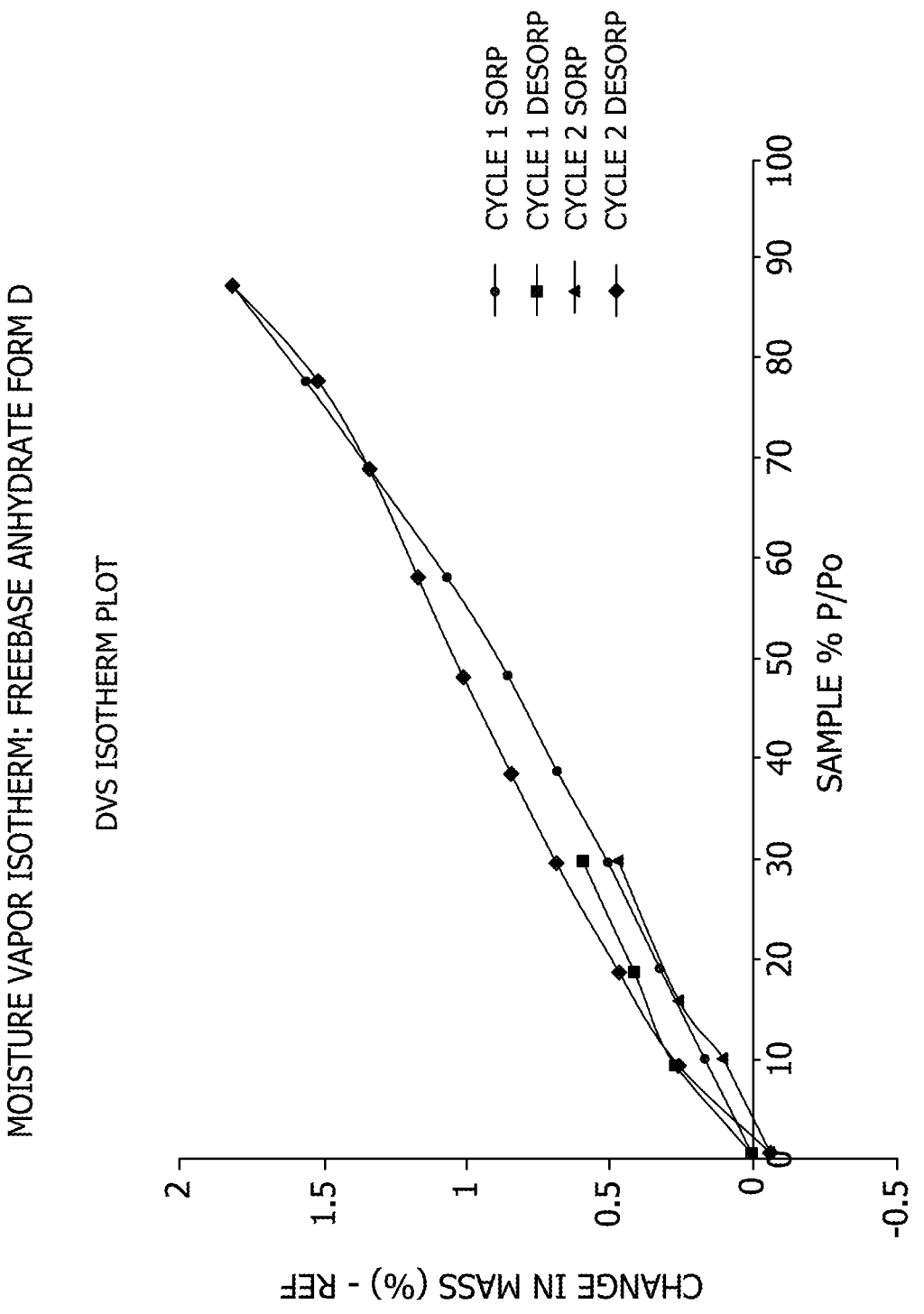
MOISTURE VAPOR ISOTHERM: FREEBASE ANHYDRATE FORM D
DVS ISOTHERM PLOT
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
SAMPLE % P/Po
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
70
80
90
100

FIG. 6D

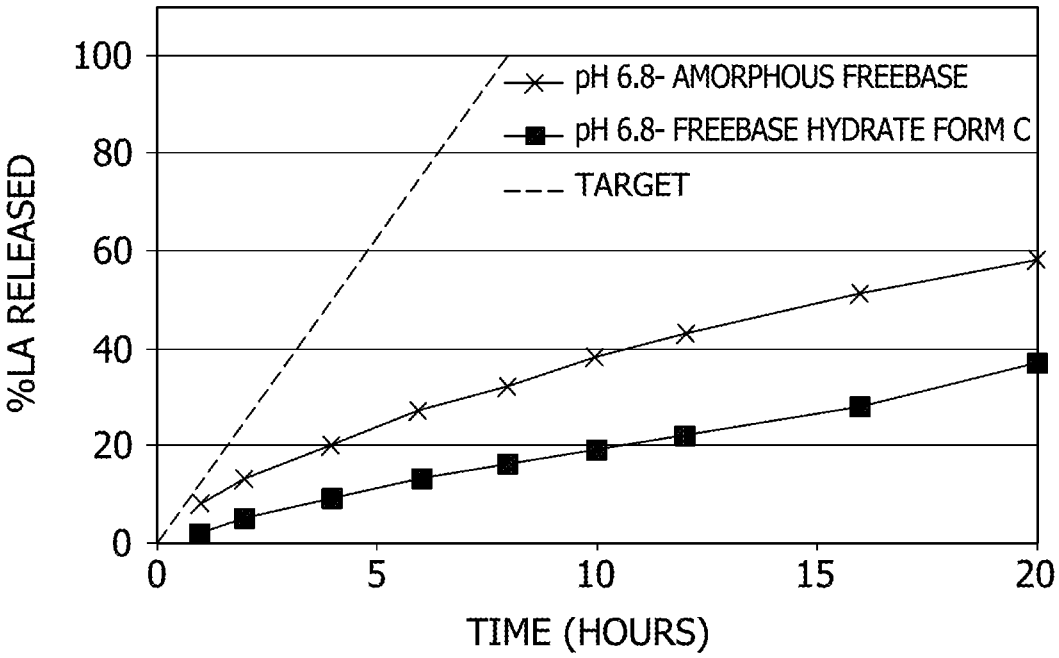
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)
pH 6.8- AMORPHOUS FREEBASE
pH 6.8- FREEBASE HYDRATE FORM C
TARGET

FIG. 7

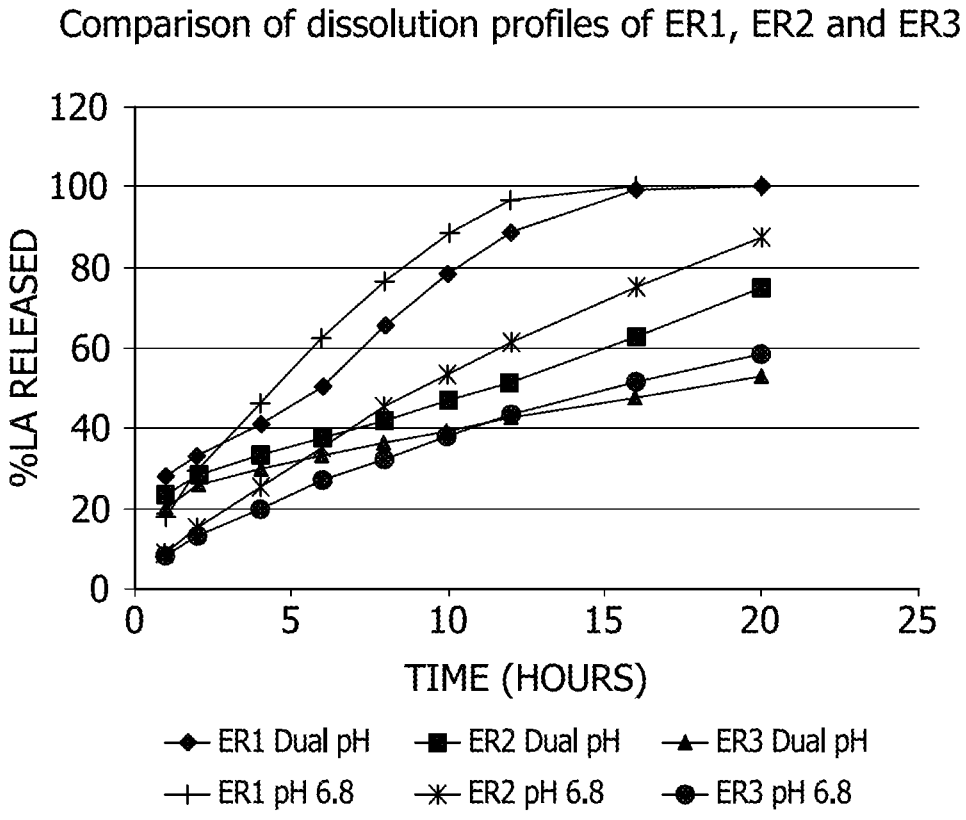
Comparison of dissolution profiles of ER1, ER2 and ER3
120
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
25
TIME (HOURS)
ER1 Dual pH
ER2 Dual pH
ER3 Dual pH
ER1 pH 6.8
ER2 pH 6.8
ER3 pH 6.8

FIG. 8

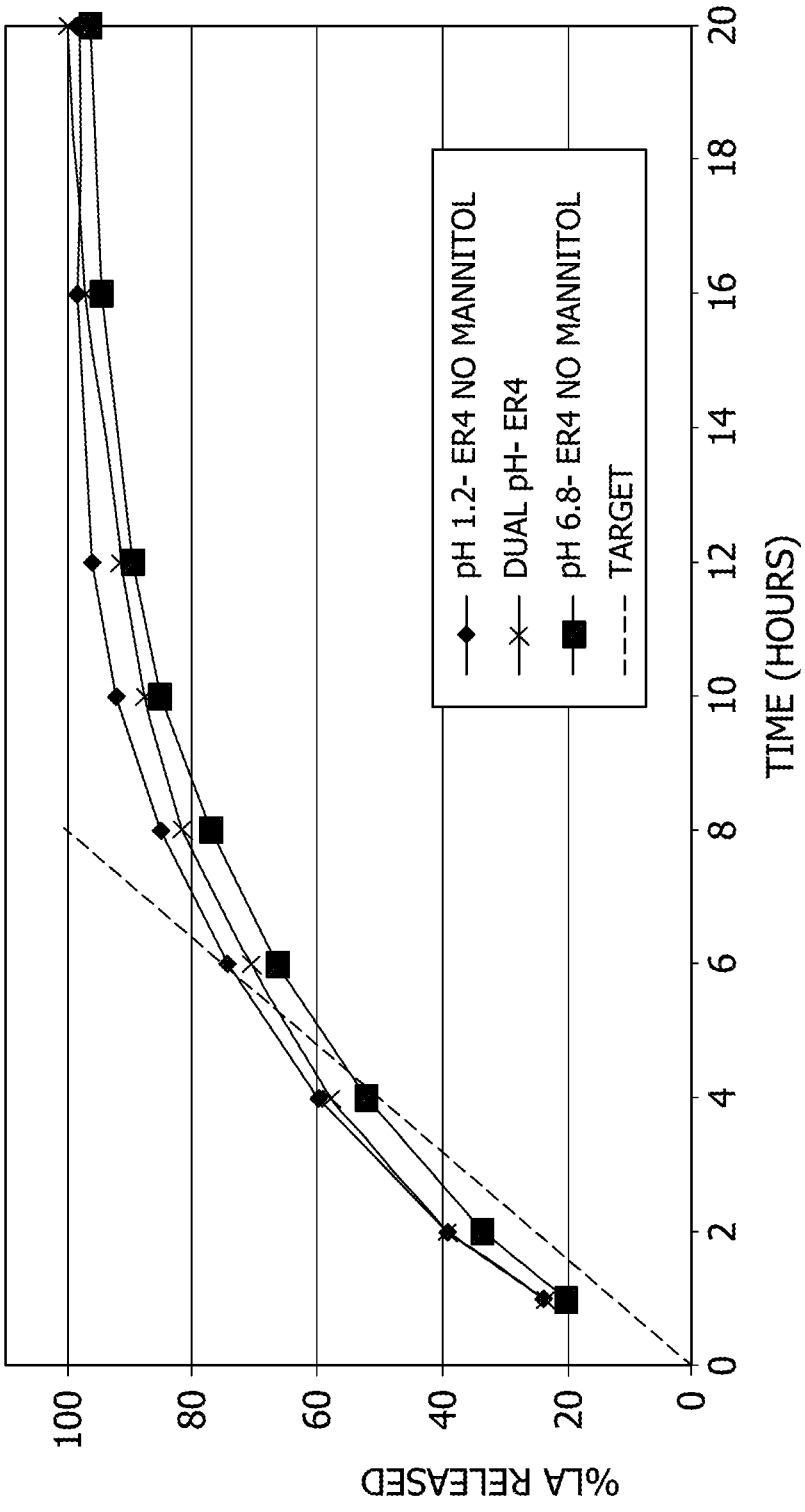
%LA RELEASED
0
20
40
60
80
100
TIME (HOURS)
0
2
4
6
8
10
12
14
16
18
20
pH 1.2- ER4 NO MANNITOL
DUAL pH- ER4
pH 6.8- ER4 NO MANNITOL
TARGET

FIG. 9

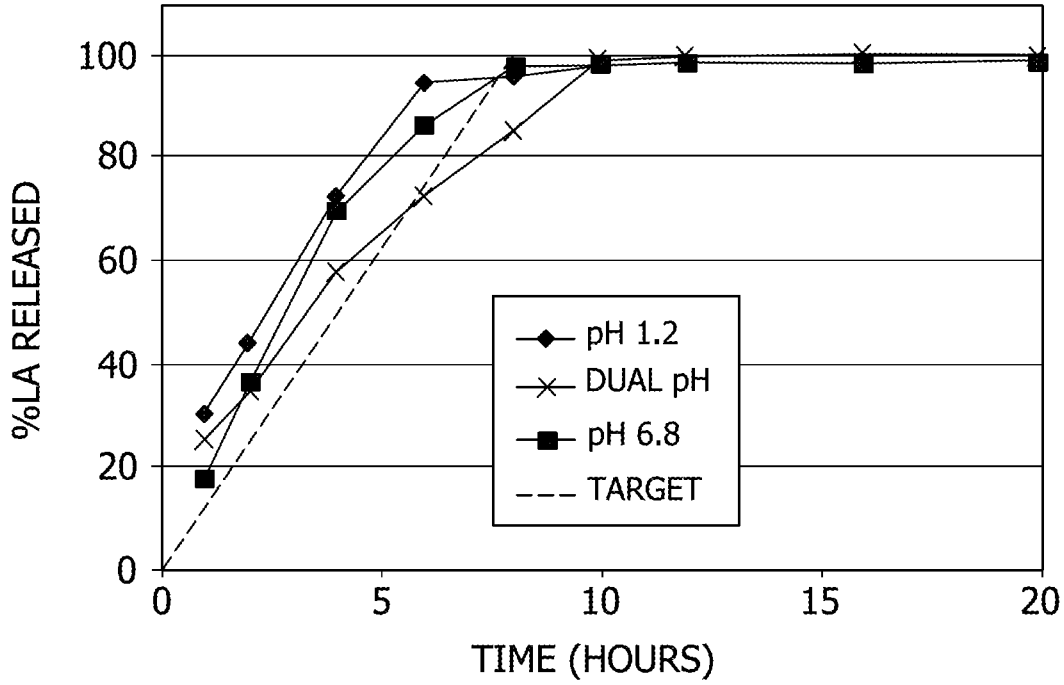
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)
pH 1.2
DUAL pH
pH 6.8
TARGET

FIG. 10

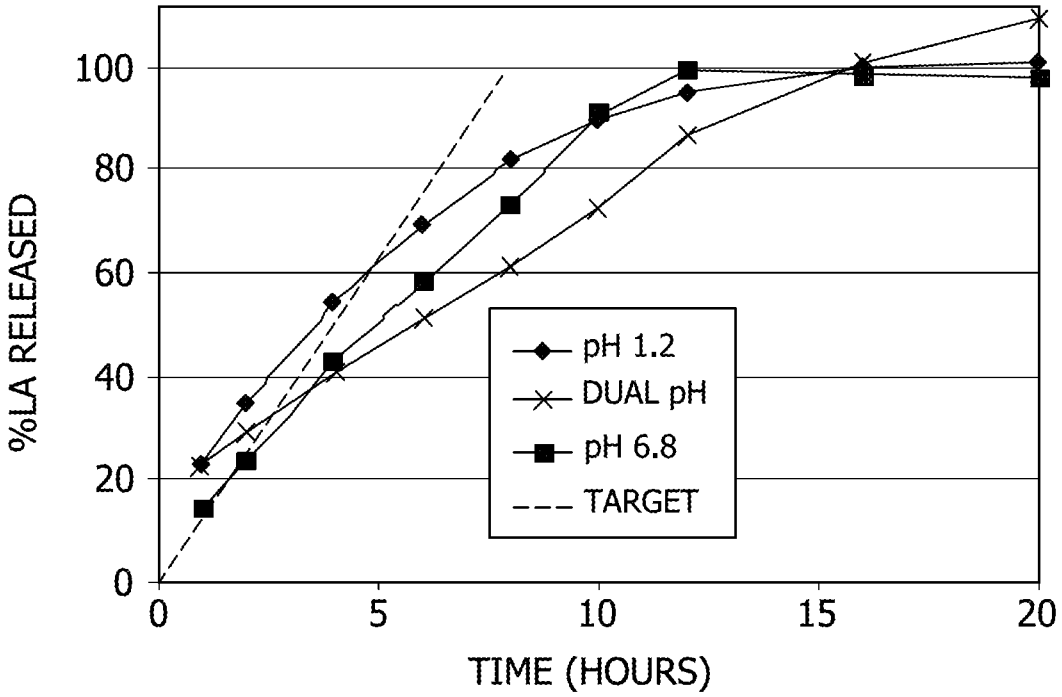
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)
pH 1.2
DUAL pH
pH 6.8
TARGET

FIG. 11

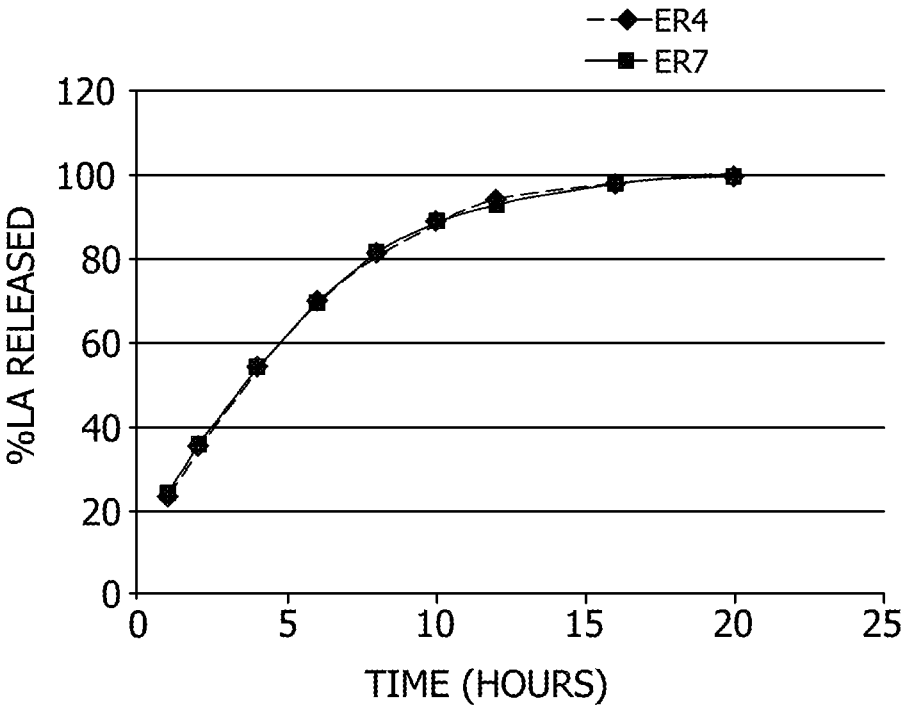
ER4
ER7
120
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
25
TIME (HOURS)

FIG. 12

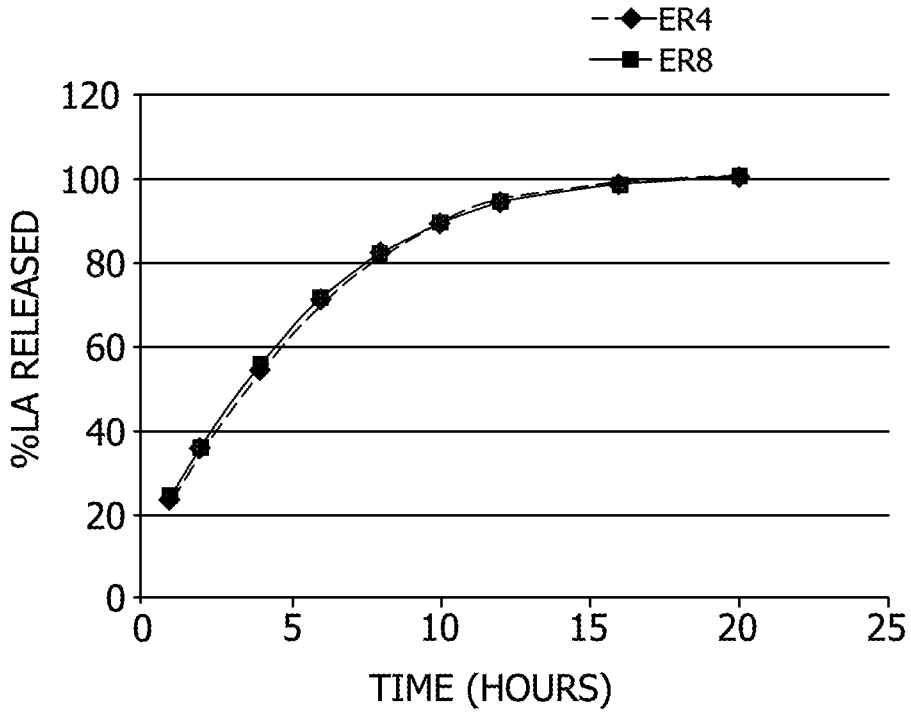
ER4
ER8
120
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
25
TIME (HOURS)

FIG. 13

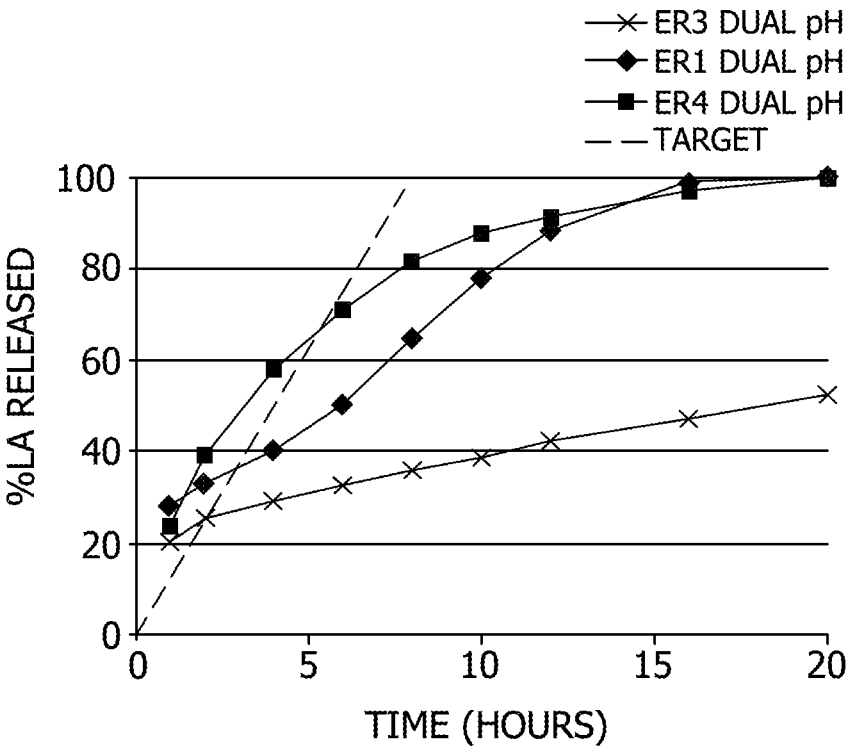
ER3 DUAL pH
ER1 DUAL pH
ER4 DUAL pH
TARGET
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)

FIG. 14

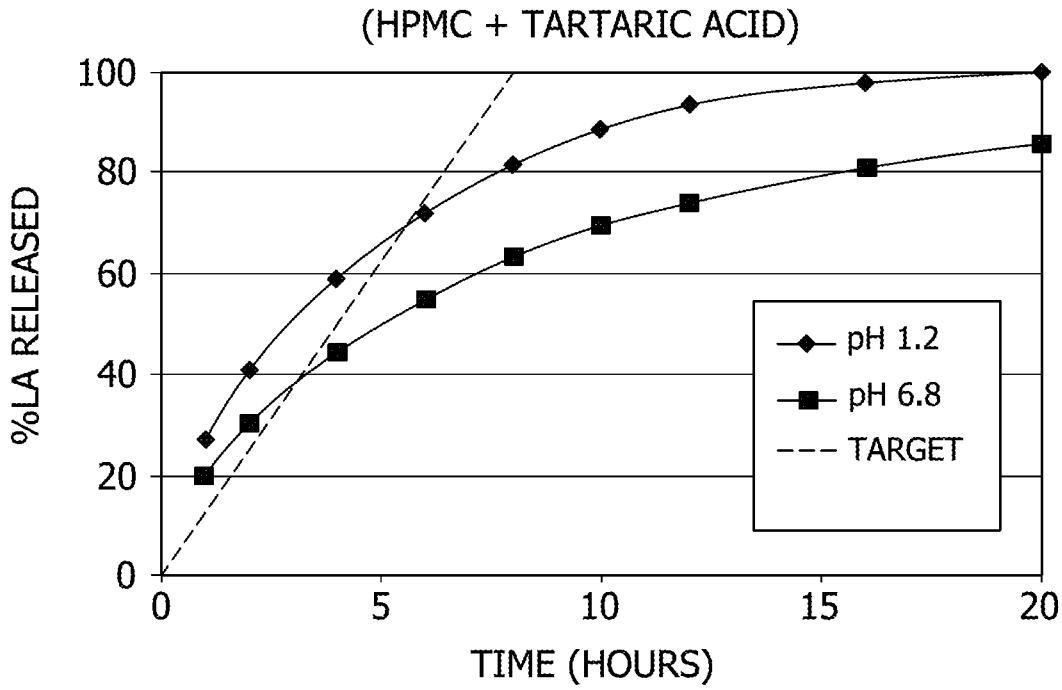

FIG. 15A

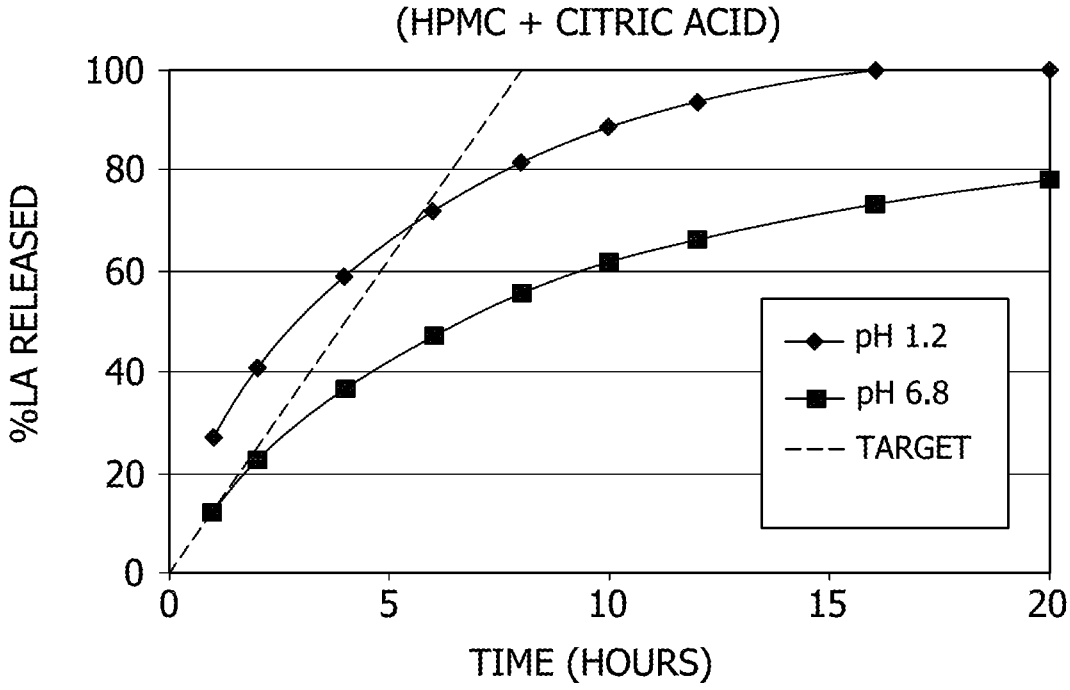

FIG. 15B

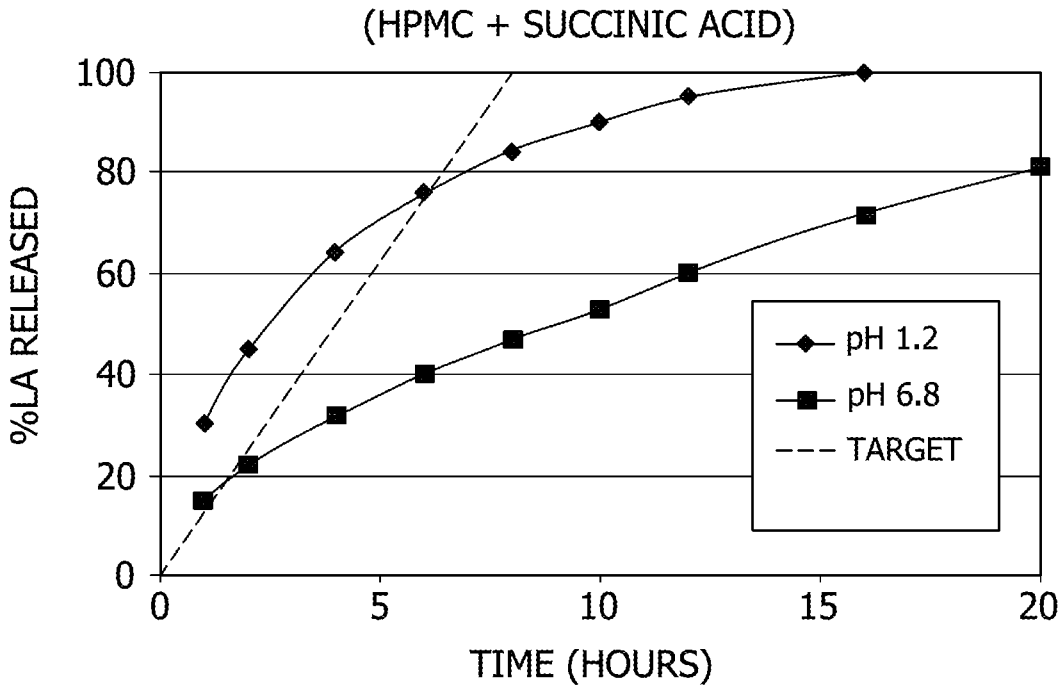

FIG. 15C

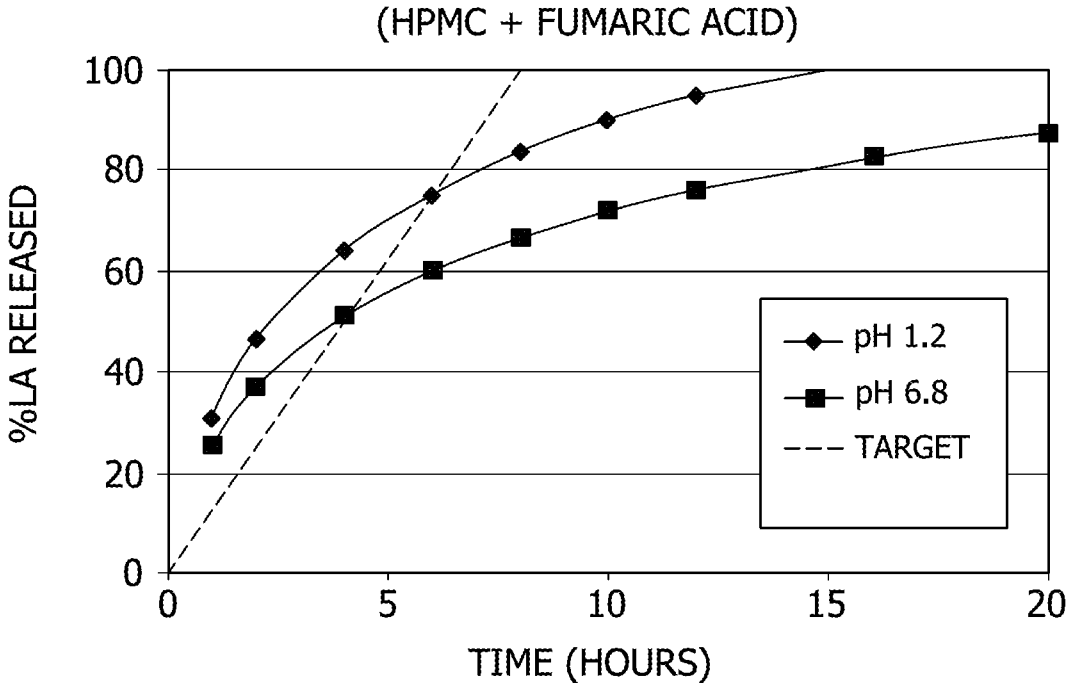

FIG. 15D

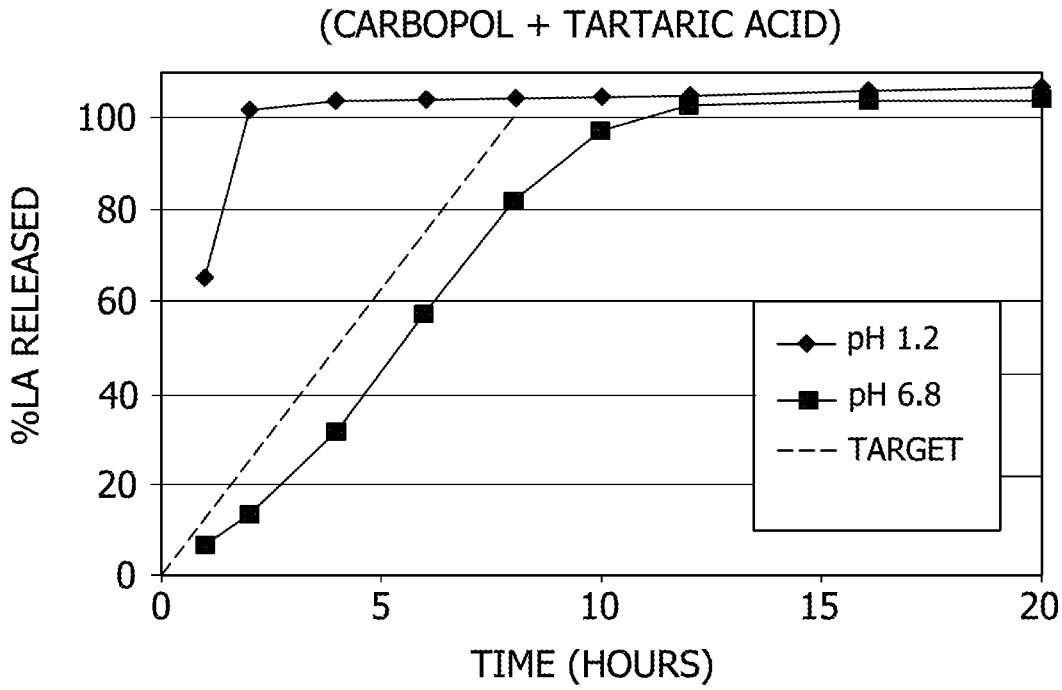

FIG. 15E

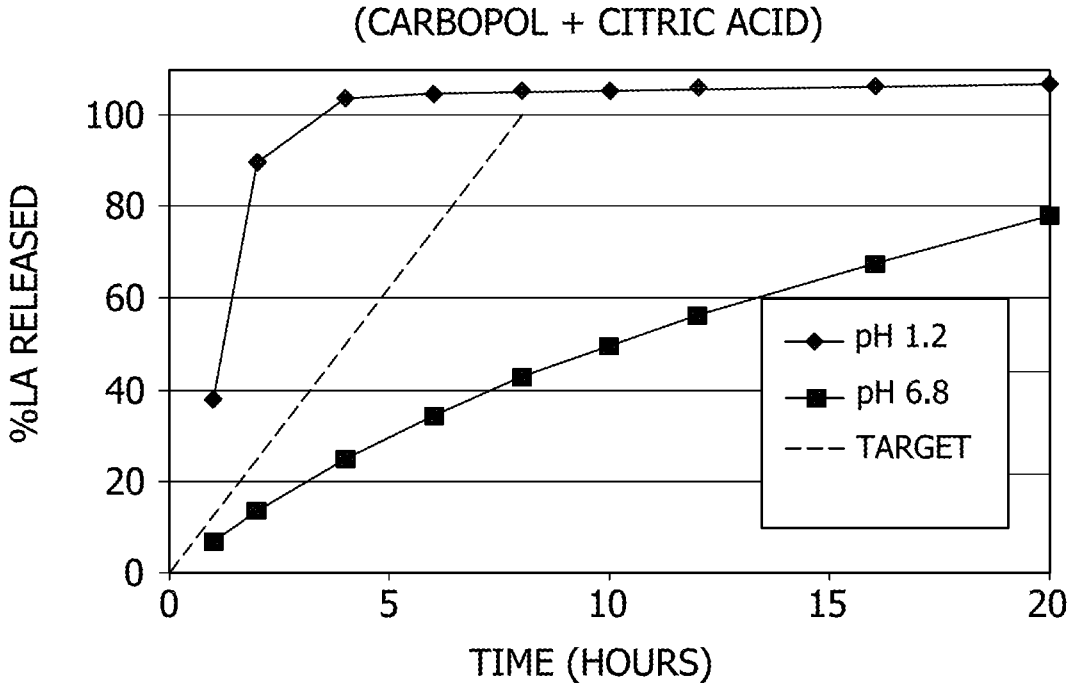

FIG. 15F

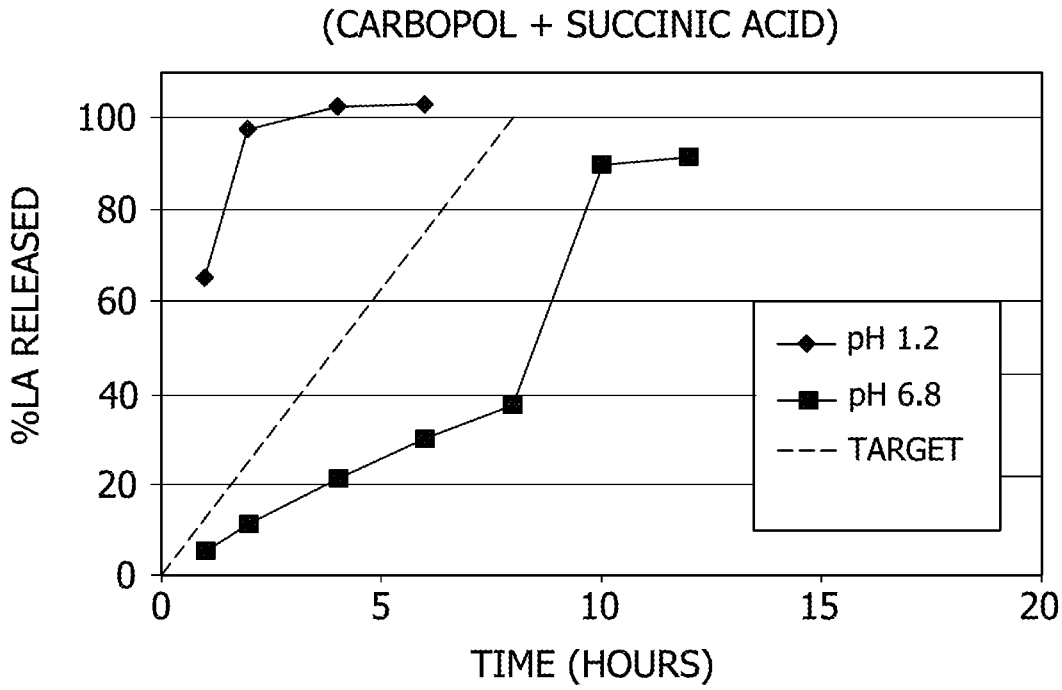

FIG. 15G

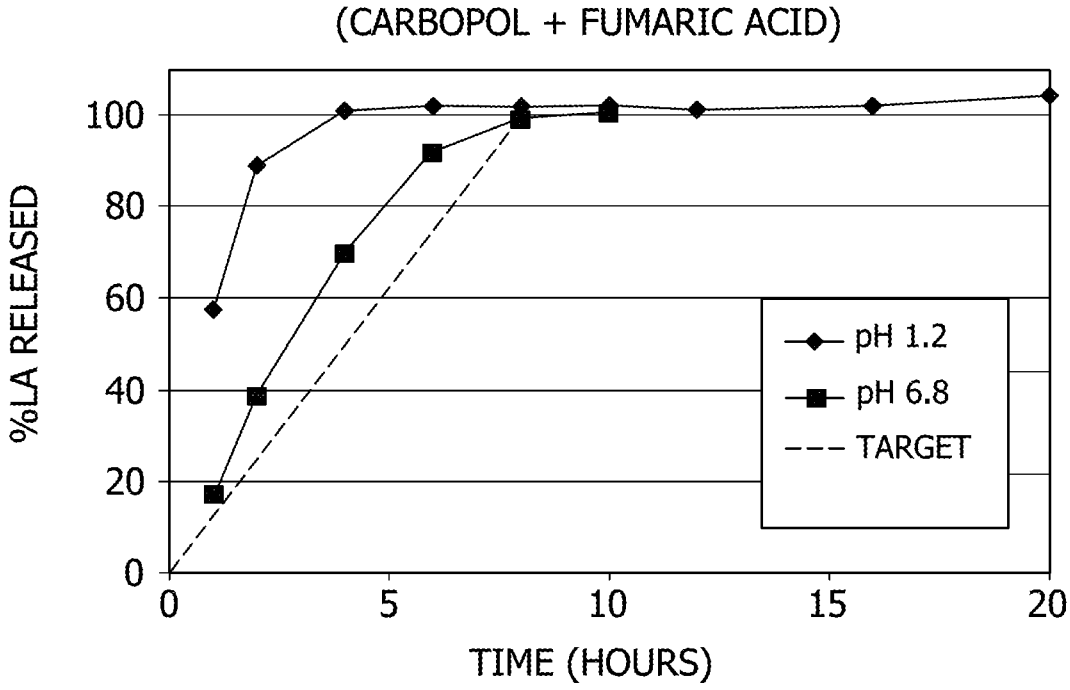

FIG. 15H

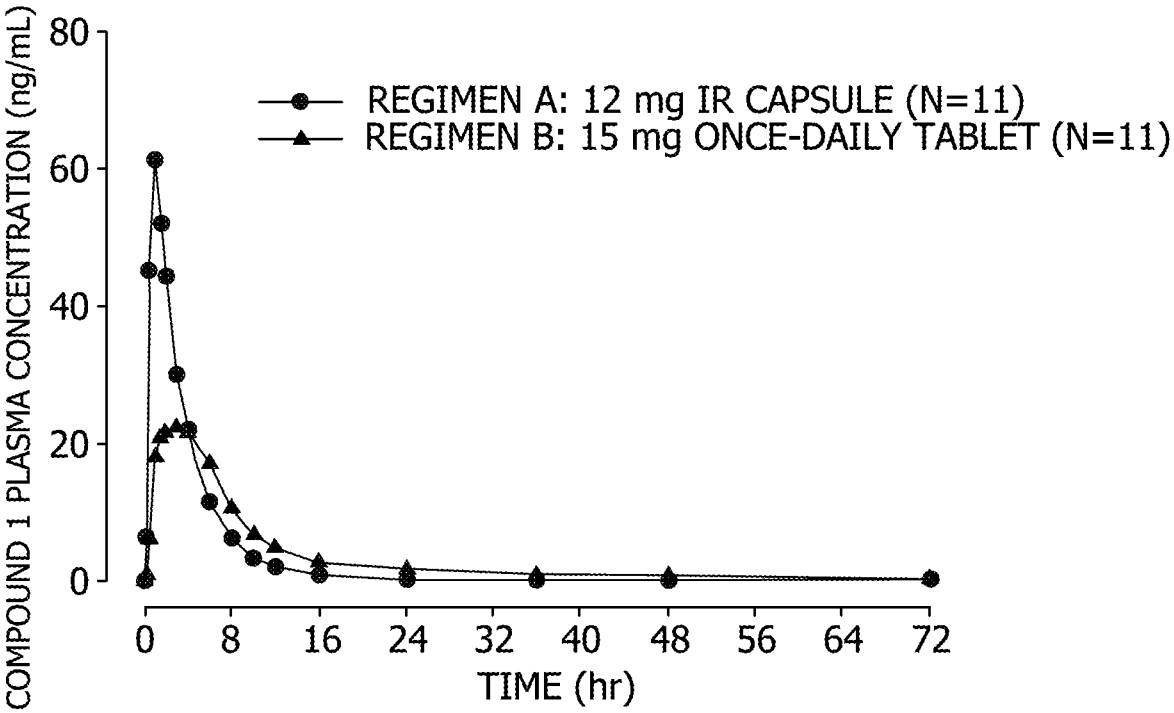

FIG. 16A

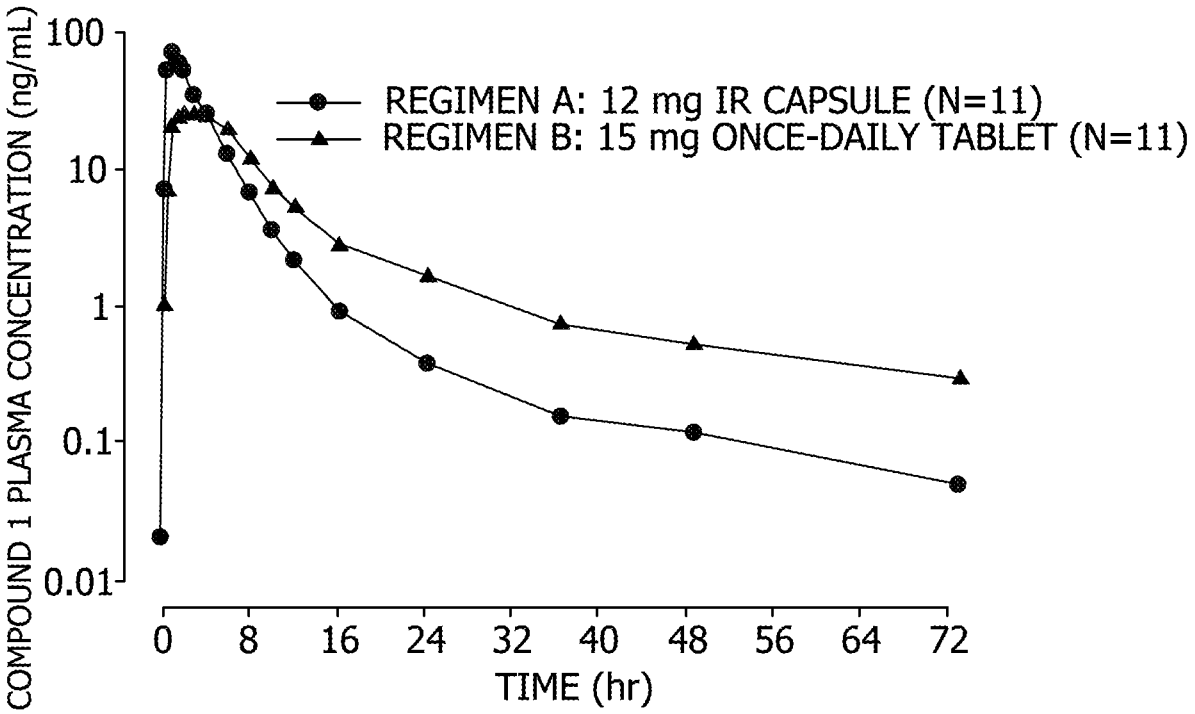

FIG. 16B

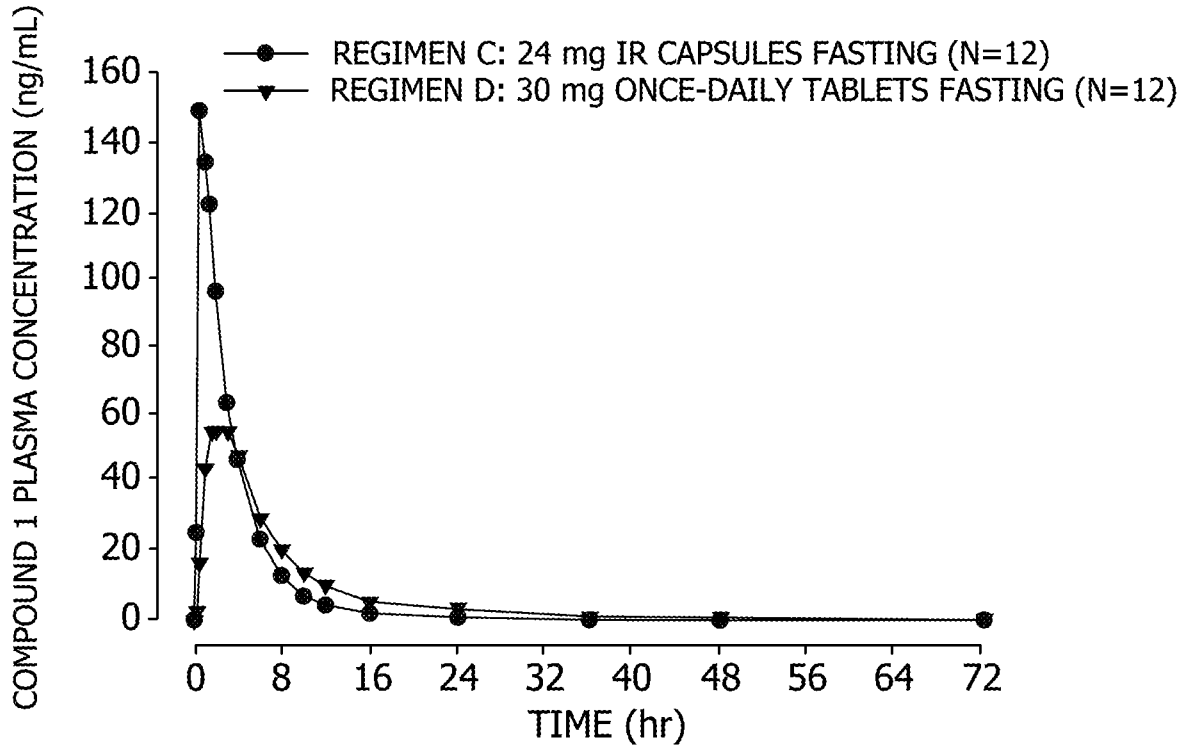

FIG. 17A

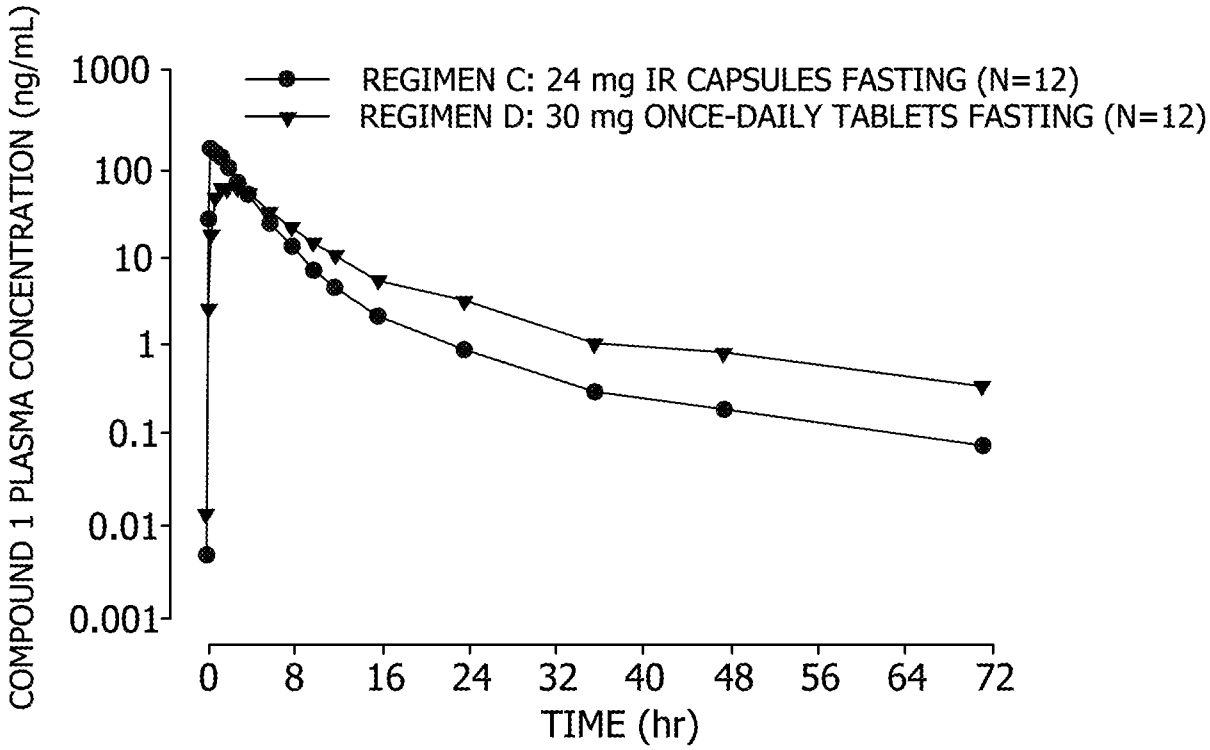

FIG. 17B

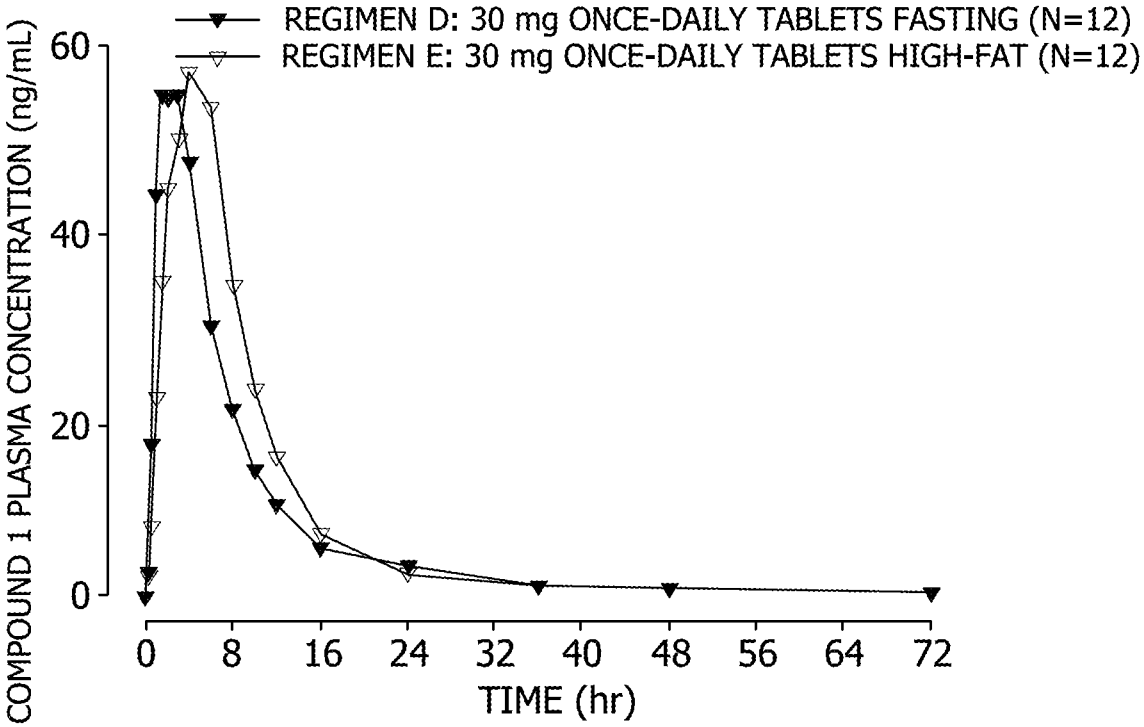

FIG. 18A

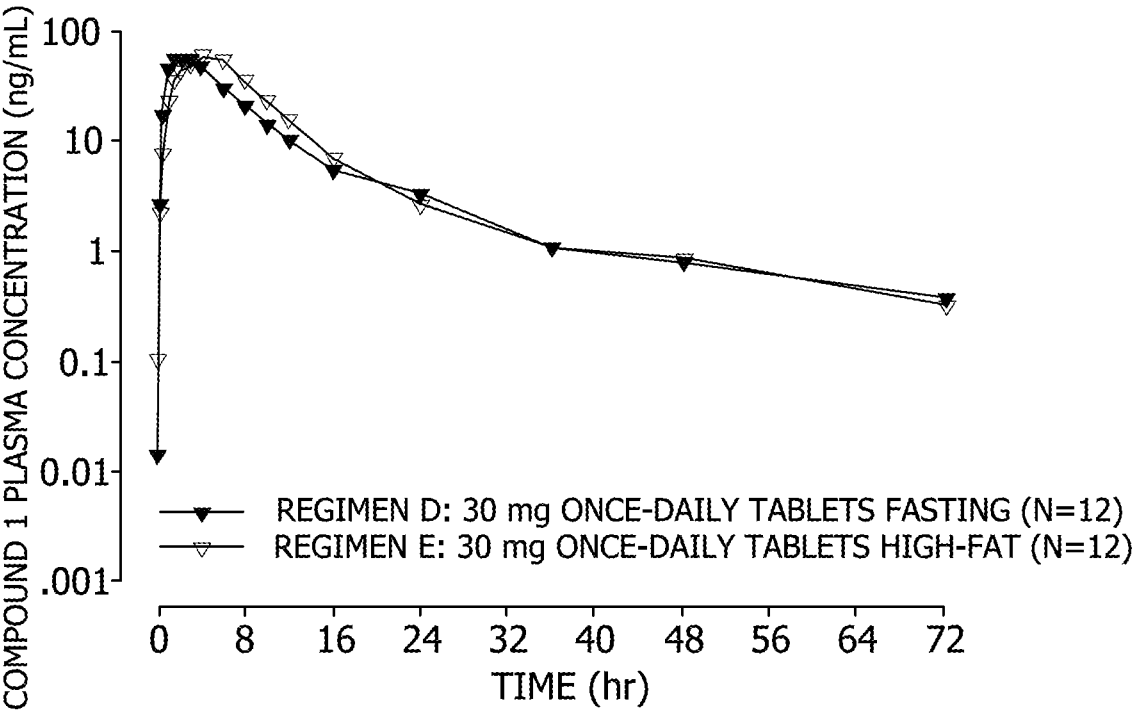

FIG. 18B

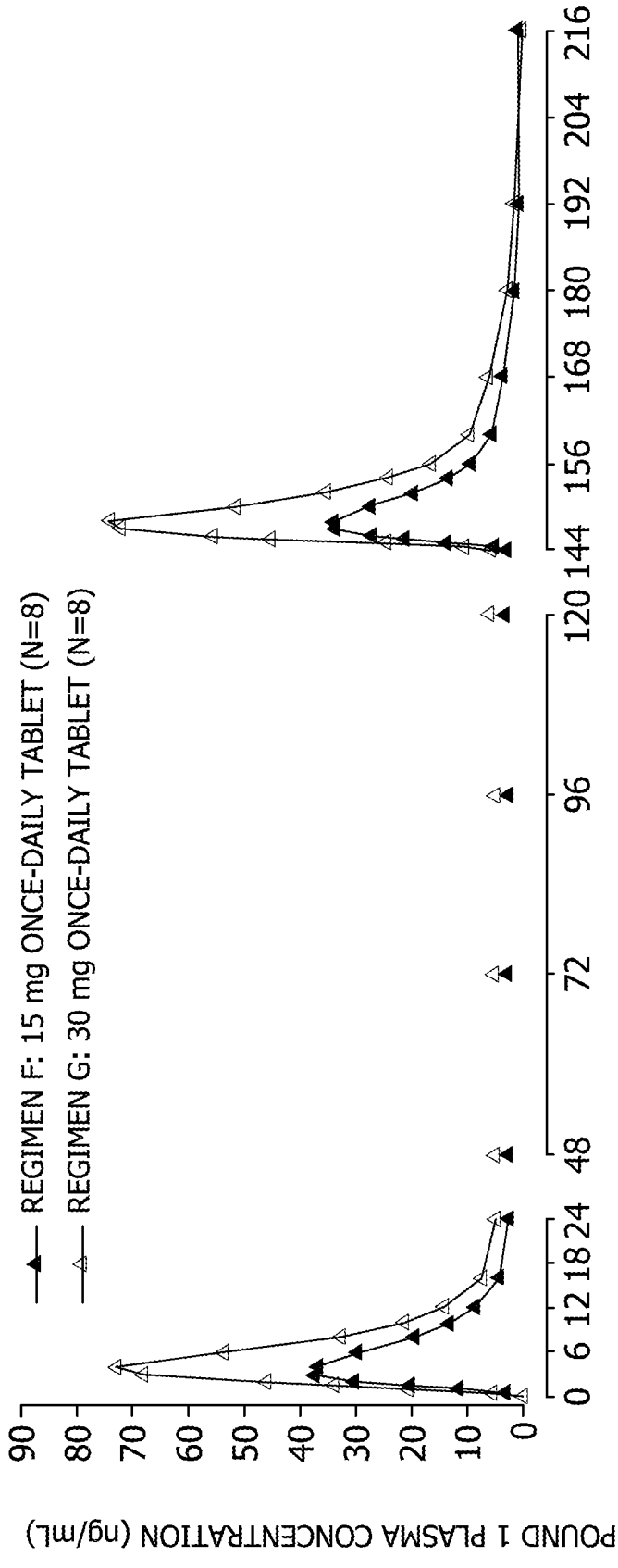
DAY 1
DAYS 3-6
DAY 7
REGIMEN F: 15 mg ONCE-DAILY TABLET (N=8)
REGIMEN G: 30 mg ONCE-DAILY TABLET (N=8)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
TIME (hr)
0
10
20
30
40
50
60
70
80
90
0 6 12 18 24 48 72 96 120 144 156 168 180 192 204 216

FIG. 19

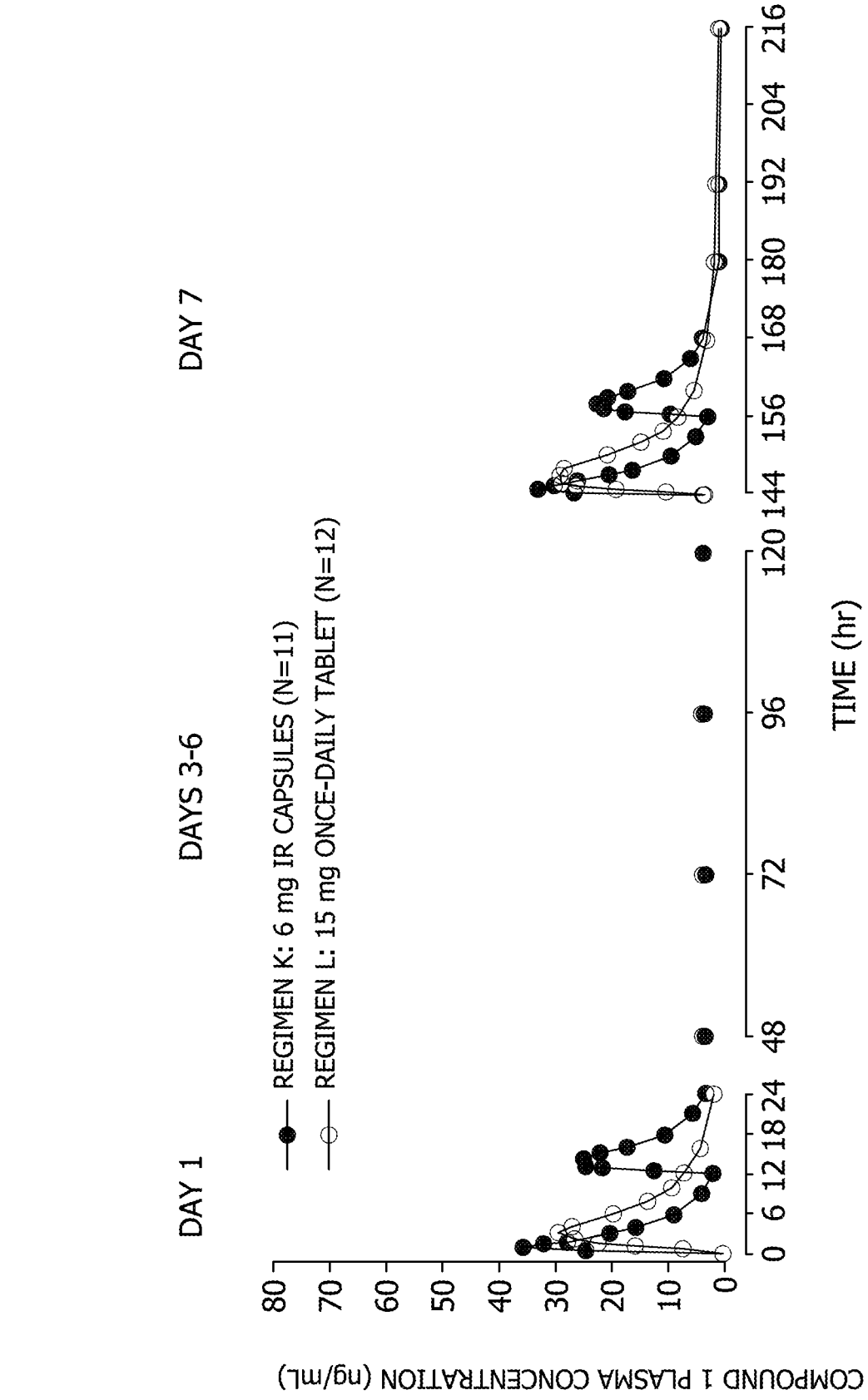
DAY 1
DAYS 3-6
DAY 7
REGIMEN K: 6 mg IR CAPSULES (N=11)
REGIMEN L: 15 mg ONCE-DAILY TABLET (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
10
20
30
40
50
60
70
80
0 6 12 18 24 48 72 96 120 144 156 168 180 192 204 216
TIME (hr)

FIG. 20

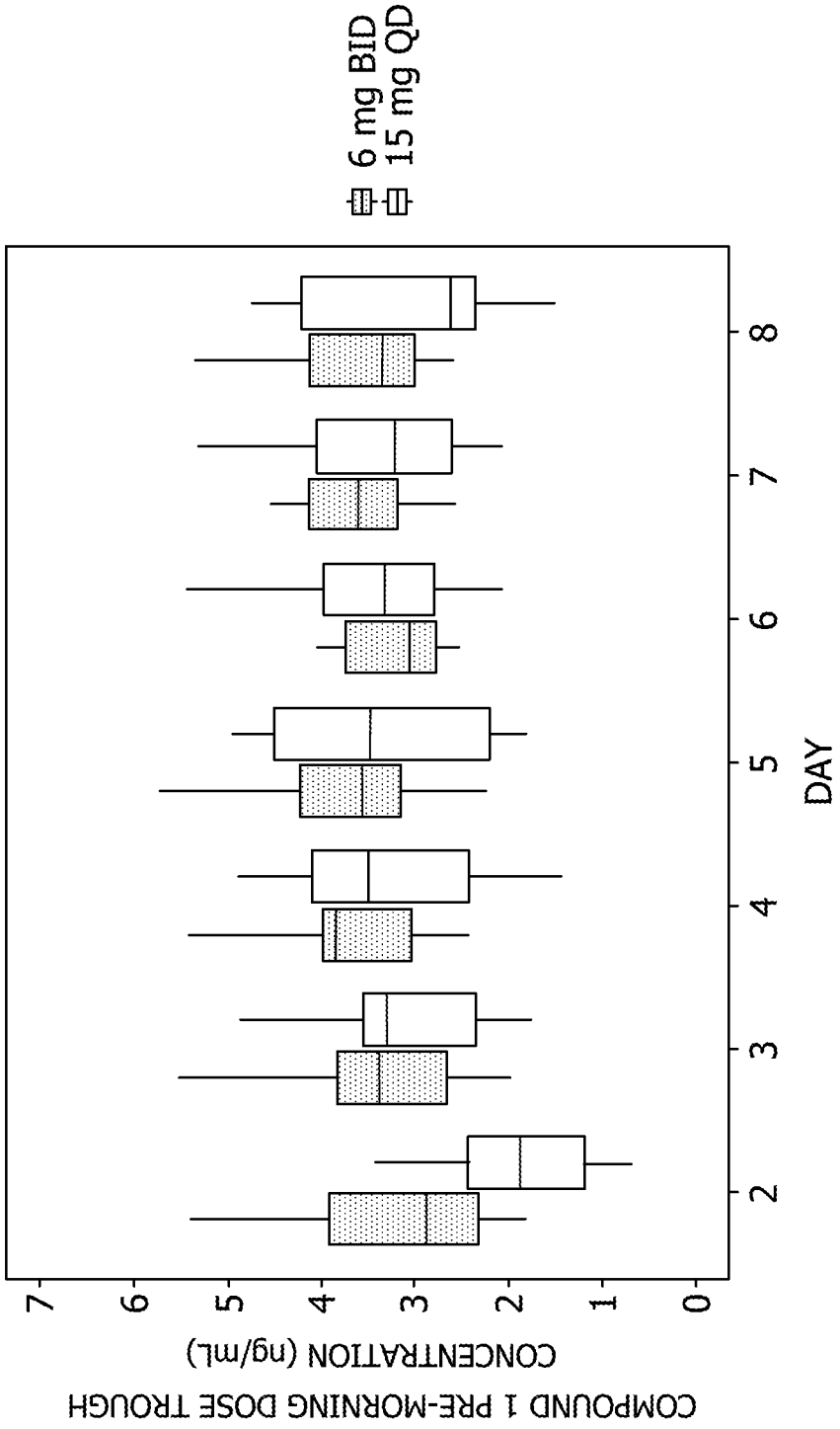
6 mg BID
15 mg QD
COMPOUND 1 PRE-MORNING DOSE TROUGH
CONCENTRATION (ng/mL)
0
1
2
3
4
5
6
7
2
3
4
5
6
7
8
DAY

FIG. 21

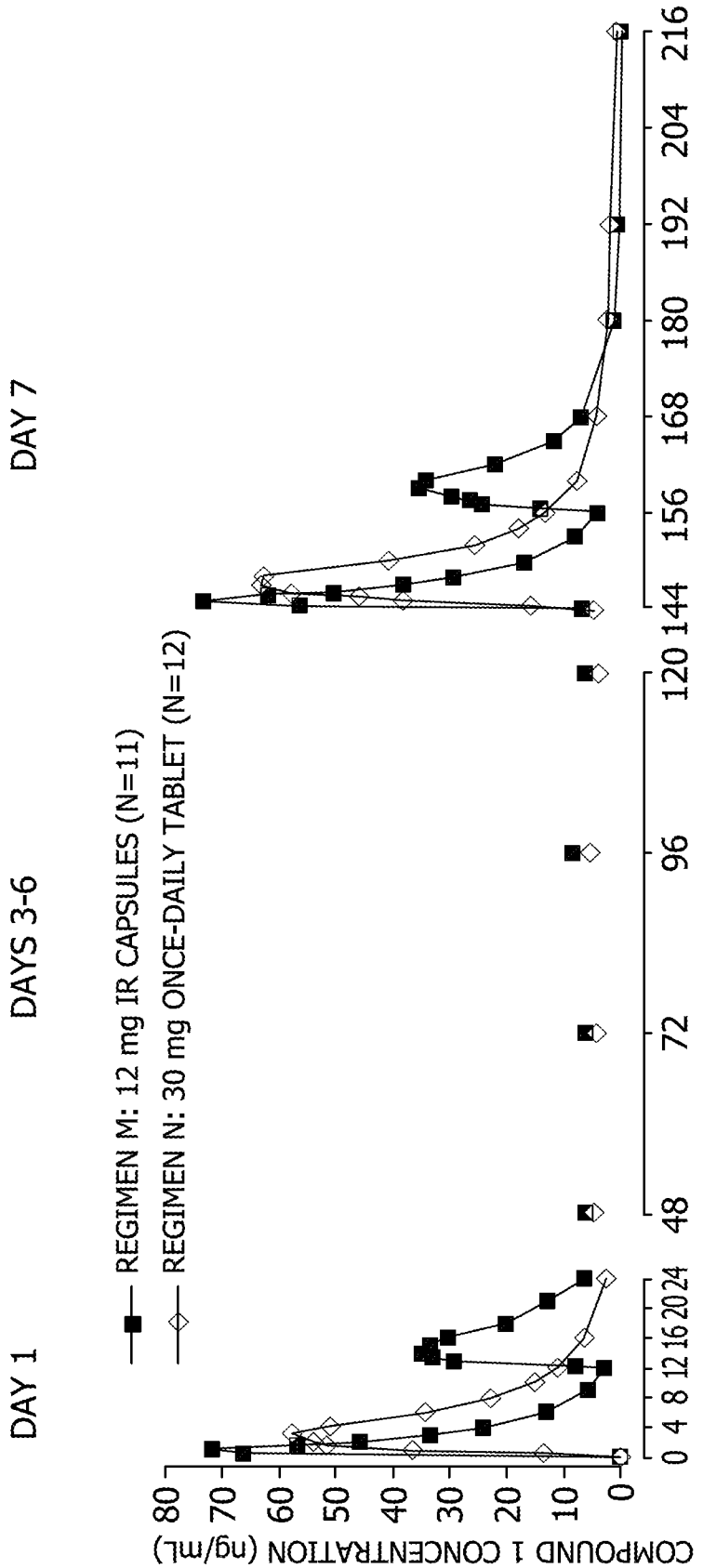
DAY 1
DAYS 3-6
DAY 7
REGIMEN M: 12 mg IR CAPSULES (N=11)
REGIMEN N: 30 mg ONCE-DAILY TABLET (N=12)
COMPOUND 1 CONCENTRATION (ng/mL)
0
10
20
30
40
50
60
70
80
0 4 8 12 16 20 24
48
72
96
120 144
156
168
180
192
204
216
TIME (hr)

FIG. 22

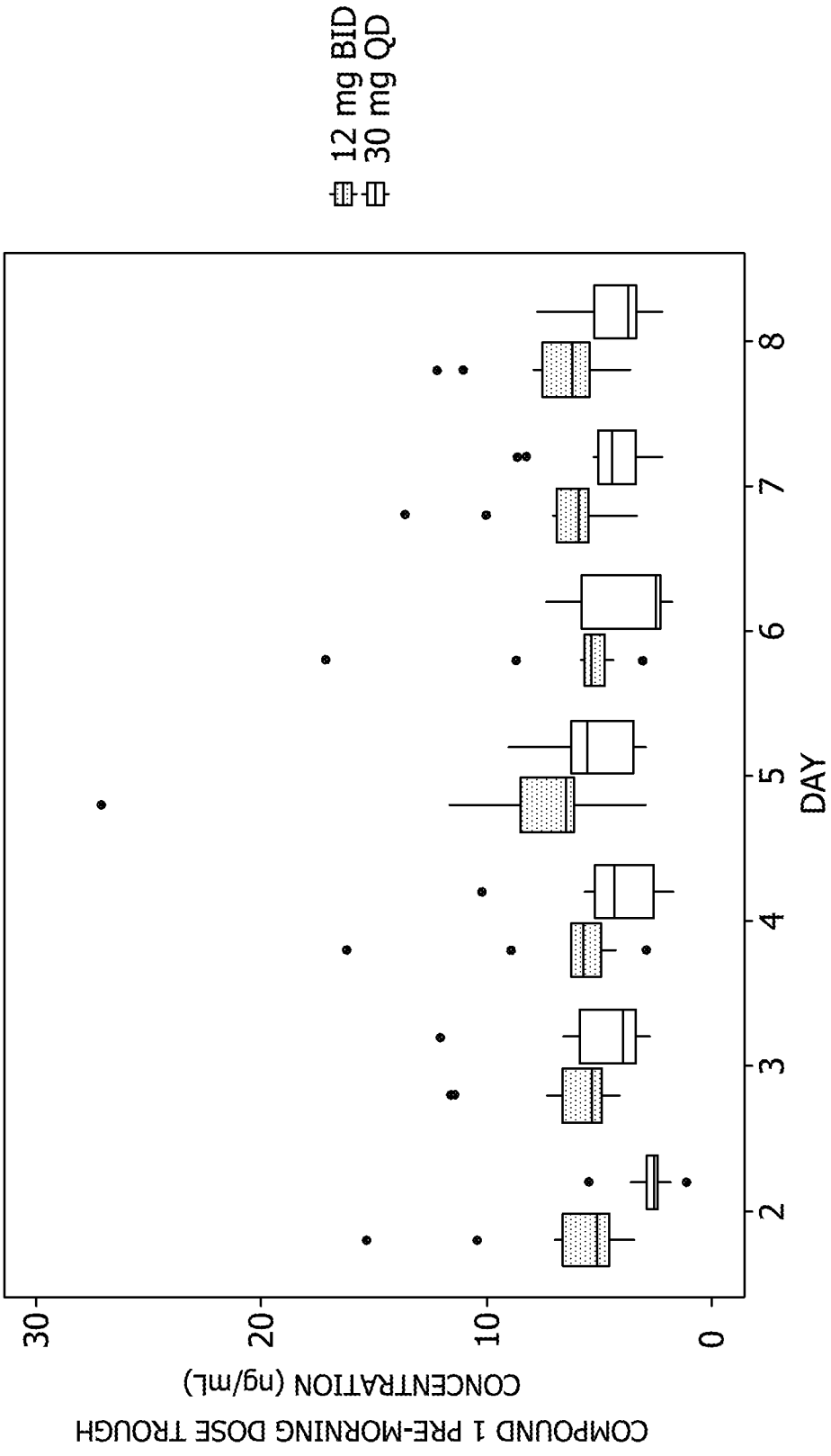
12 mg BID
30 mg QD
COMPOUND 1 PRE-MORNING DOSE TROUGH
CONCENTRATION (ng/mL)
0
10
20
30
2
3
4
5
6
7
8
DAY

FIG. 23

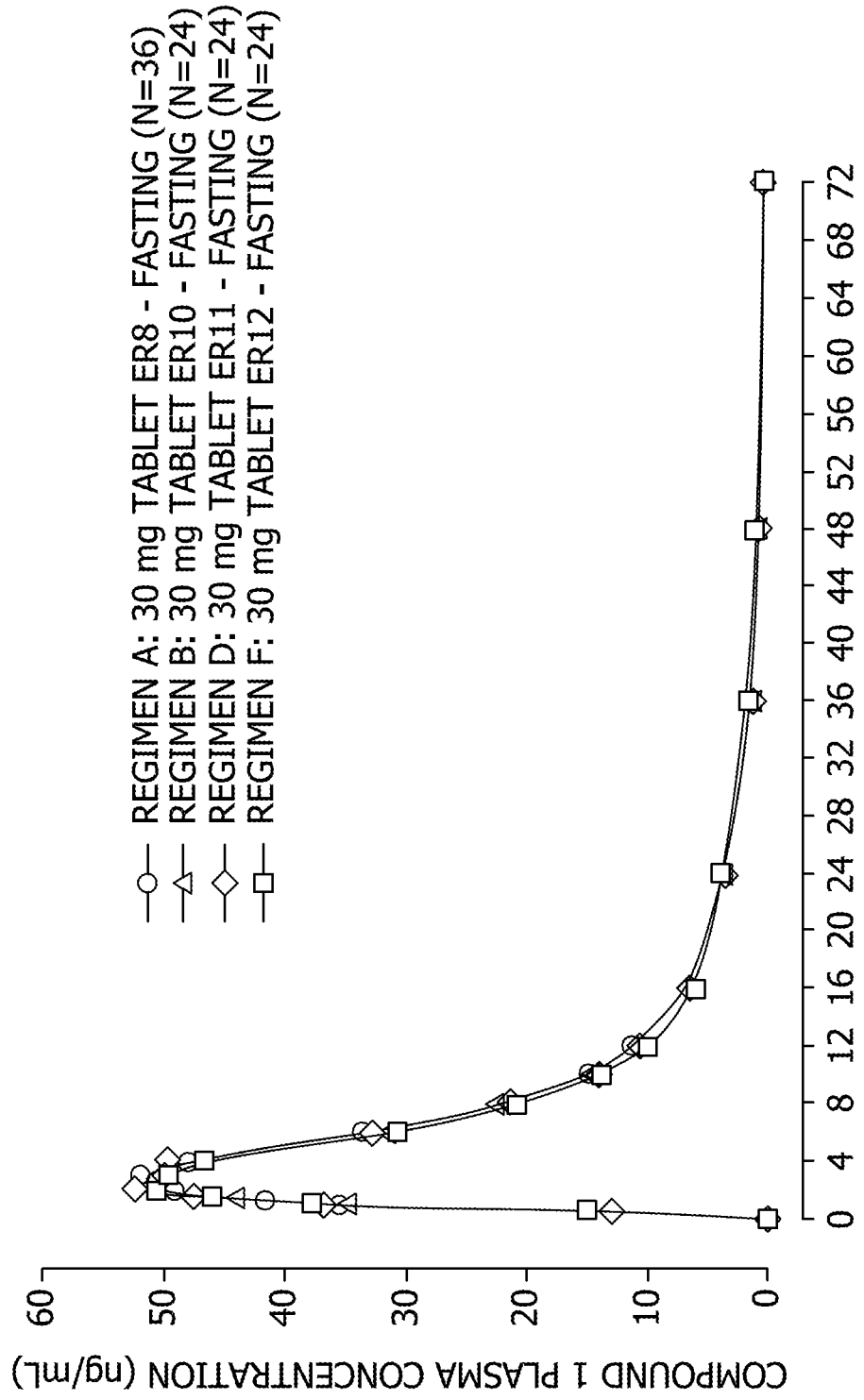
REGIMEN A: 30 mg TABLET ER8 - FASTING (N=36)
REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
10
20
30
40
50
60
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 24A

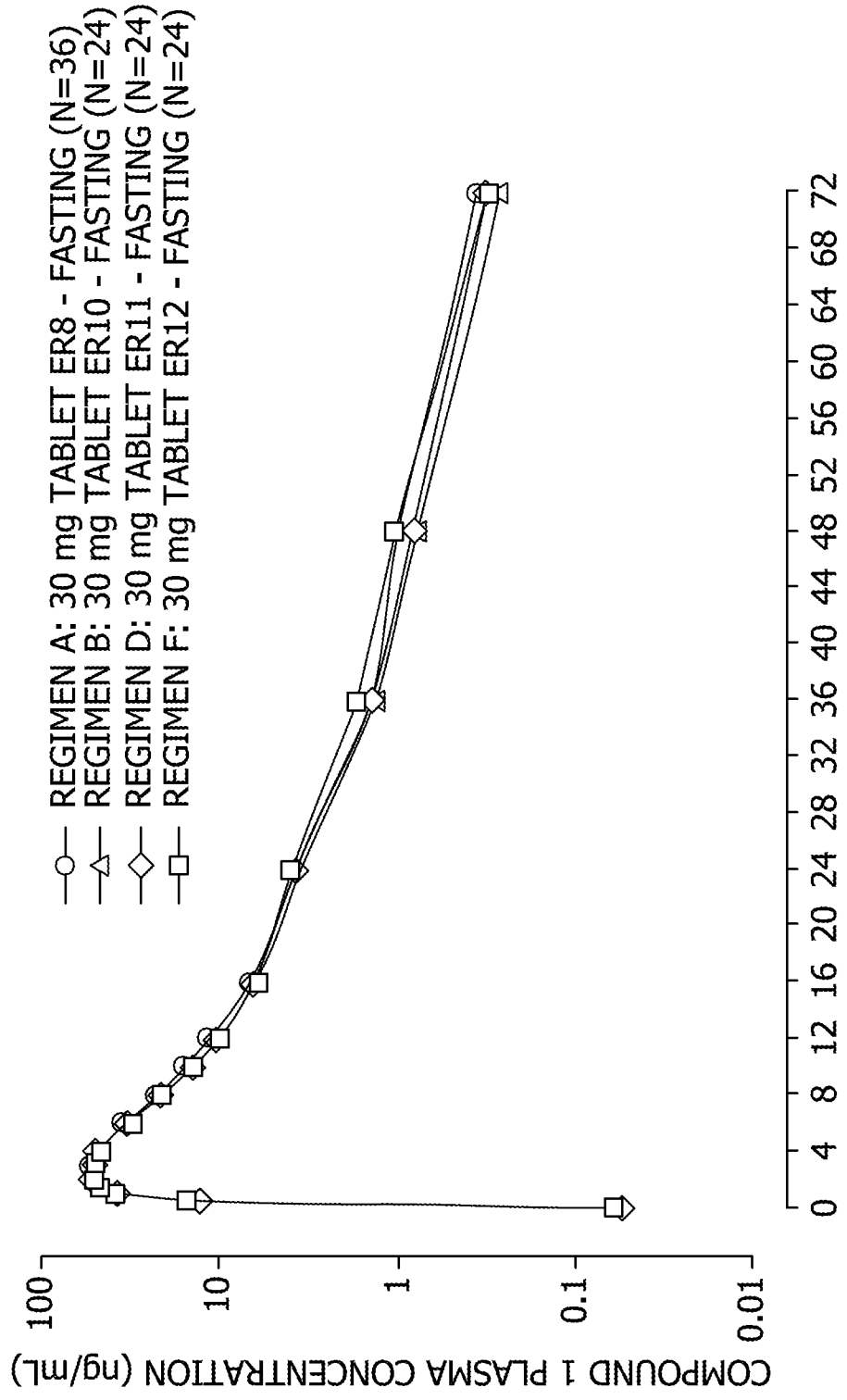
REGIMEN A: 30 mg TABLET ER8 - FASTING (N=36)
REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
TIME (hr)

FIG. 24B

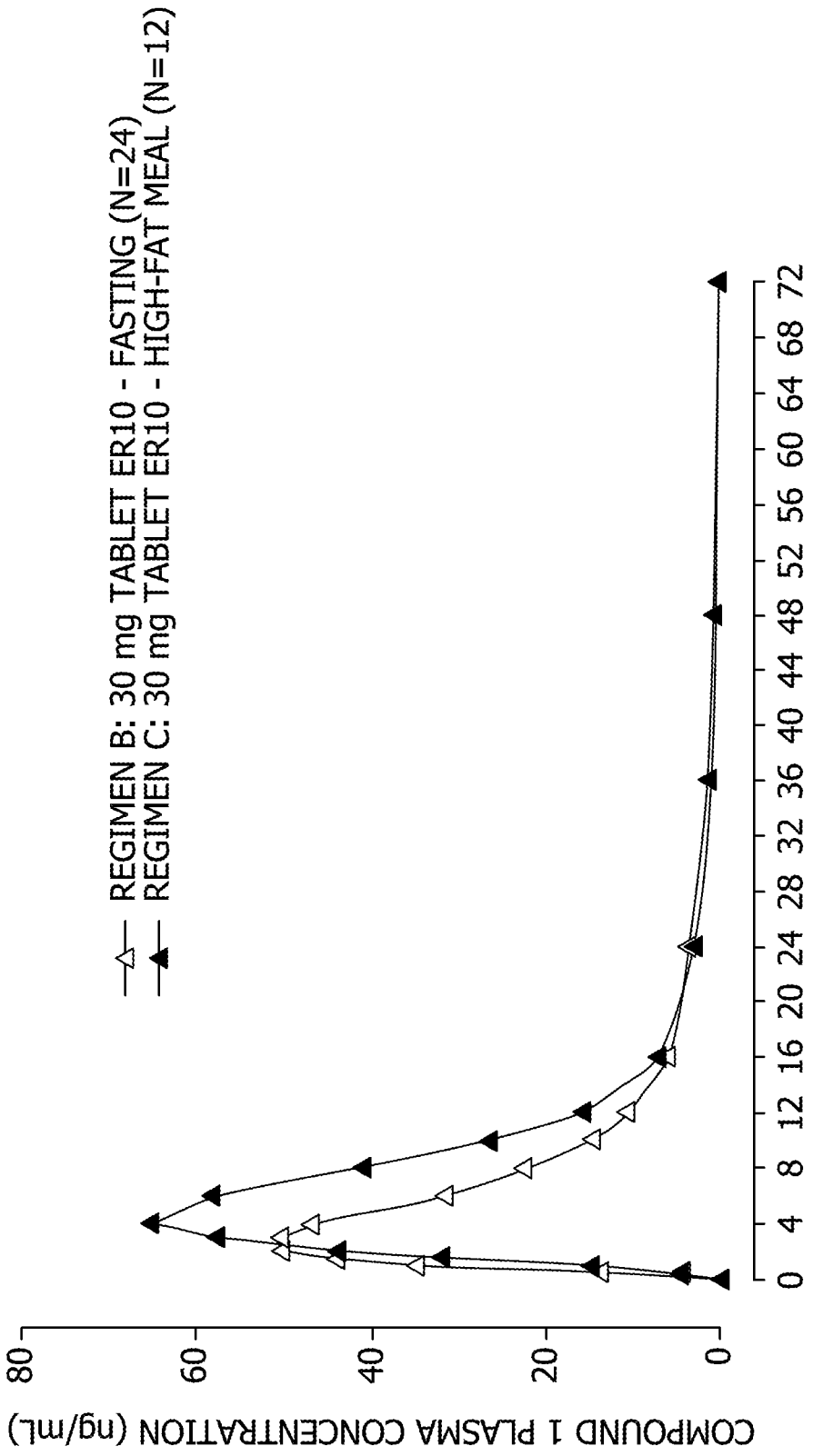
REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN C: 30 mg TABLET ER10 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 25A

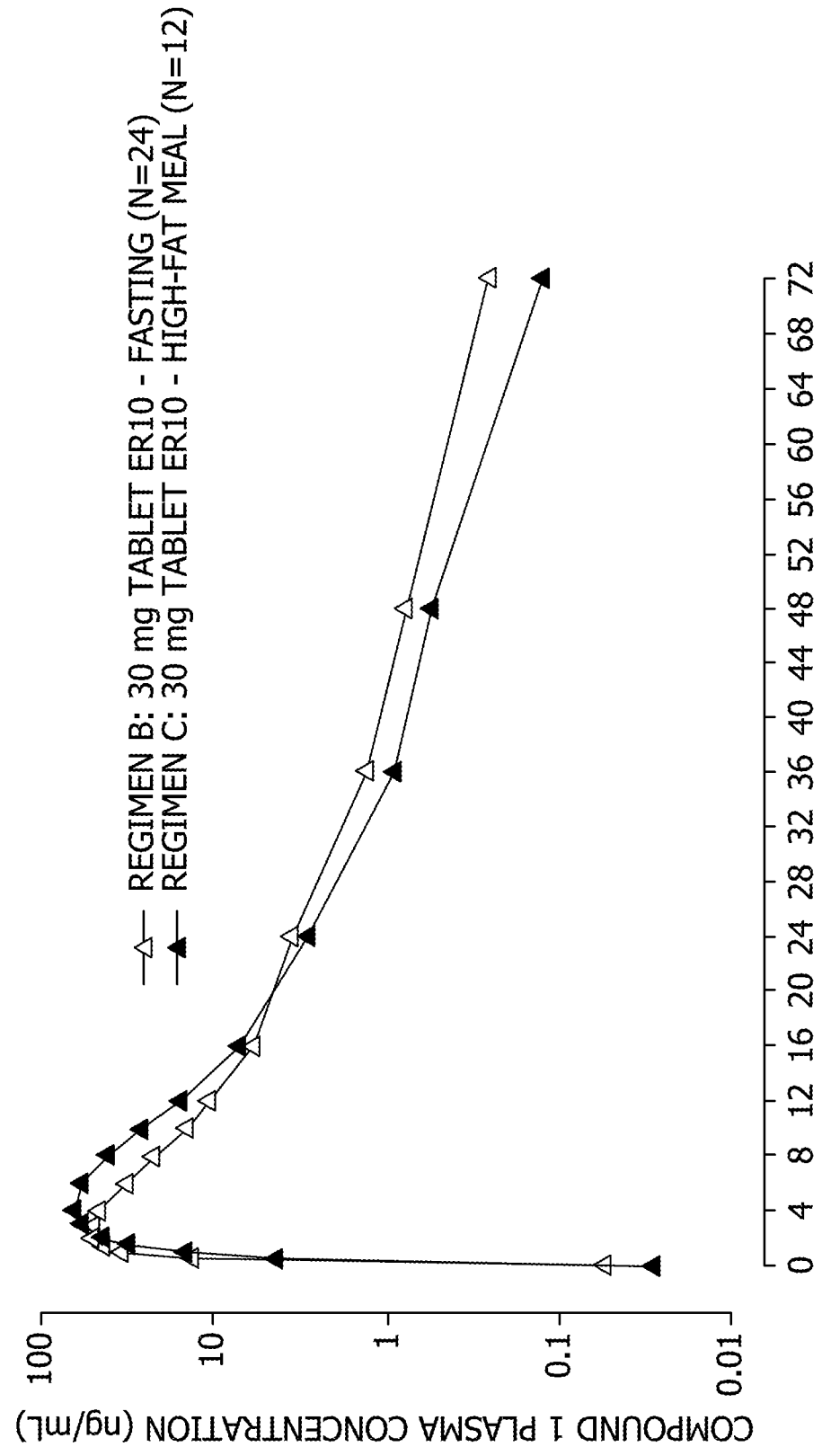
REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN C: 30 mg TABLET ER10 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
TIME (hr)

FIG. 25B

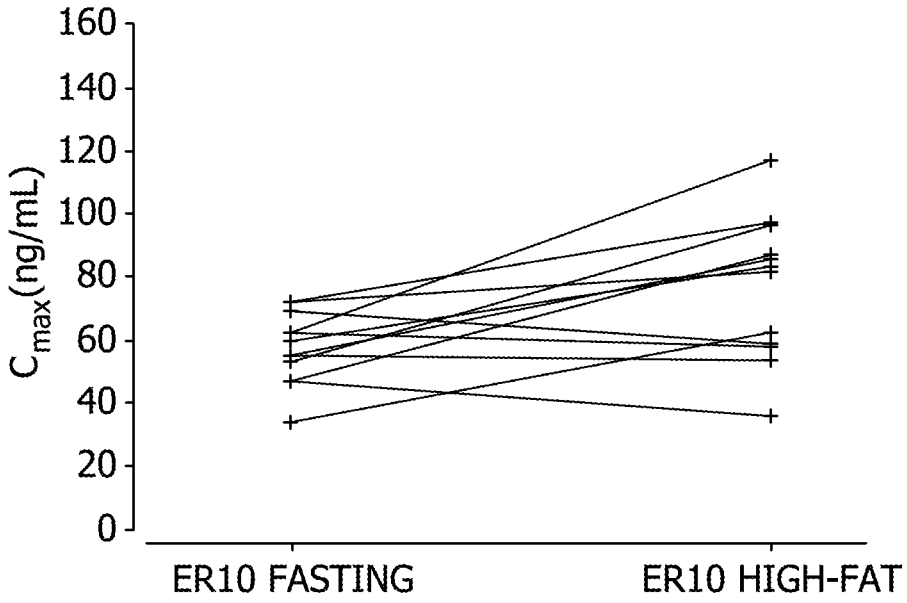

FIG. 26A

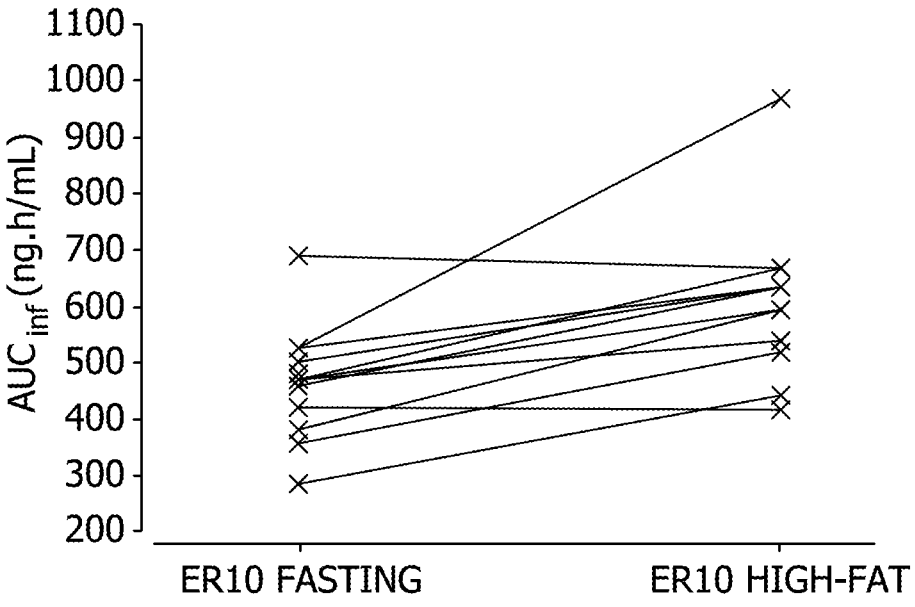

FIG. 26B

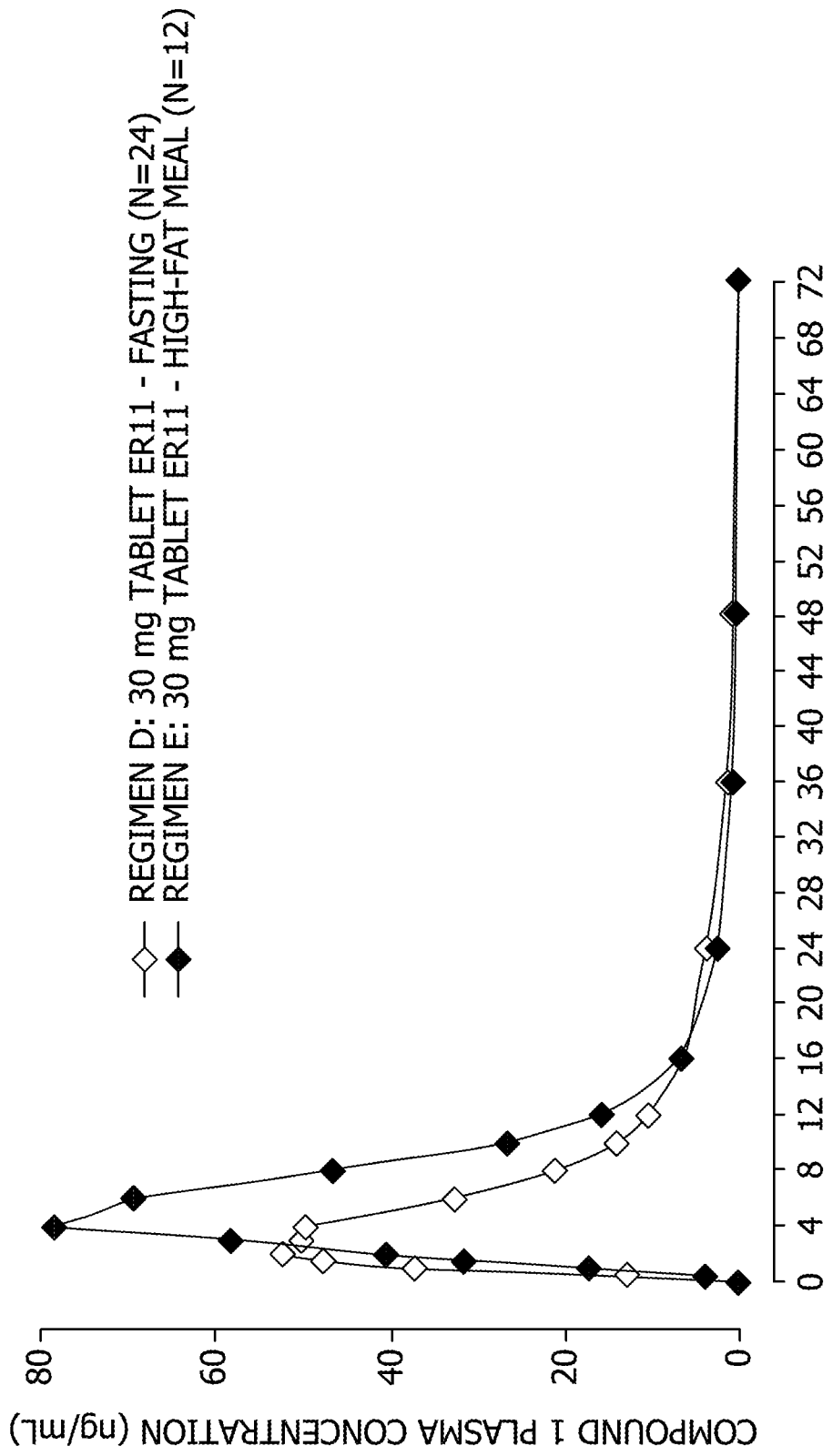
REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN E: 30 mg TABLET ER11 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 27A

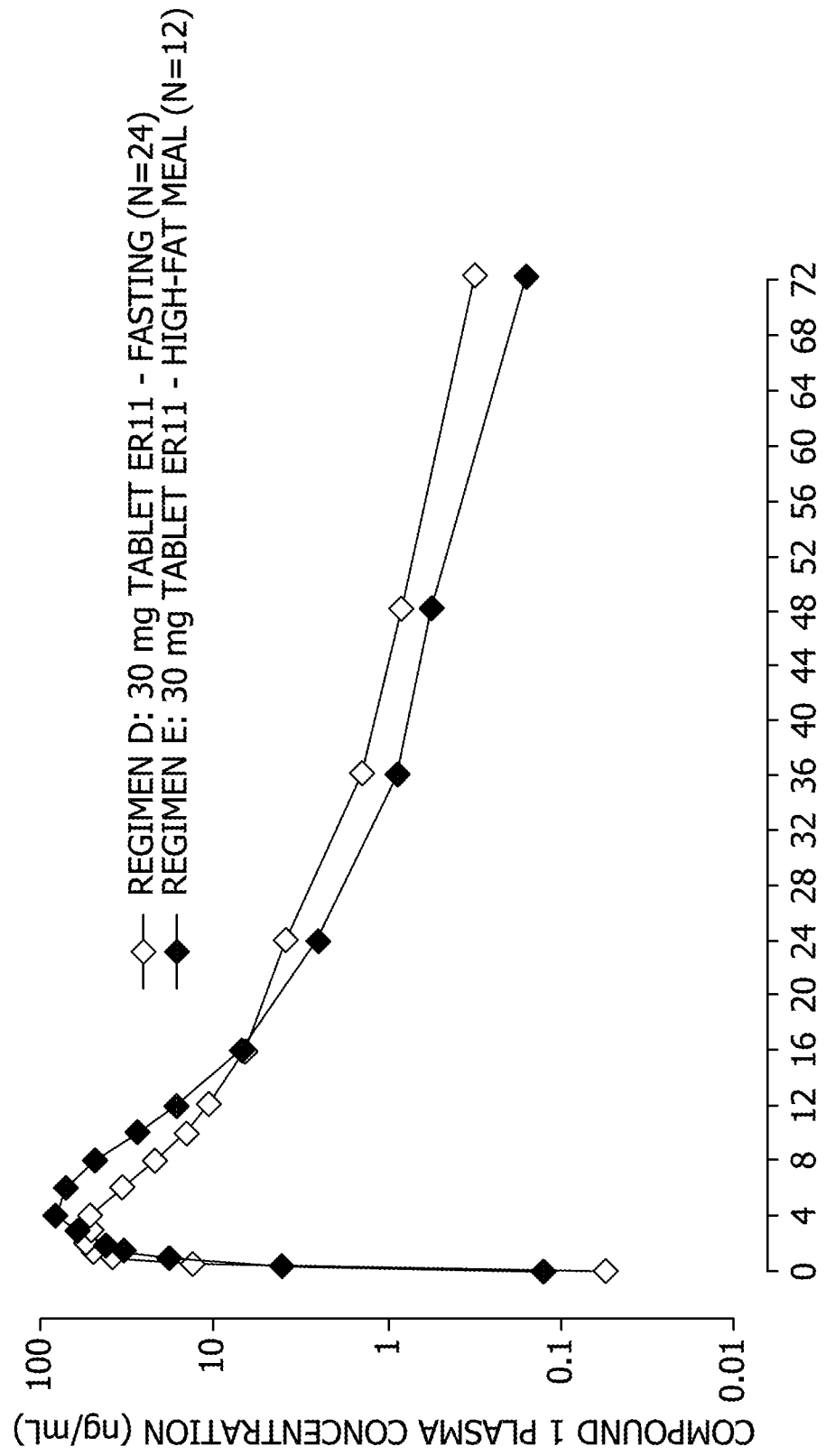
REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN E: 30 mg TABLET ER11 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 27B

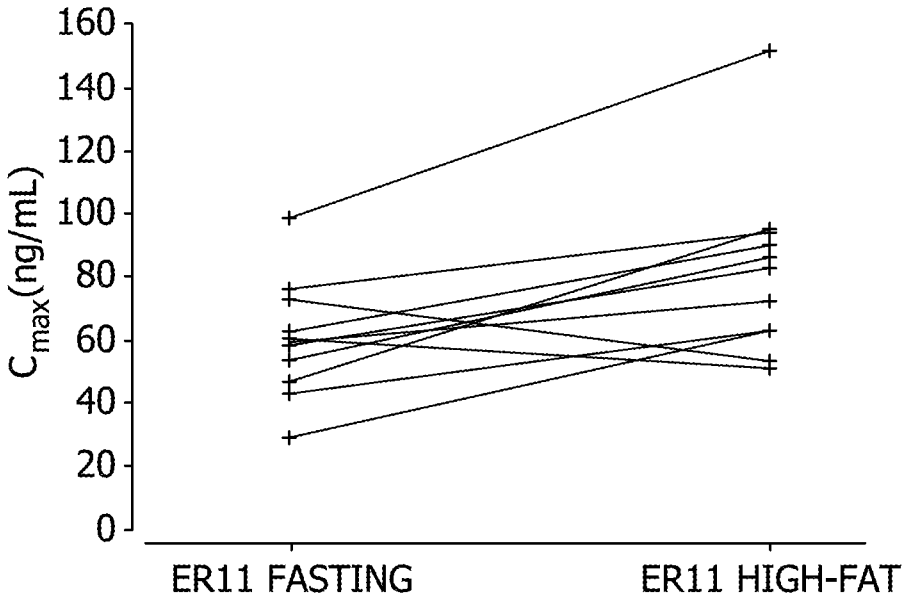

FIG. 28A

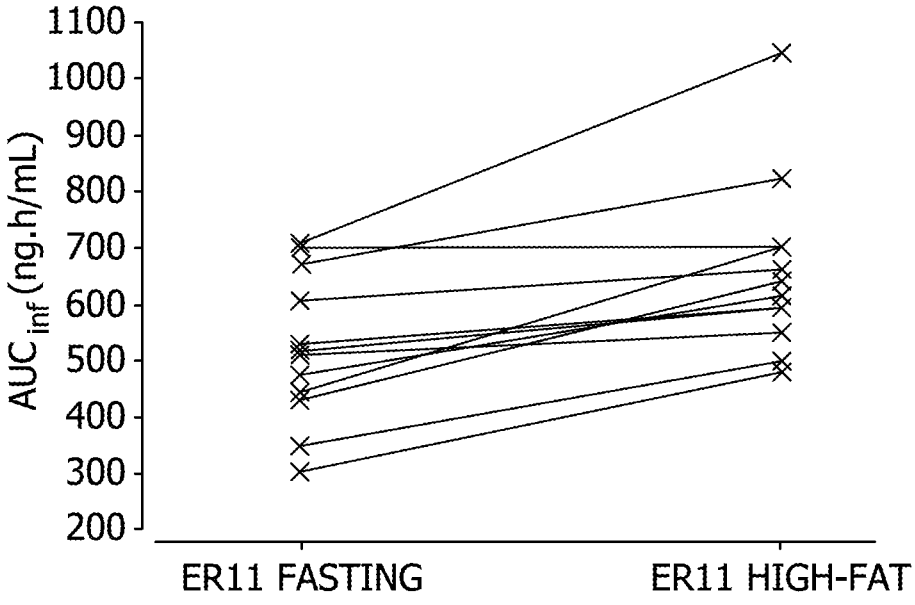

FIG. 28B

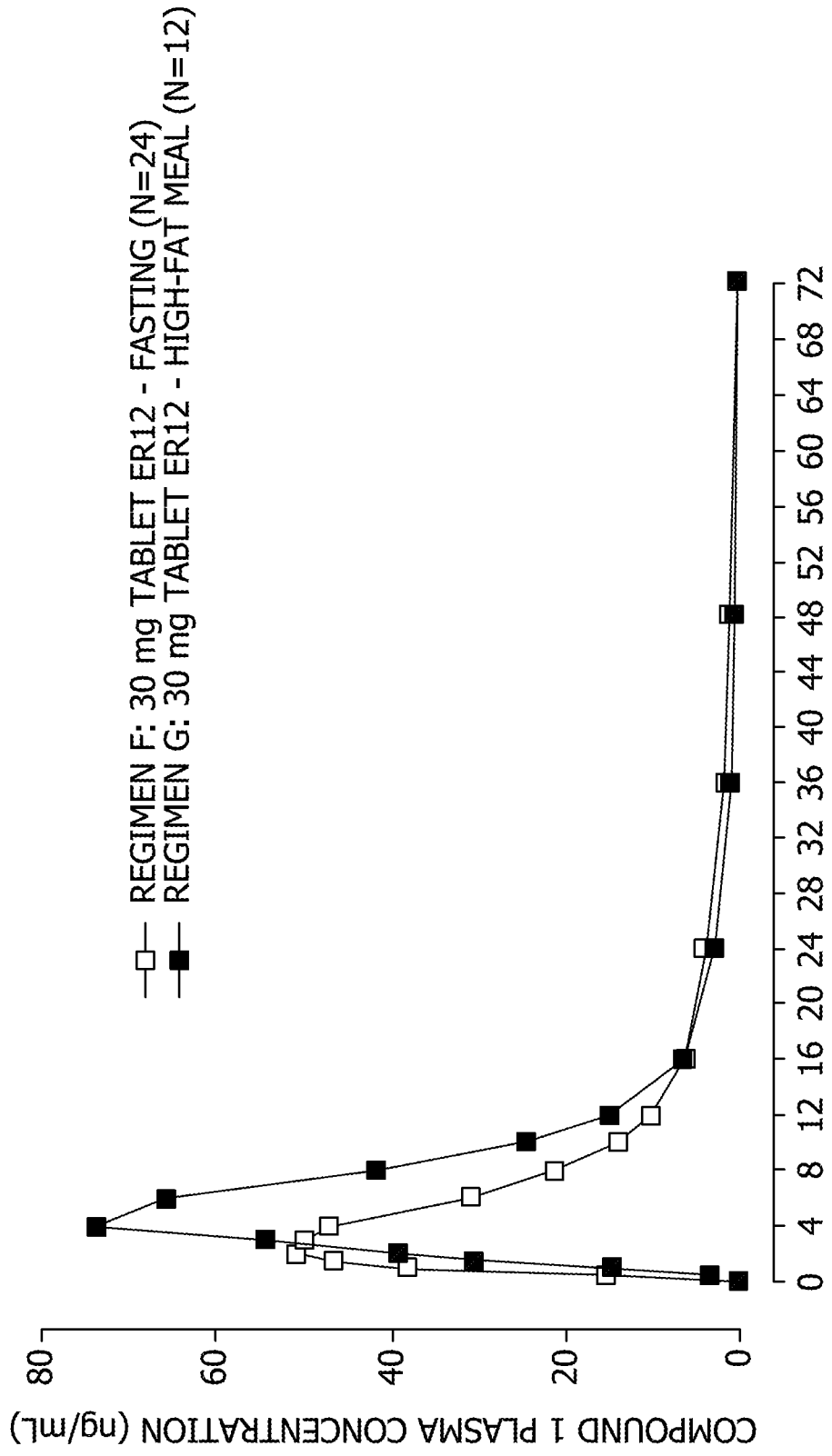
REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
REGIMEN G: 30 mg TABLET ER12 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 29A

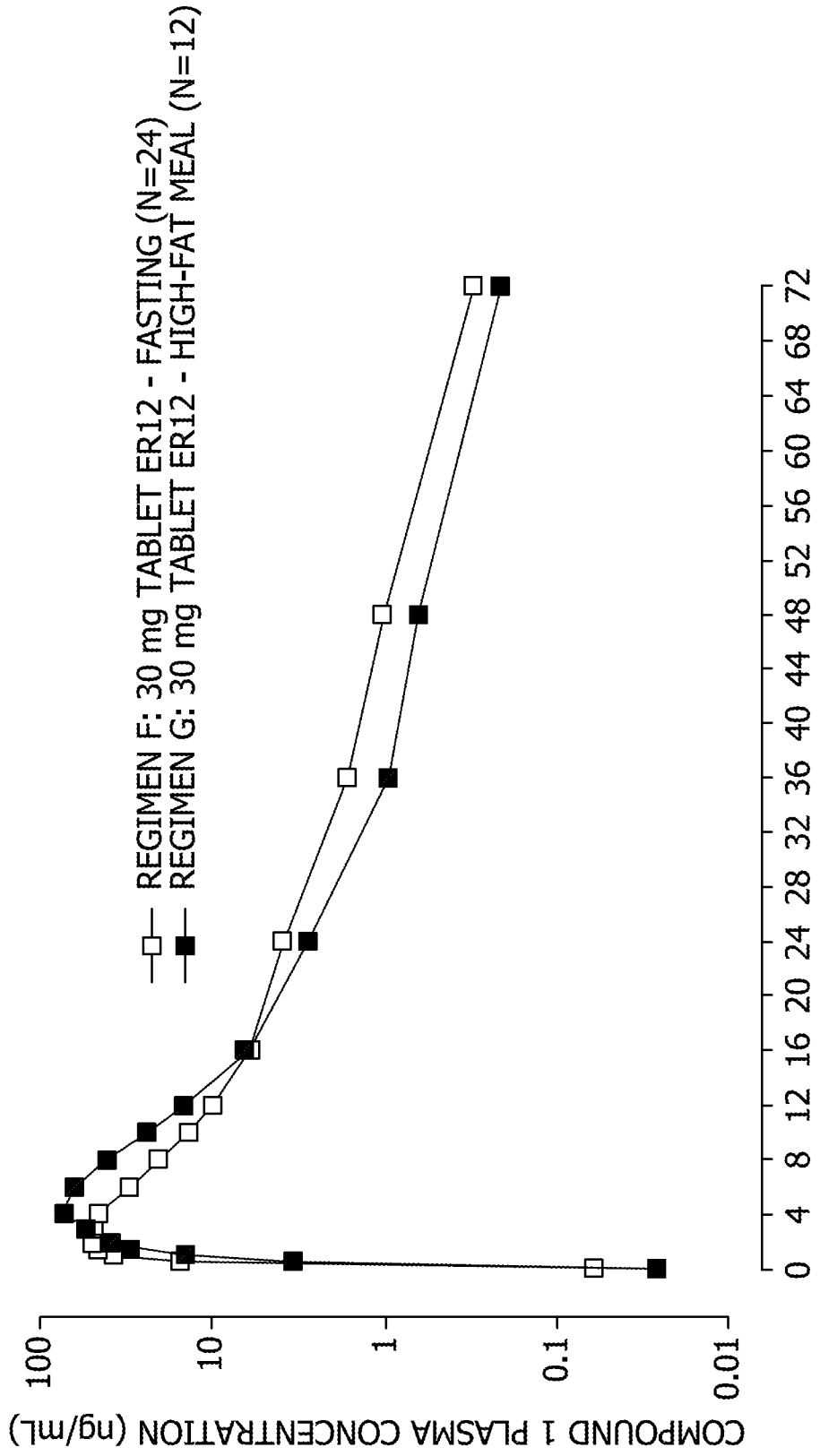
REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
REGIMEN G: 30 mg TABLET ER12 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 29B

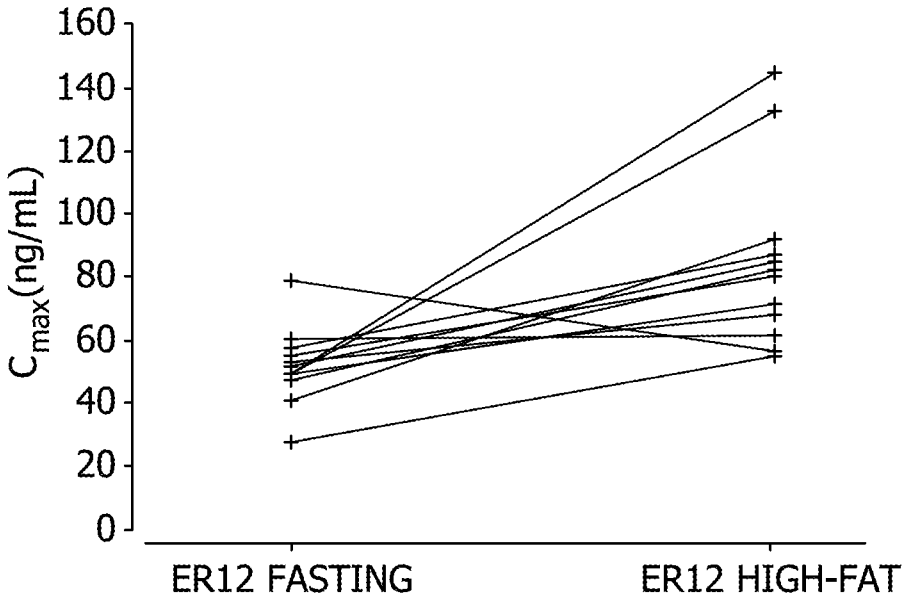

FIG. 30A

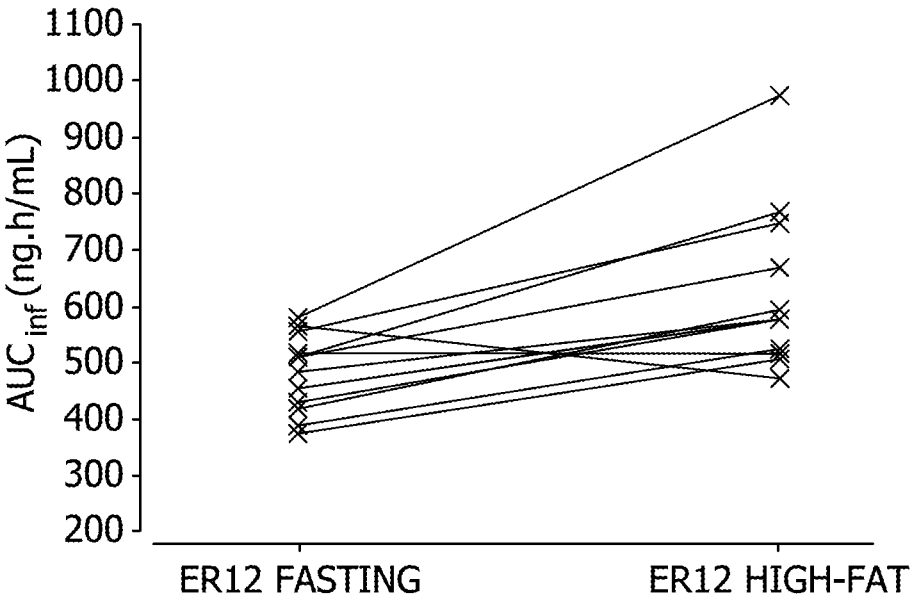

FIG. 30B

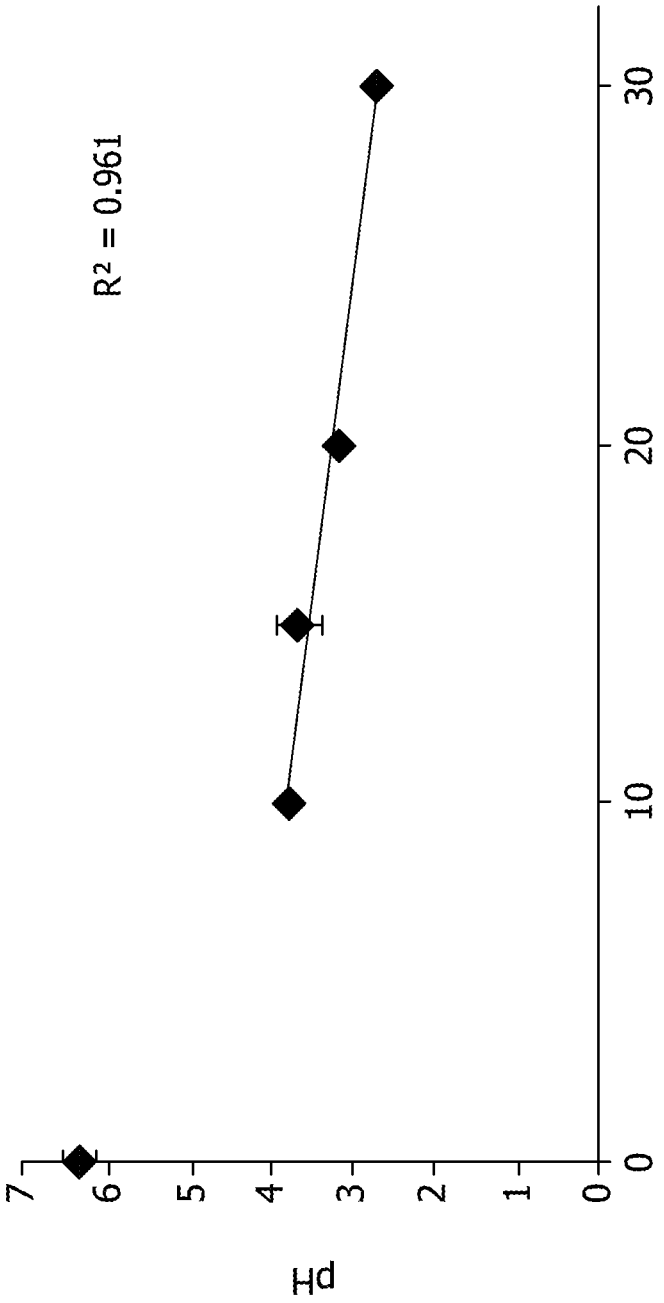

FIG. 31

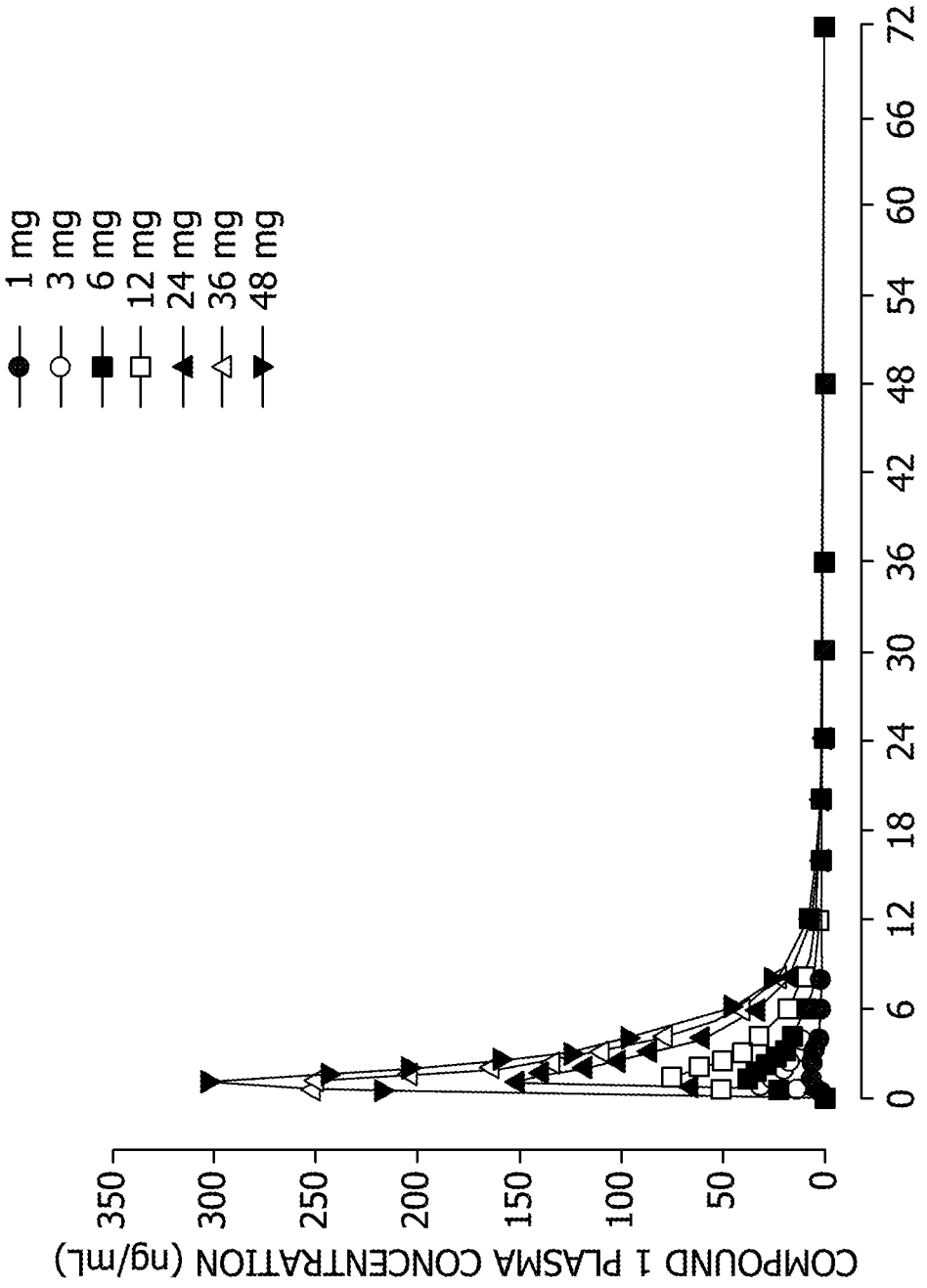
1 mg
3 mg
6 mg
12 mg
24 mg
36 mg
48 mg
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
50
100
150
200
250
300
350
TIME (hr)
0
6
12
18
24
30
36
42
48
54
60
66
72

FIG. 32A

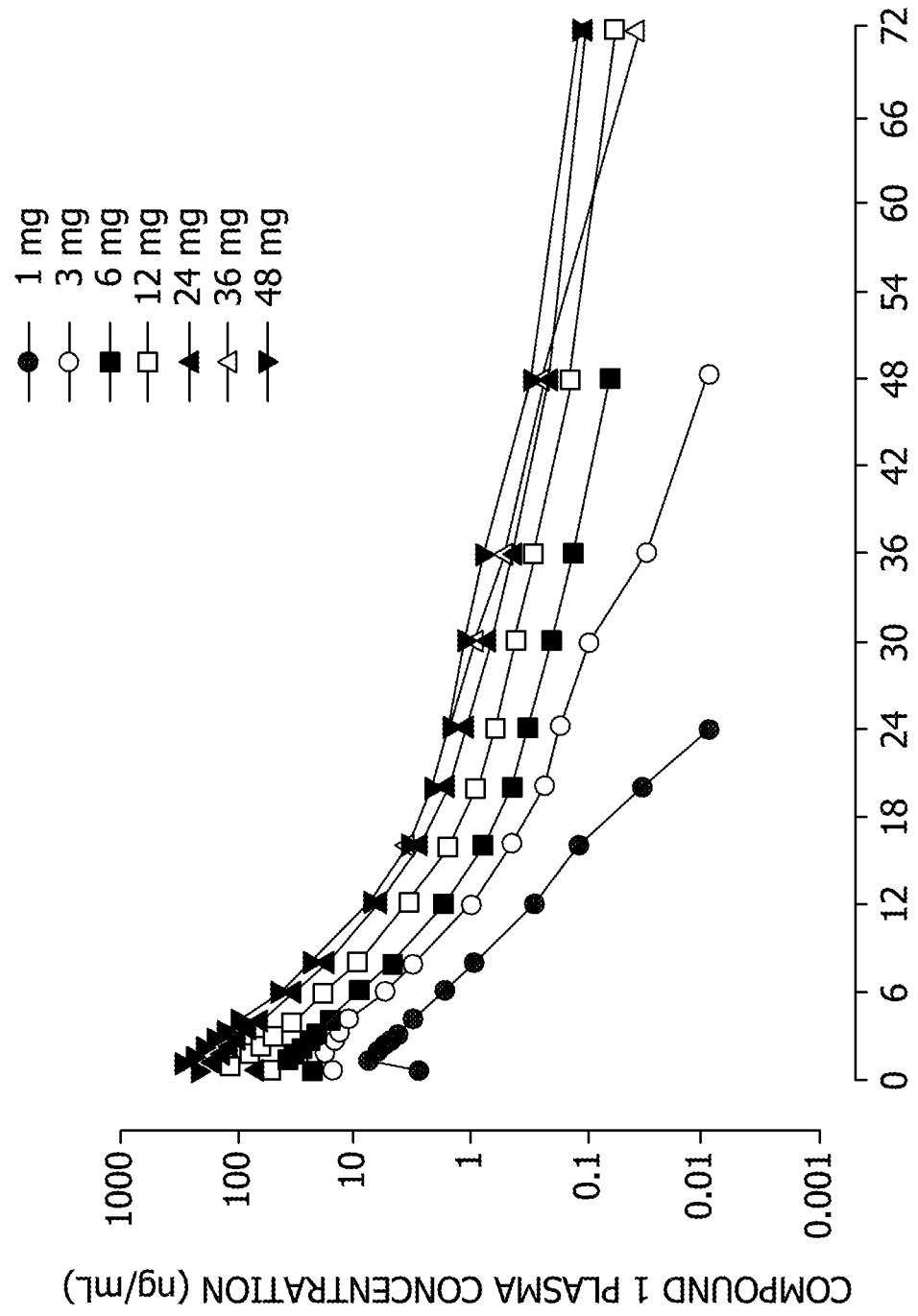
1 mg
3 mg
6 mg
12 mg
24 mg
36 mg
48 mg
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
1000
100
10
1
0.1
0.01
0.001
TIME (hr)
0
6
12
18
24
30
36
42
48
54
60
66
72

FIG. 32B

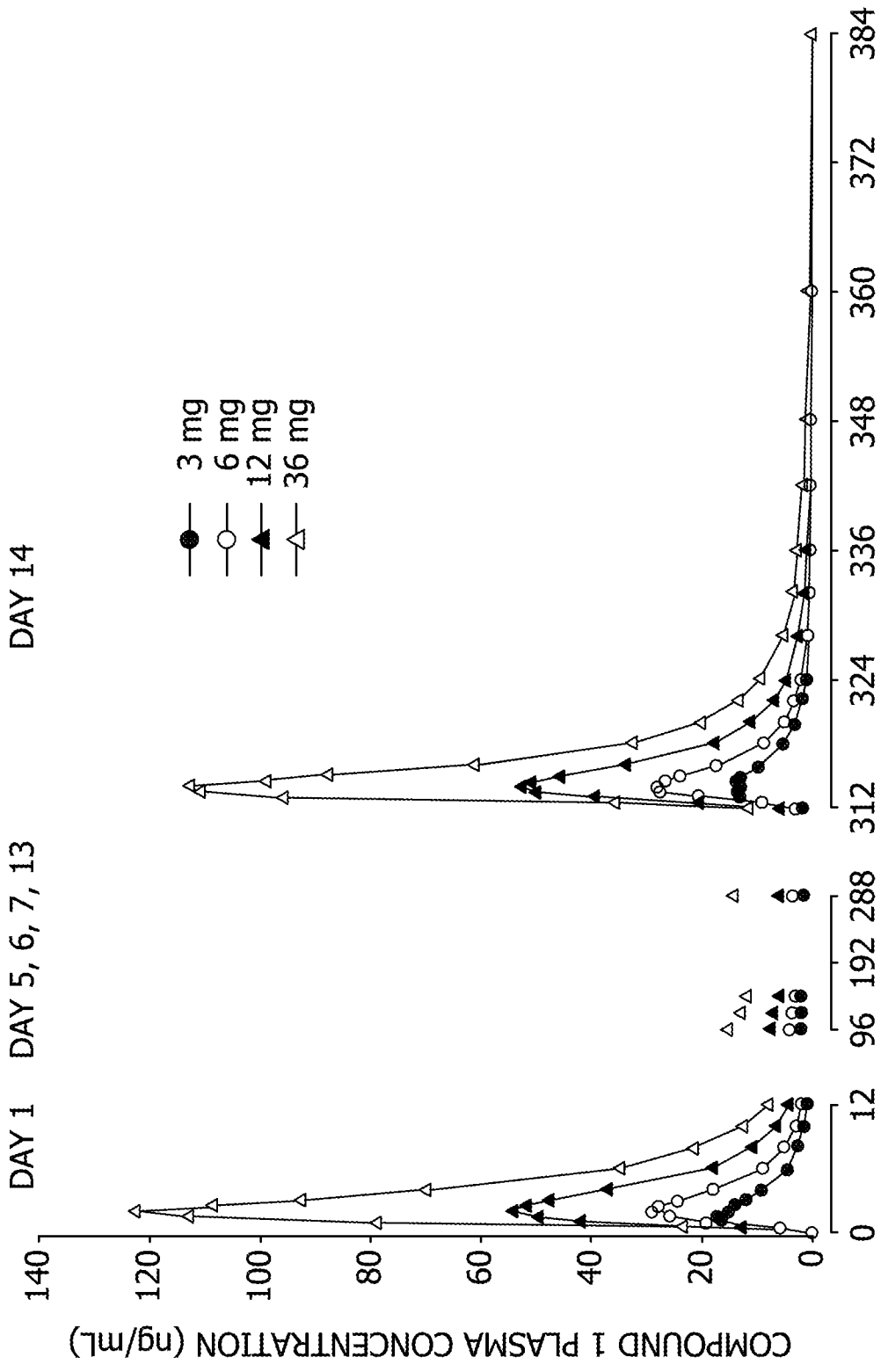
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
100
120
140
DAY 1
DAY 5, 6, 7, 13
DAY 14
0
12
96
192
288
312
324
336
348
360
372
384
TIME (hr)
3 mg
6 mg
12 mg
36 mg

FIG. 33

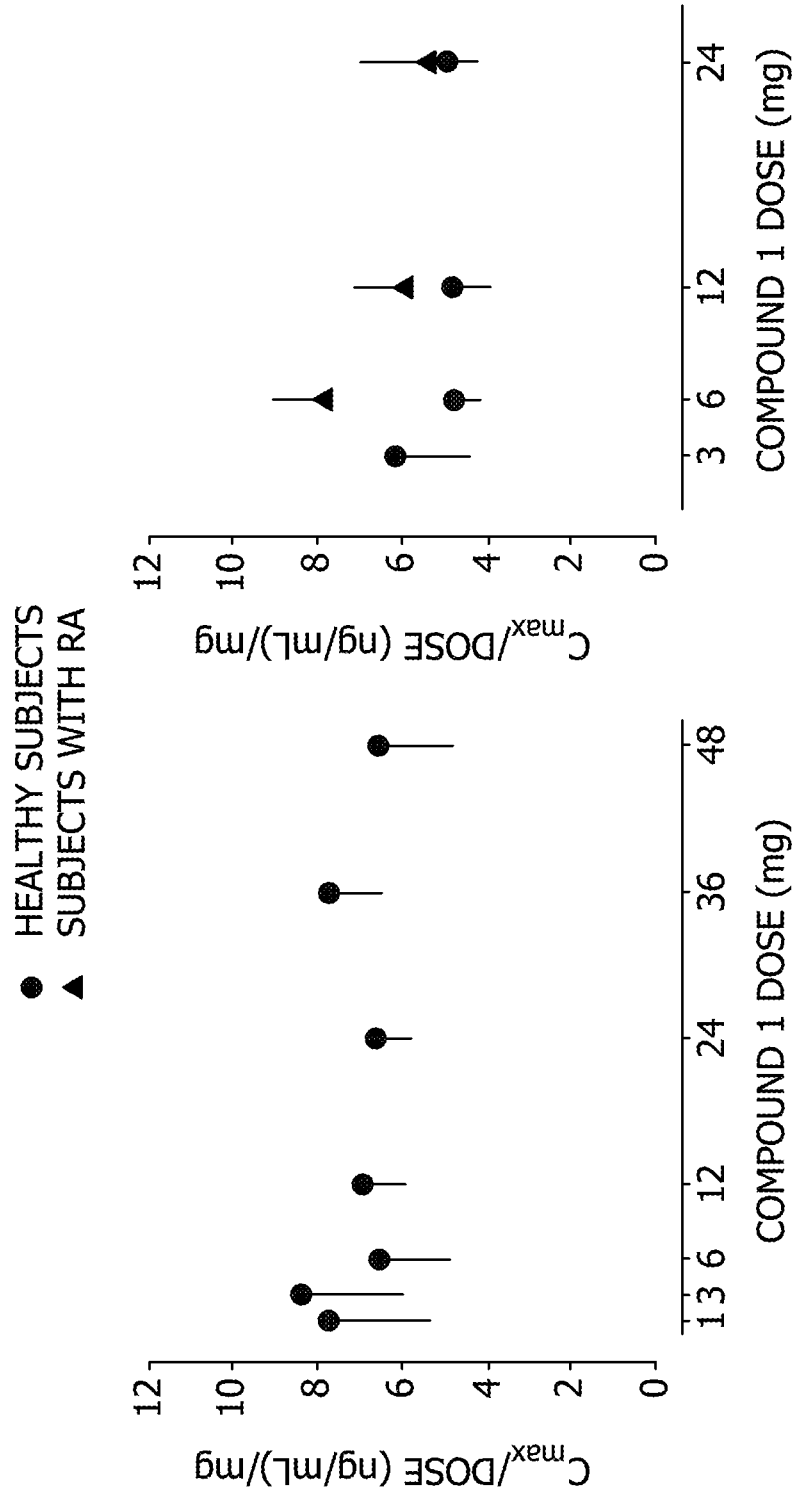

FIG. 34A

FIG. 34B

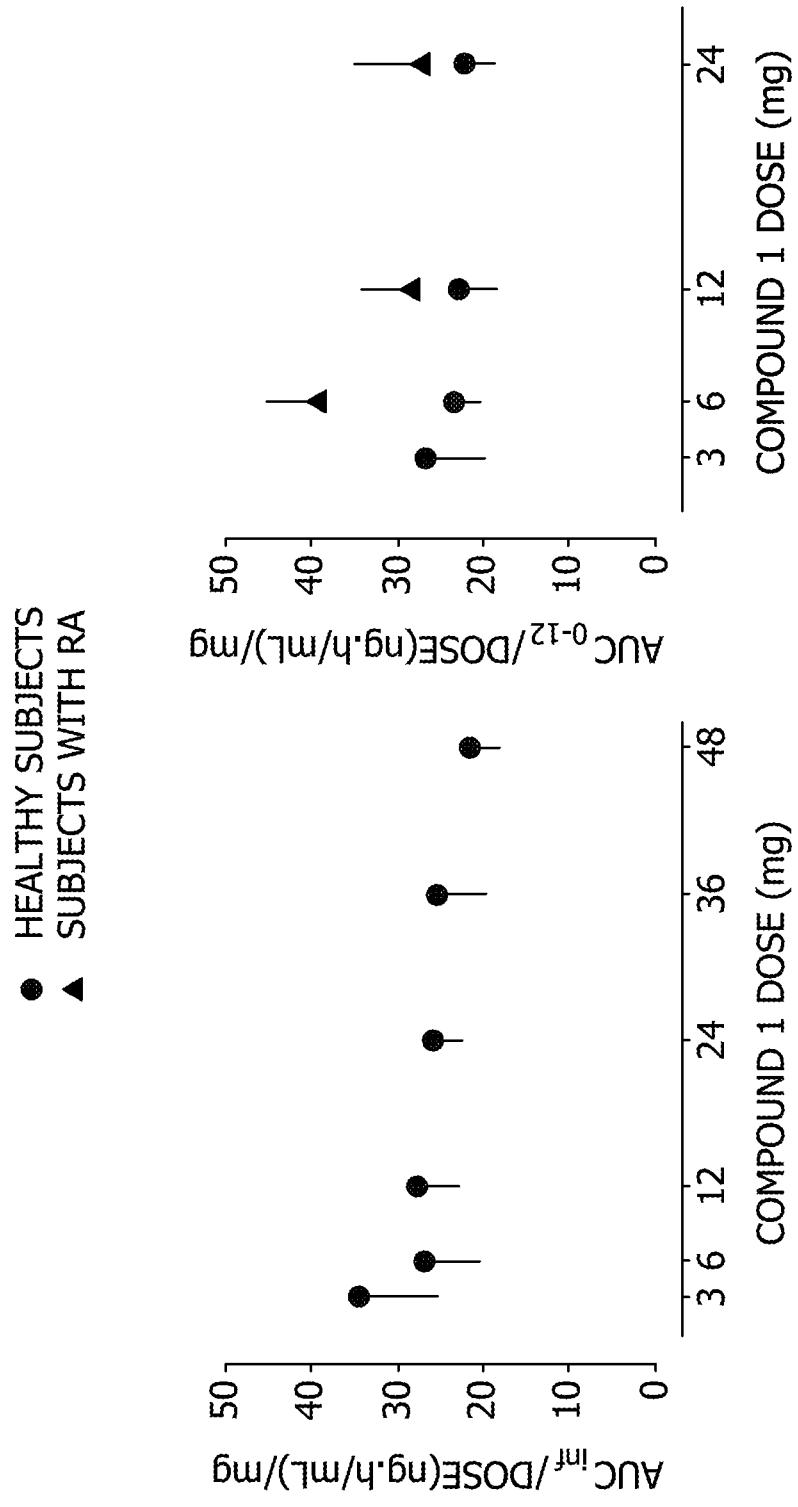

FIG. 34C

FIG. 34D

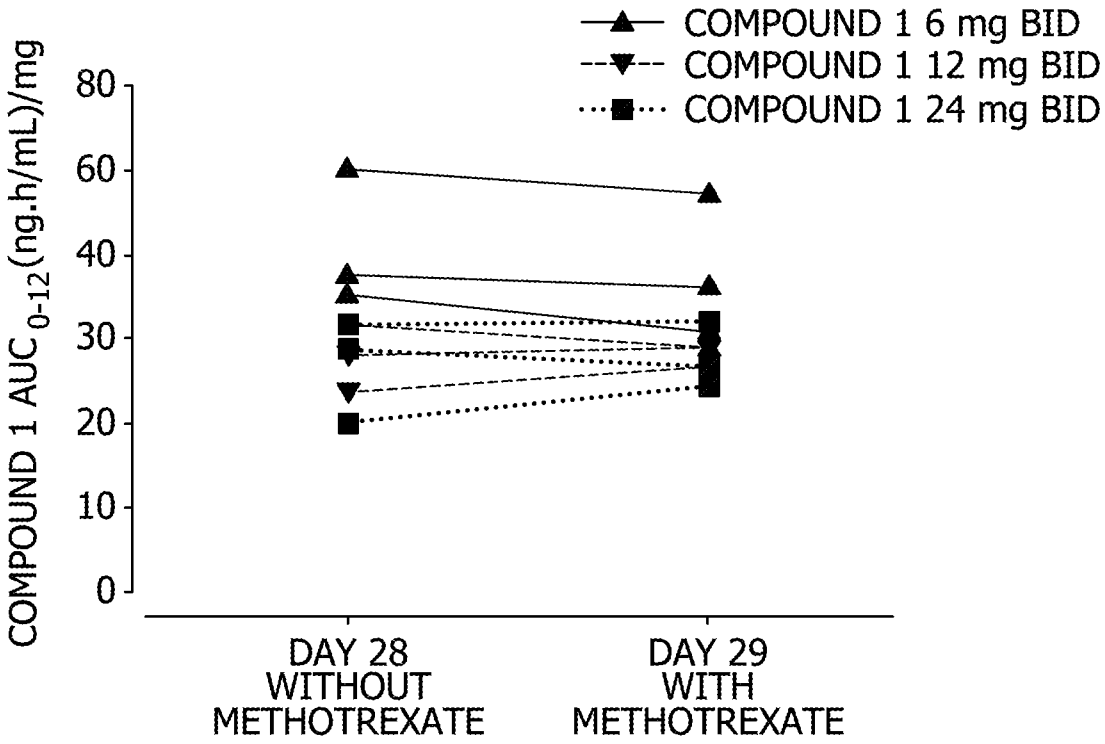

FIG. 35A

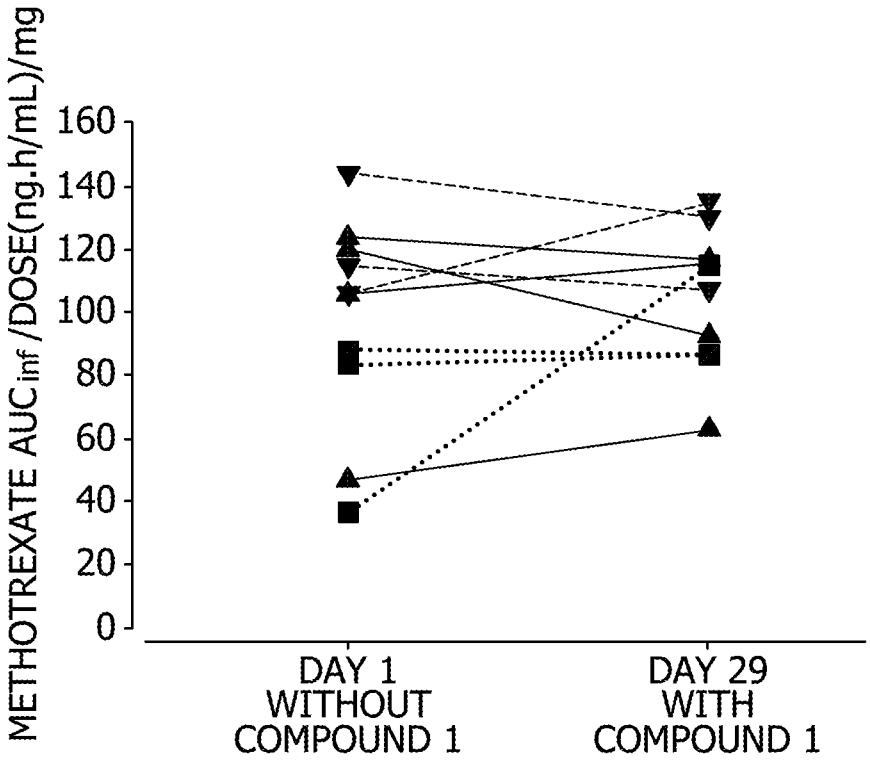

FIG. 35B

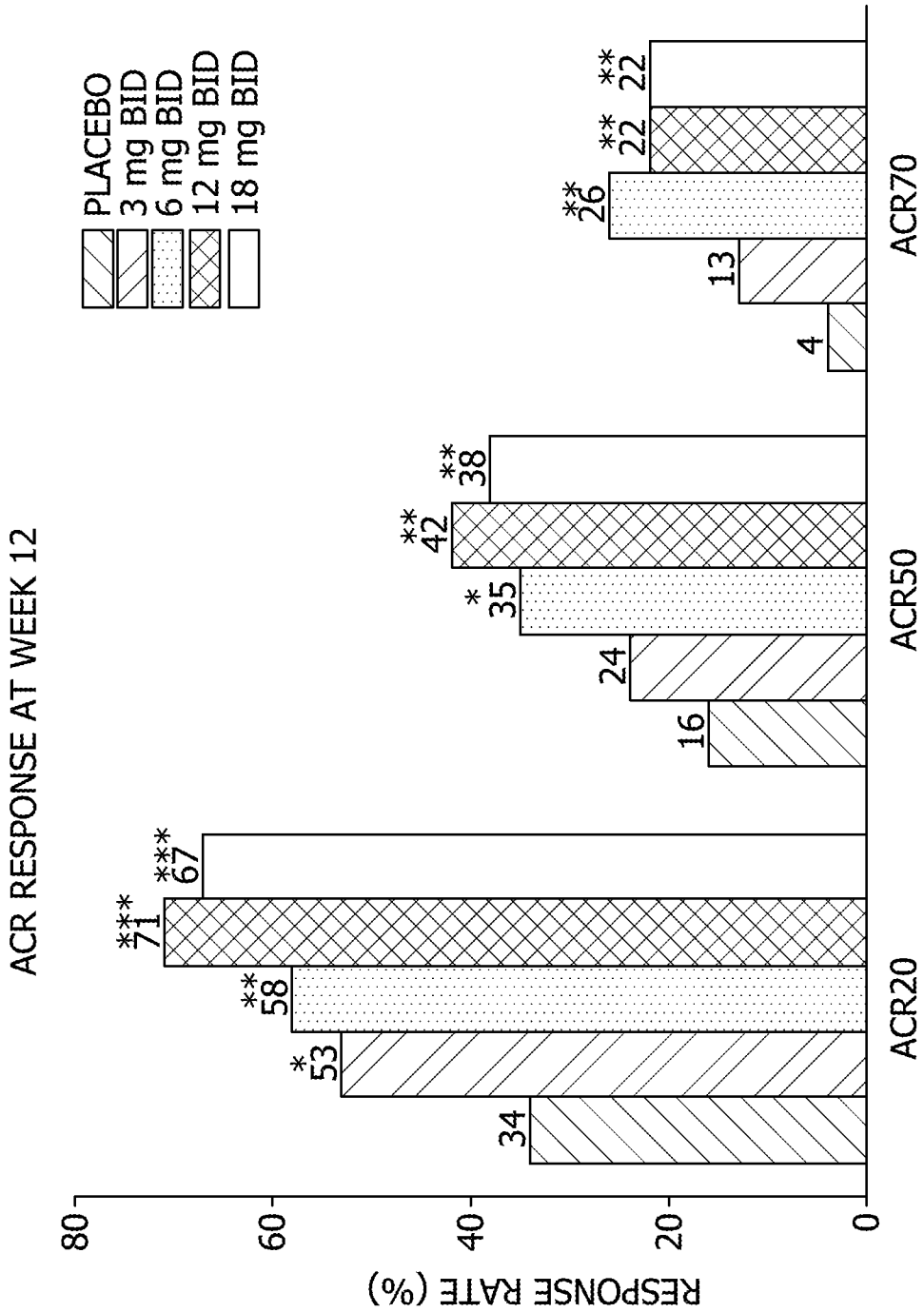
ACR RESPONSE AT WEEK 12
RESPONSE RATE (%)
0
20
40
60
80
PLACEBO
3 mg BID
6 mg BID
12 mg BID
18 mg BID
34
*53
**58
***71
67***
16
24
*35
**42
38**
4
13
**26
**22
**22
ACR20
ACR50
ACR70

FIG. 36A

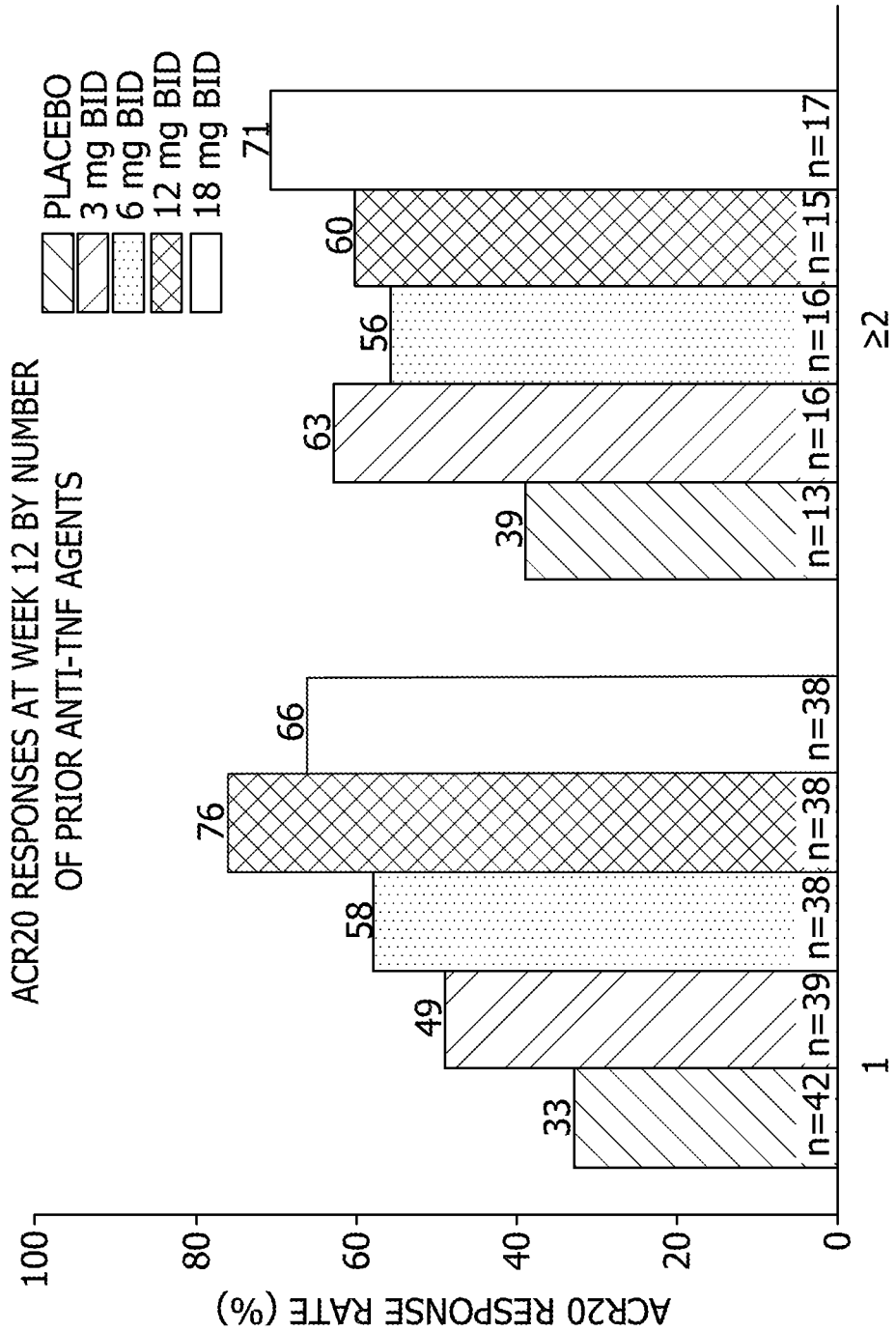
ACR20 RESPONSES AT WEEK 12 BY NUMBER OF PRIOR ANTI-TNF AGENTS
PLACEBO
3 mg BID
6 mg BID
12 mg BID
18 mg BID
ACR20 RESPONSE RATE (%)
0
20
40
60
80
100
33
49
58
76
66
39
63
56
60
71
n=42
n=39
n=38
n=38
n=38
n=13
n=16
n=16
n=15
n=17
1
≥2
NUMBER OF PRIOR ANTI-TNFS

FIG. 36B

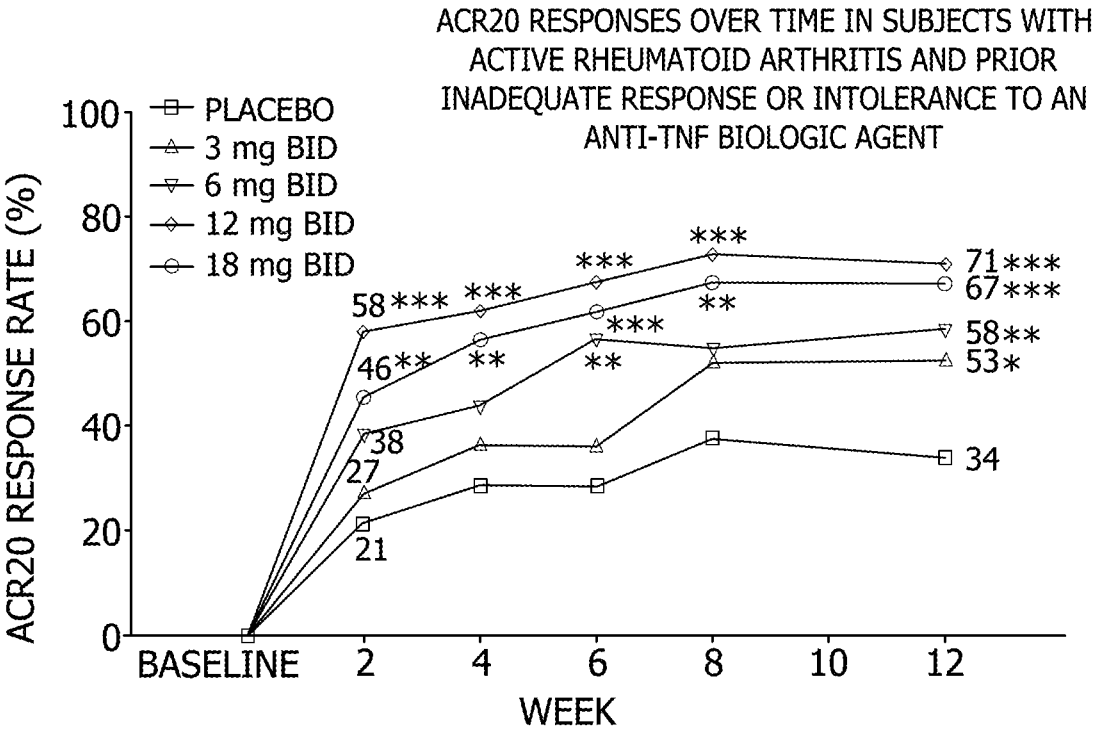

FIG. 37A

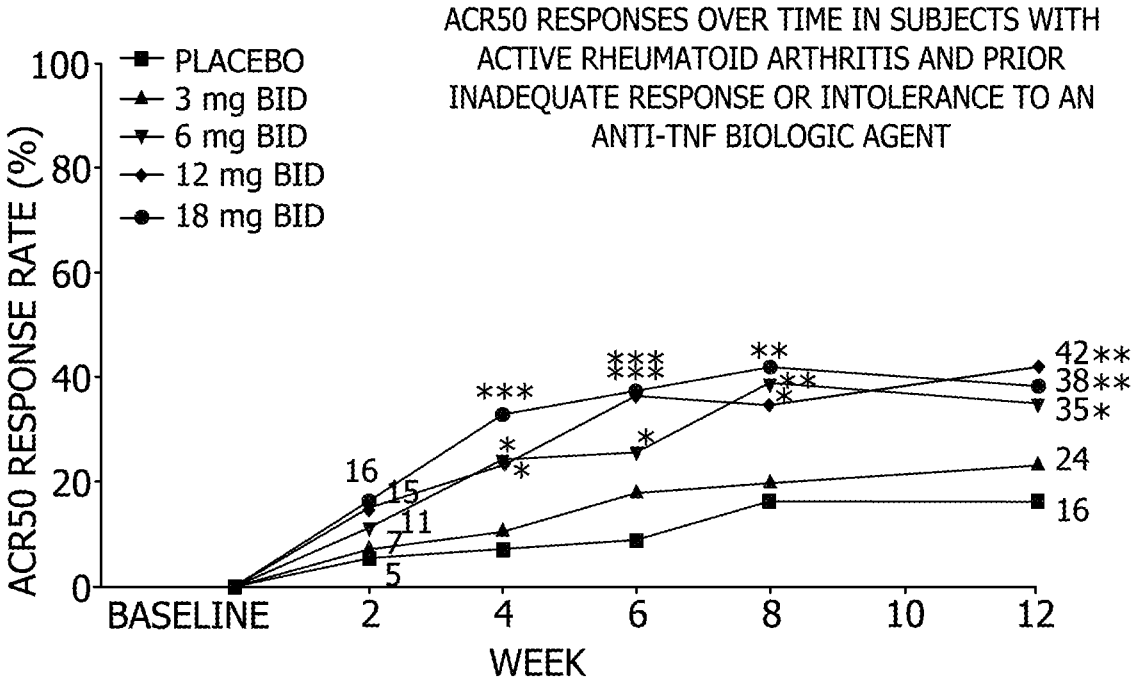

FIG. 37B

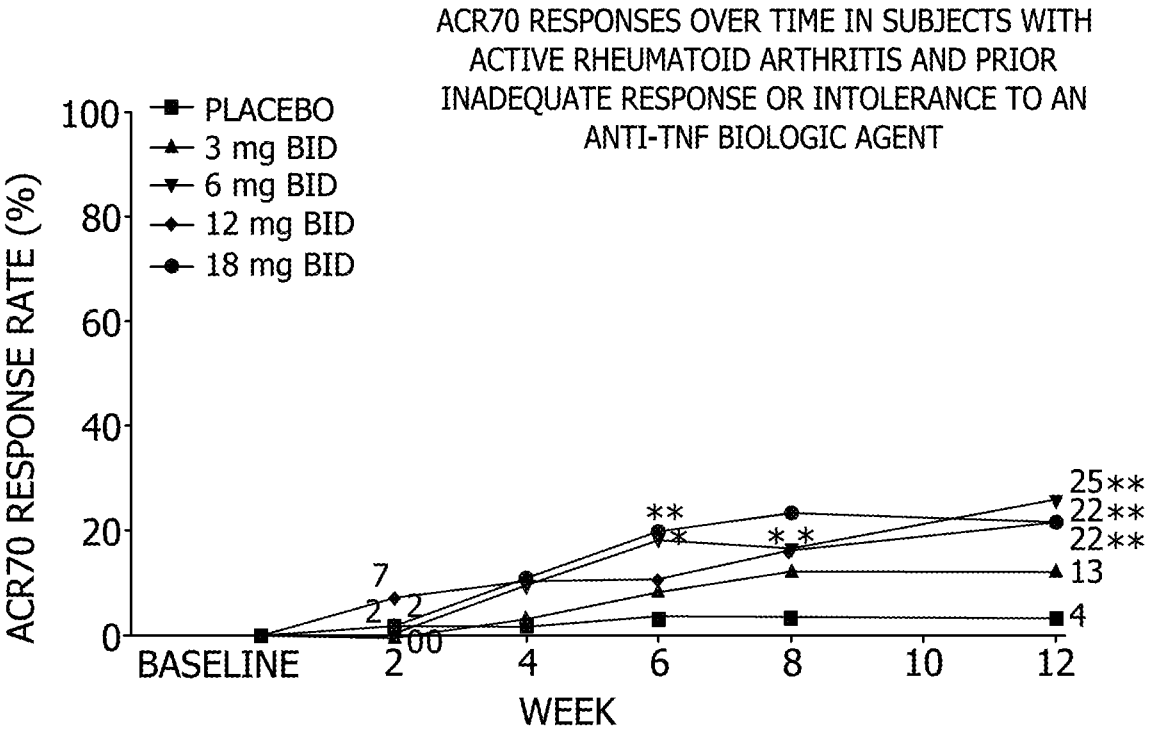

FIG. 37C

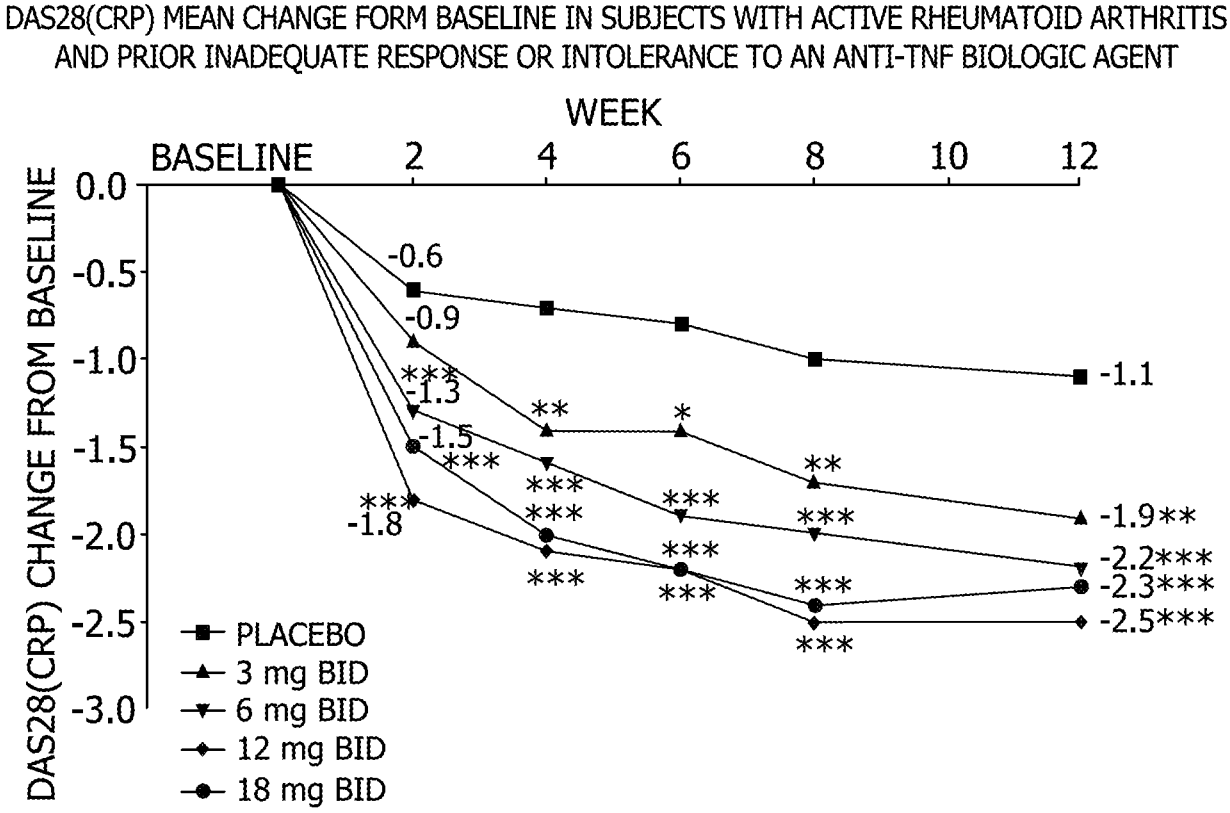

FIG. 37D

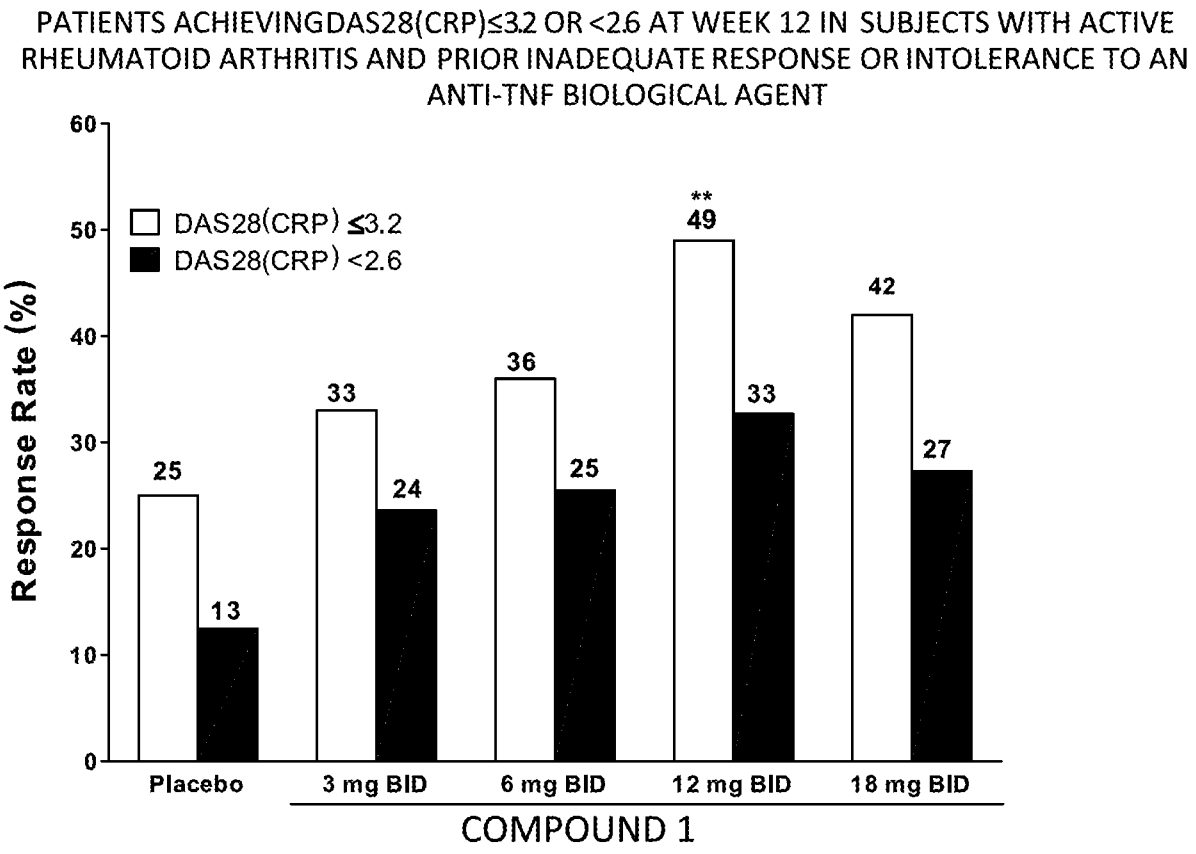

FIG. 37E

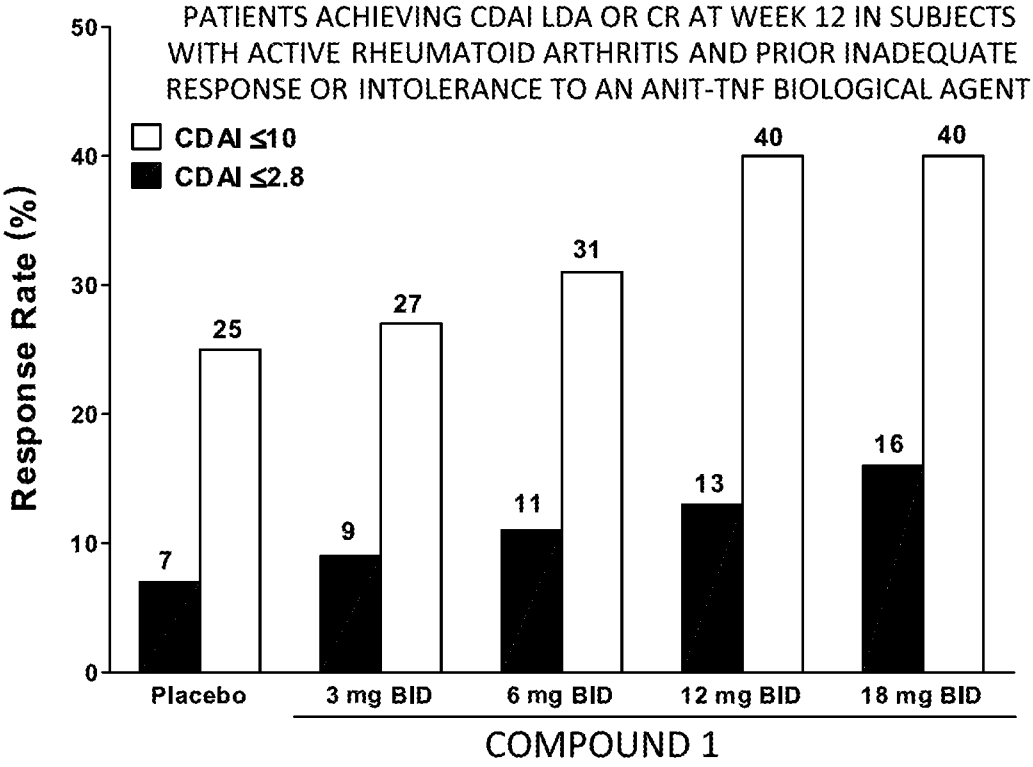

FIG. 37F

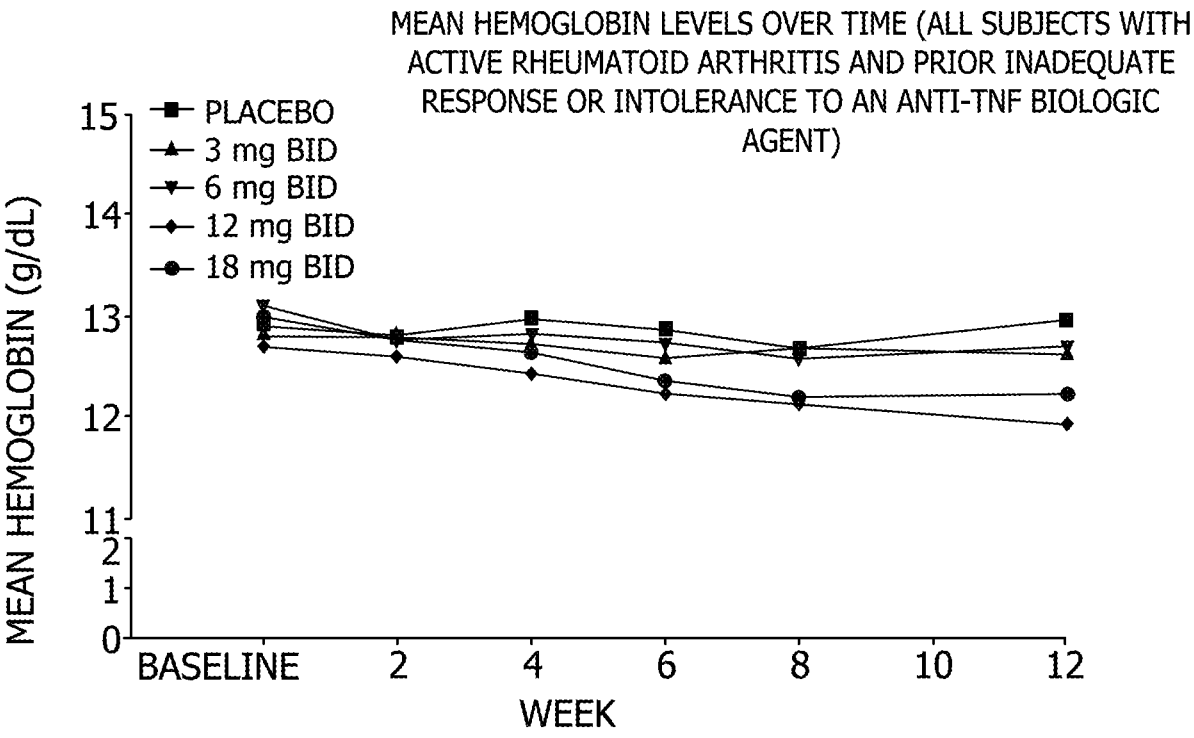

FIG. 38A

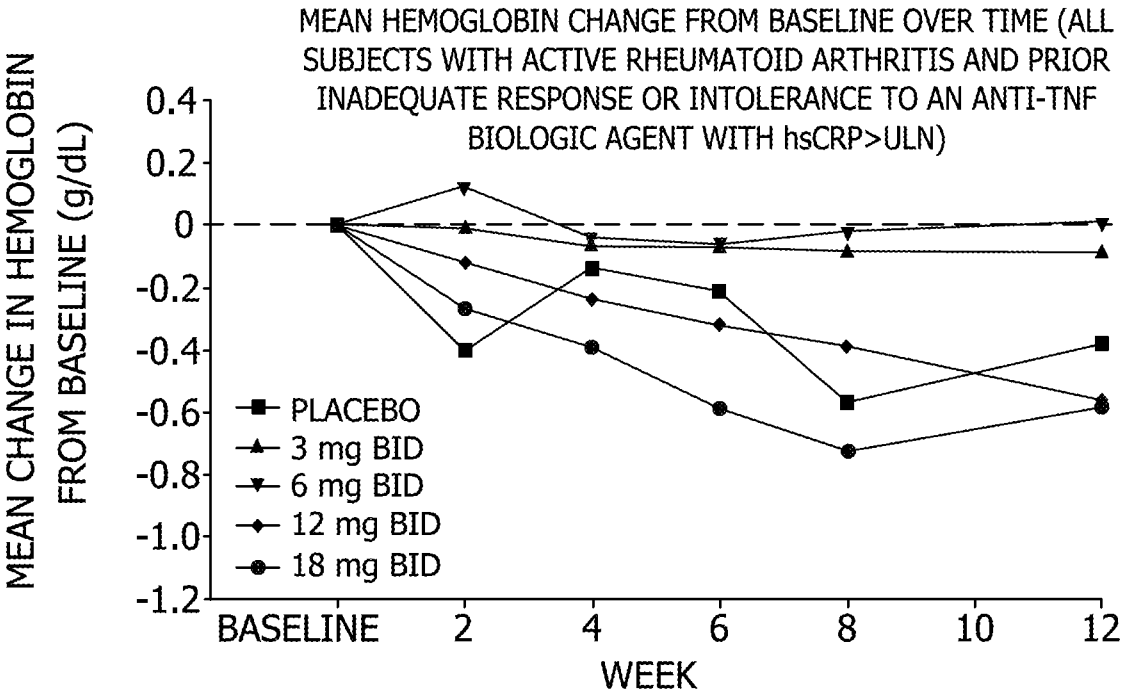

FIG. 38B

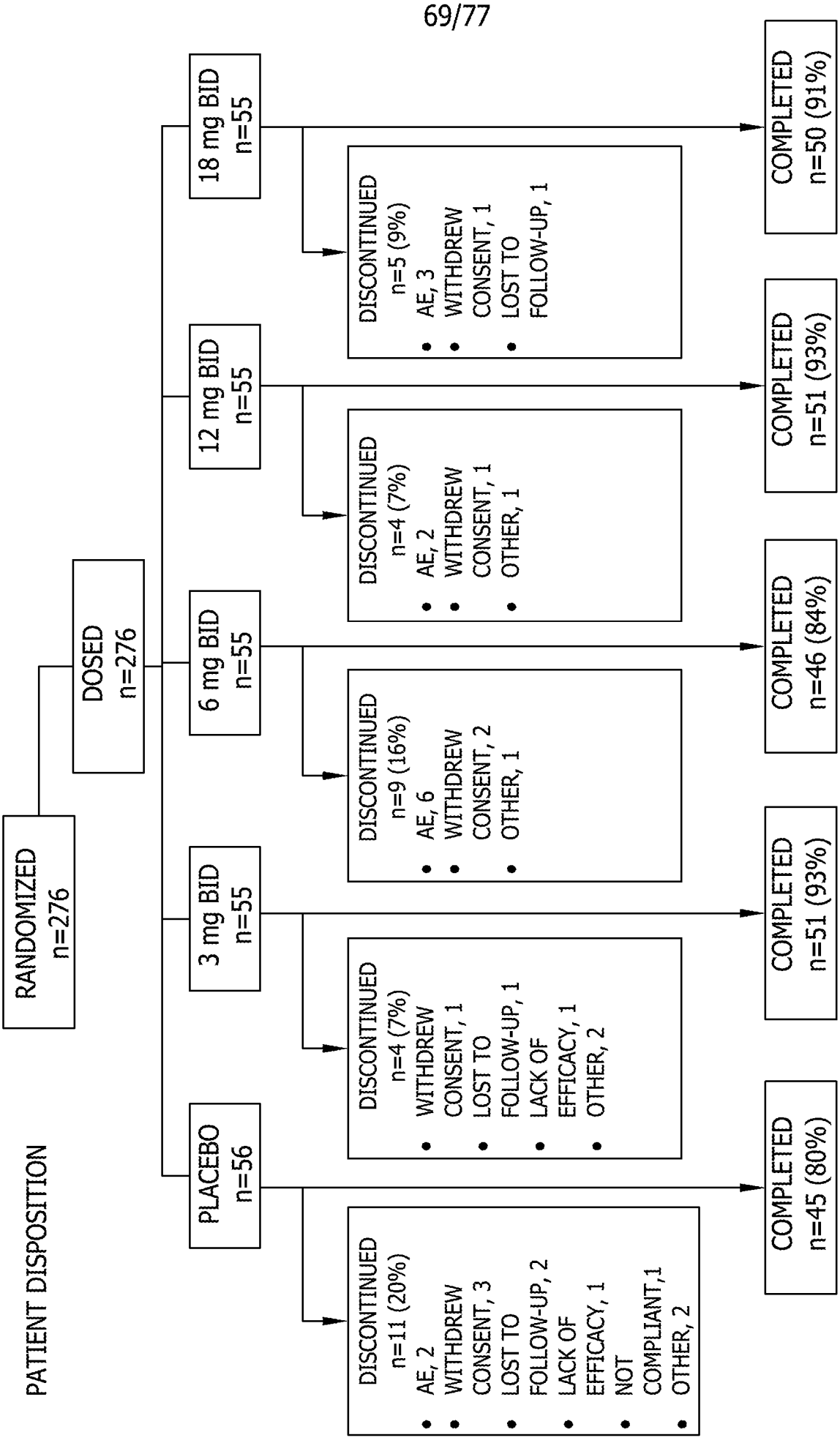
PATIENT DISPOSITION
RANDOMIZED n=276
DOSED n=276
PLACEBO n=56
3 mg BID n=55
6 mg BID n=55
12 mg BID n=55
18 mg BID n=55
DISCONTINUED n=11 (20%)
AE, 2
WITHDREW CONSENT, 3
LOST TO FOLLOW-UP, 2
LACK OF EFFICACY, 1
NOT COMPLIANT,1
OTHER, 2
DISCONTINUED n=4 (7%)
WITHDREW CONSENT, 1
LOST TO FOLLOW-UP, 1
LACK OF EFFICACY, 1
OTHER, 2
DISCONTINUED n=9 (16%)
AE, 6
WITHDREW CONSENT, 2
OTHER, 1
DISCONTINUED n=4 (7%)
AE, 2
WITHDREW CONSENT, 1
OTHER, 1
DISCONTINUED n=5 (9%)
AE, 3
WITHDREW CONSENT, 1
LOST TO FOLLOW-UP, 1
COMPLETED n=45 (80%)
COMPLETED n=51 (93%)
COMPLETED n=46 (84%)
COMPLETED n=51 (93%)
COMPLETED n=50 (91%)

FIG. 39

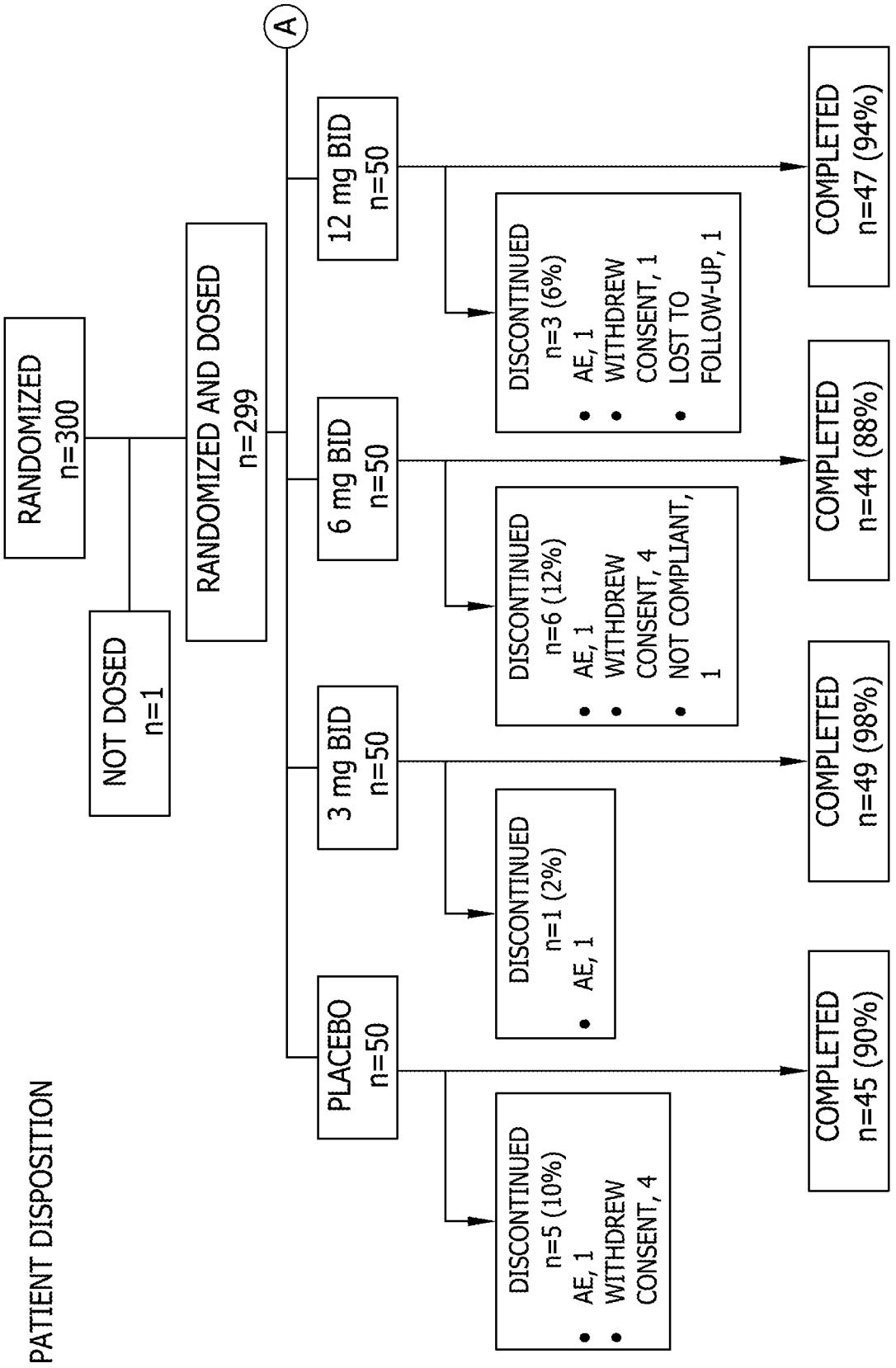
PATIENT DISPOSITION
RANDOMIZED n=300
NOT DOSED n=1
RANDOMIZED AND DOSED n=299
A
PLACEBO n=50
3 mg BID n=50
6 mg BID n=50
12 mg BID n=50
DISCONTINUED n=5 (10%)
• AE, 1
• WITHDREW CONSENT, 4
DISCONTINUED n=1 (2%)
• AE, 1
DISCONTINUED n=6 (12%)
• AE, 1
• WITHDREW CONSENT, 4
• NOT COMPLIANT, 1
DISCONTINUED n=3 (6%)
• AE, 1
• WITHDREW CONSENT, 1
• LOST TO FOLLOW-UP, 1
COMPLETED n=45 (90%)
COMPLETED n=49 (98%)
COMPLETED n=44 (88%)
COMPLETED n=47 (94%)

FIG. 40A

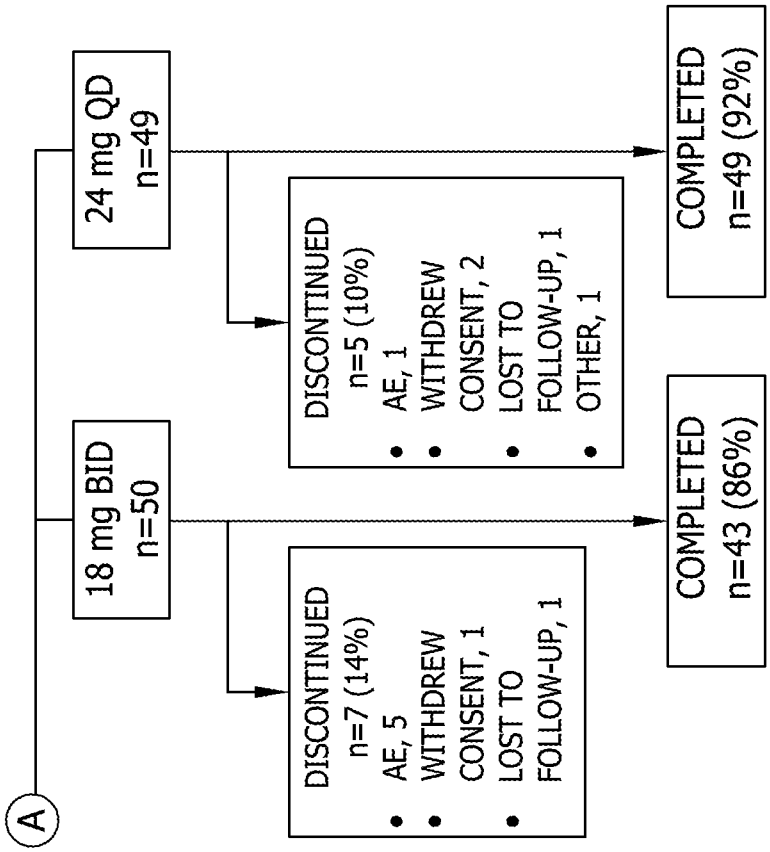
A
18 mg BID
n=50
24 mg QD
n=49
DISCONTINUED
n=7 (14%)
• AE, 5
• WITHDREW CONSENT, 1
• LOST TO FOLLOW-UP, 1
DISCONTINUED
n=5 (10%)
• AE, 1
• WITHDREW CONSENT, 2
• LOST TO FOLLOW-UP, 1
• OTHER, 1
COMPLETED
n=43 (86%)
COMPLETED
n=49 (92%)

FIG. 40B

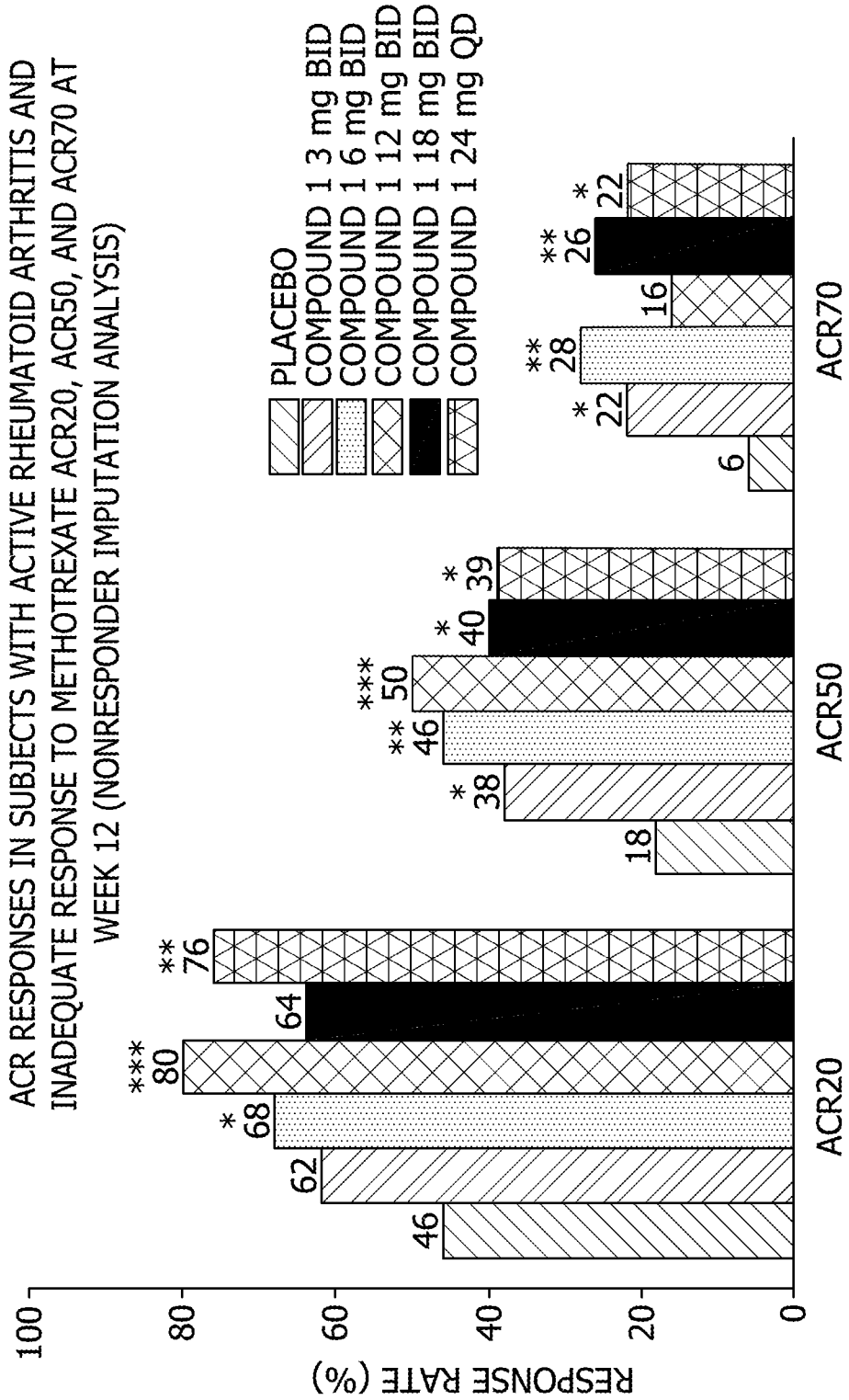
ACR RESPONSES IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE ACR20, ACR50, AND ACR70 AT WEEK 12 (NONRESPONDER IMPUTATION ANALYSIS)
RESPONSE RATE (%)
0
20
40
60
80
100
PLACEBO
COMPOUND 1 3 mg BID
COMPOUND 1 6 mg BID
COMPOUND 1 12 mg BID
COMPOUND 1 18 mg BID
COMPOUND 1 24 mg QD
46
62
*
68
***
80
64
**
76
18
*
38
**
46
***
50
40
*
39
6
*
22
**
28
16
**
26
*
22
ACR20
ACR50
ACR70

FIG. 41

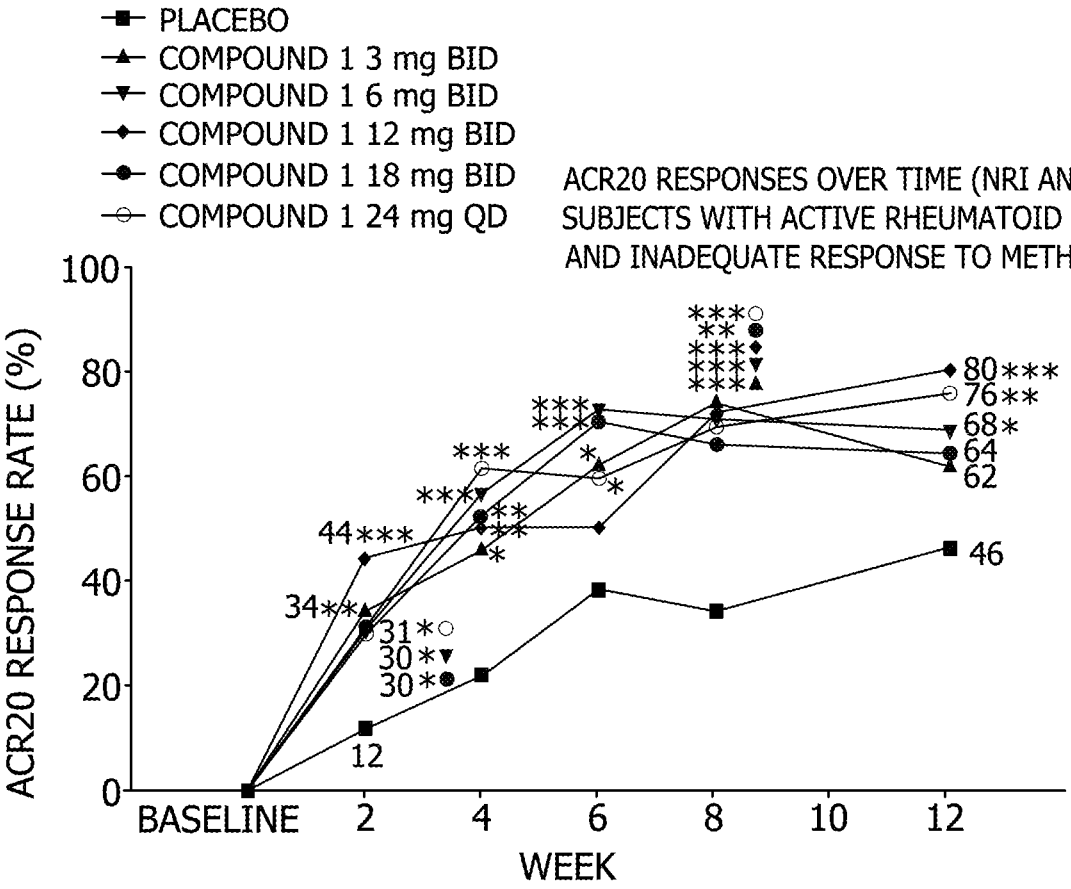

FIG. 42A

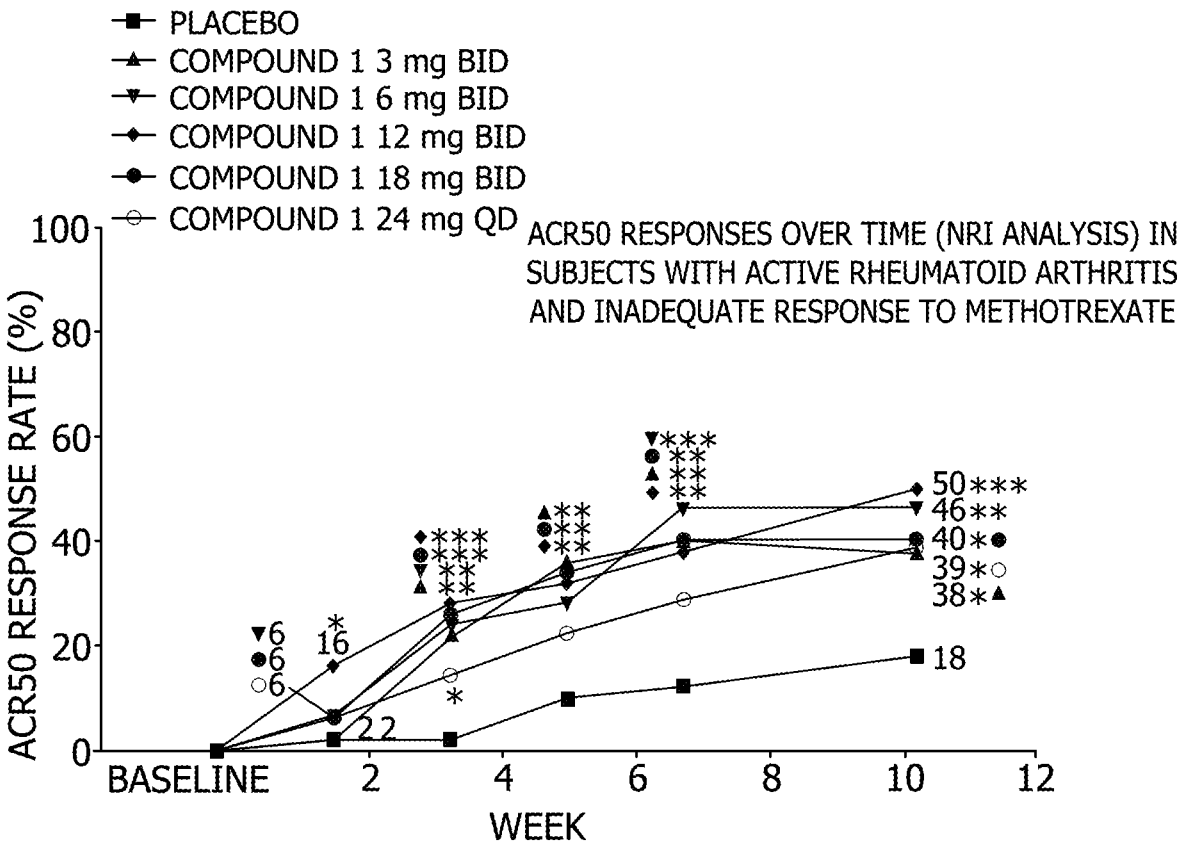

FIG. 42B

ACR70 RESPONSES OVER TIME (NRI ANALYSIS) IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE

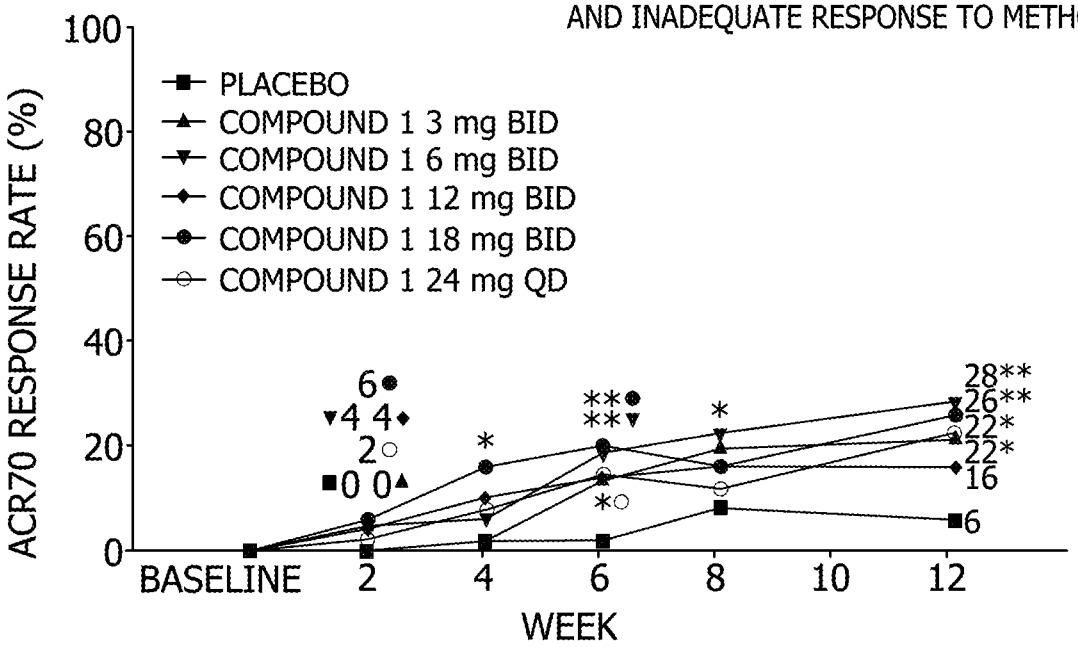

FIG. 42C

DAS28(CRP) MEAN CHANGE FROM BASELINE OVER TIME (OBSERVED CASES) IN SUBJECTS WITH ACTIVE RHEMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE

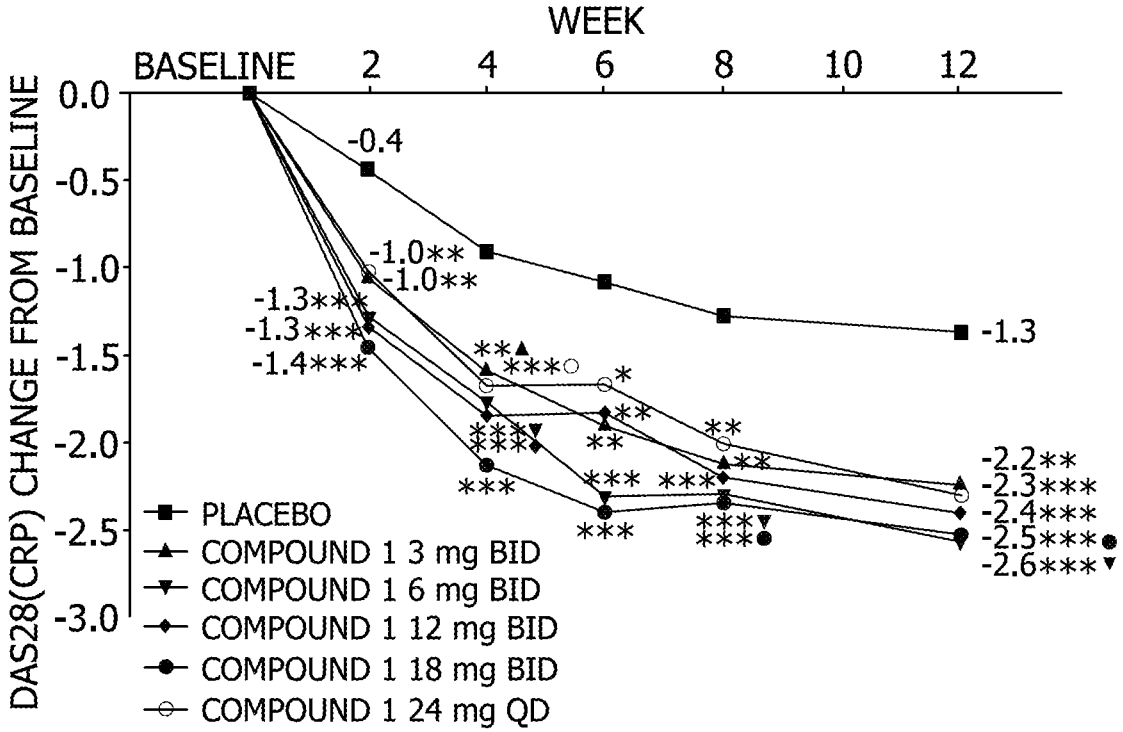

FIG. 42D

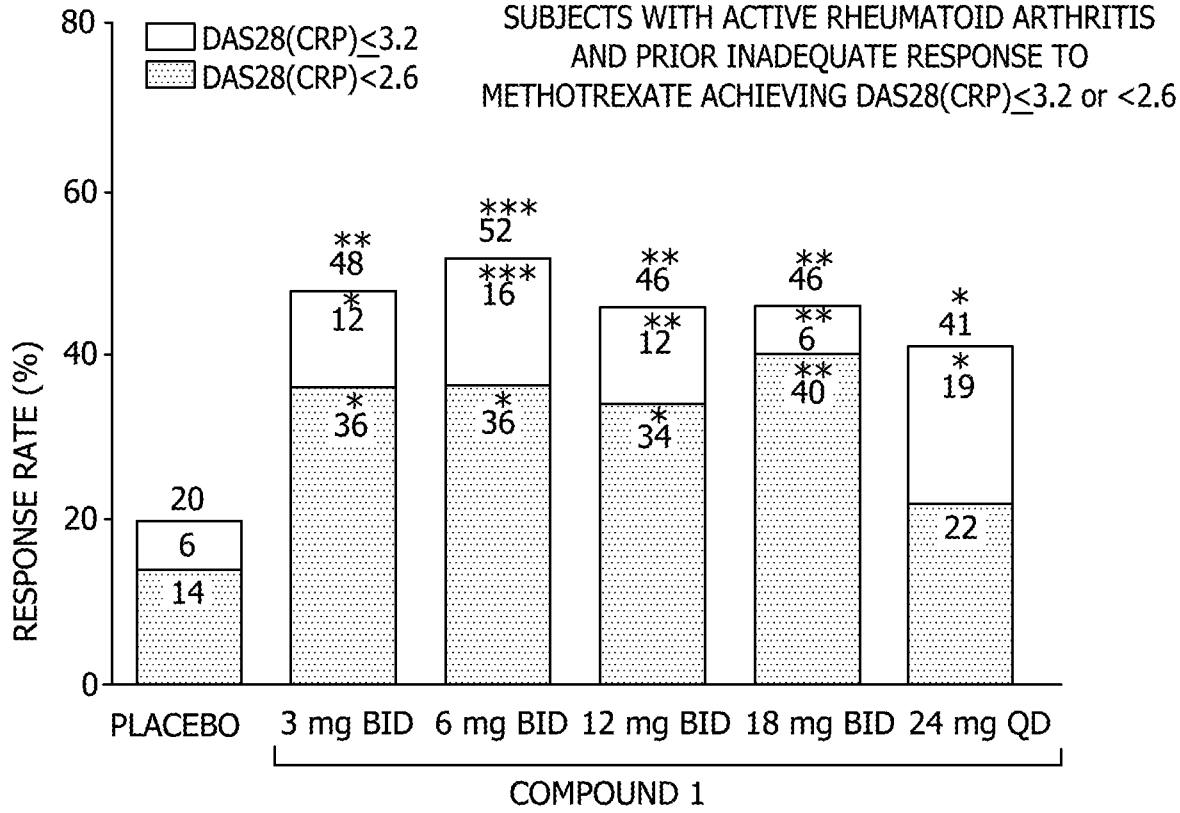

FIG. 43A

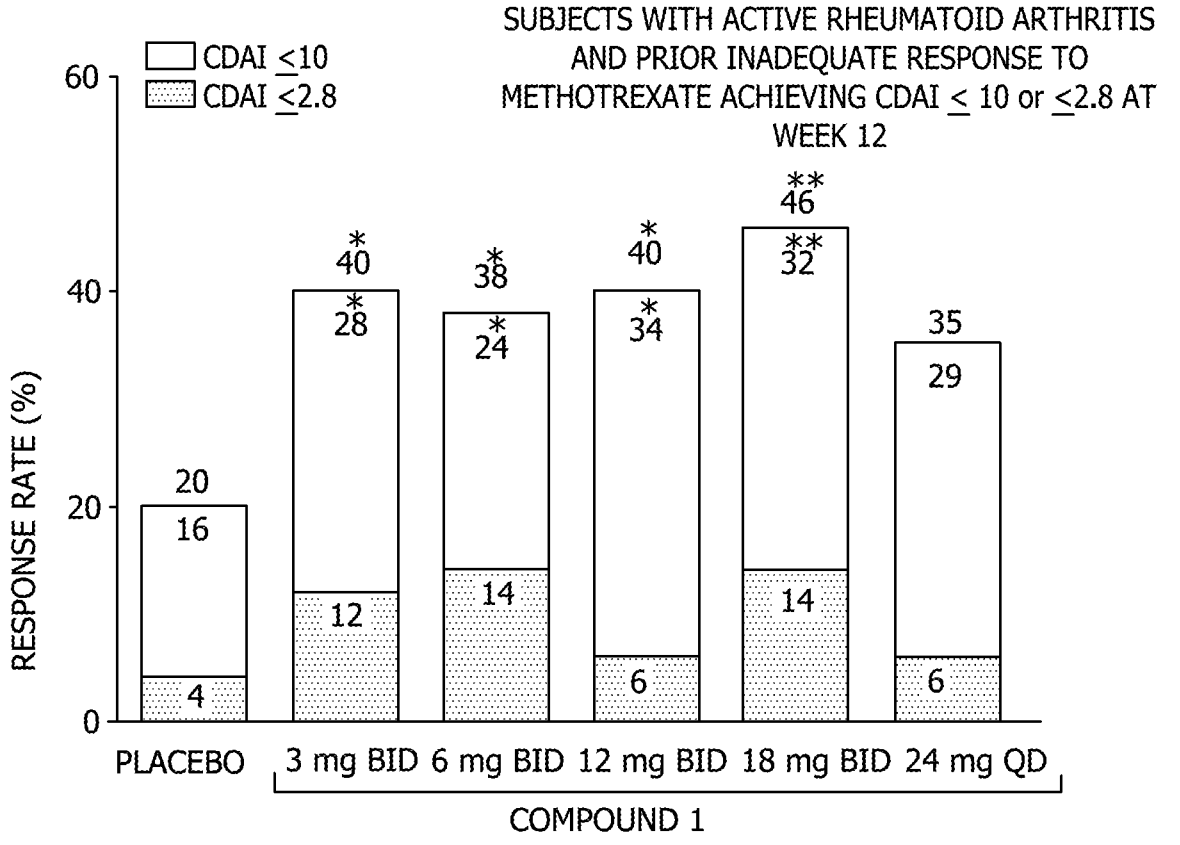

FIG. 43B

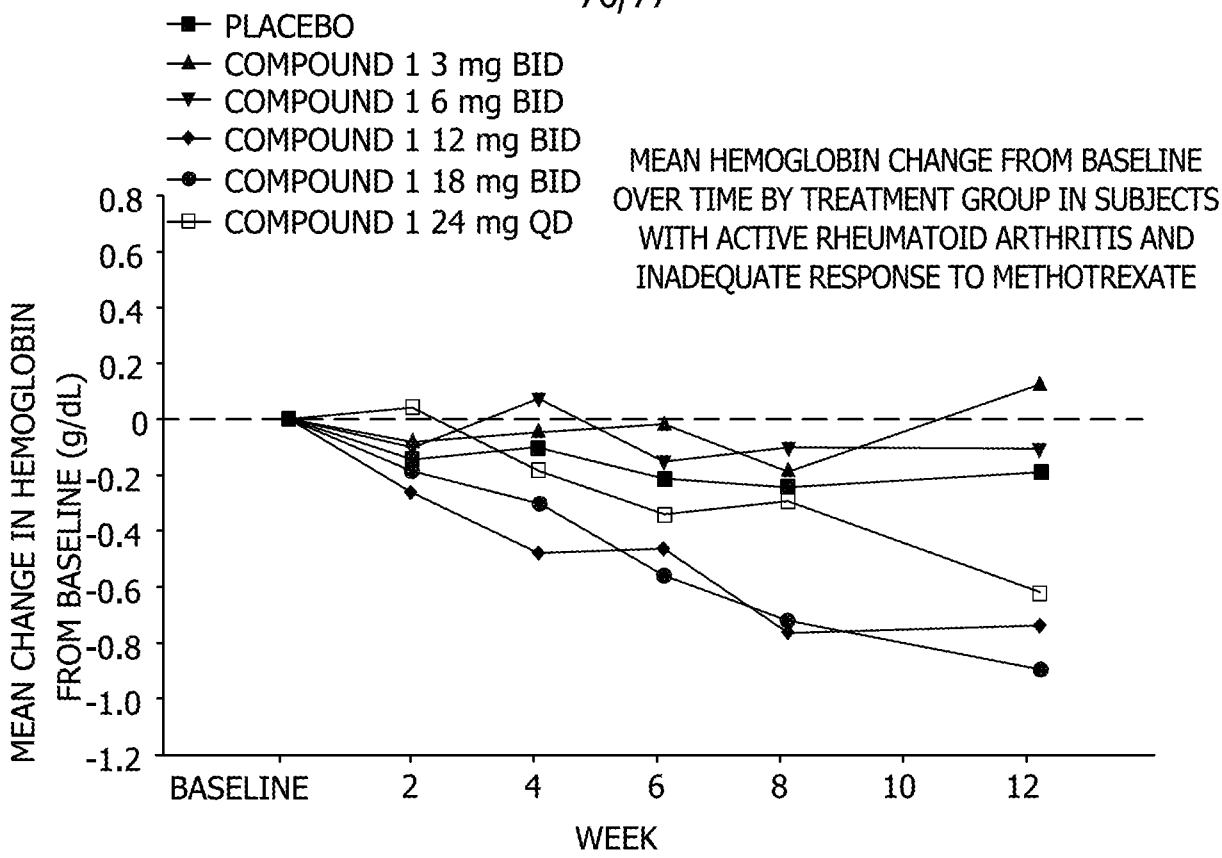

FIG. 44A

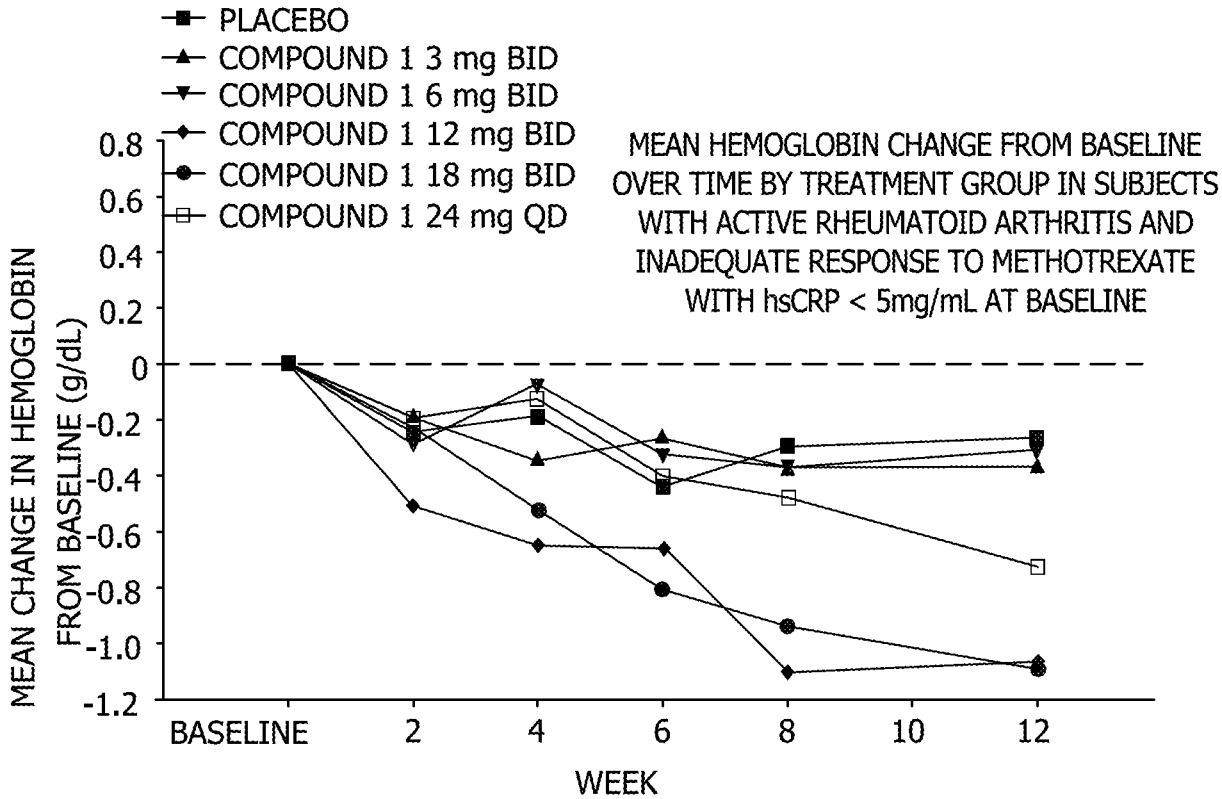

FIG. 44B

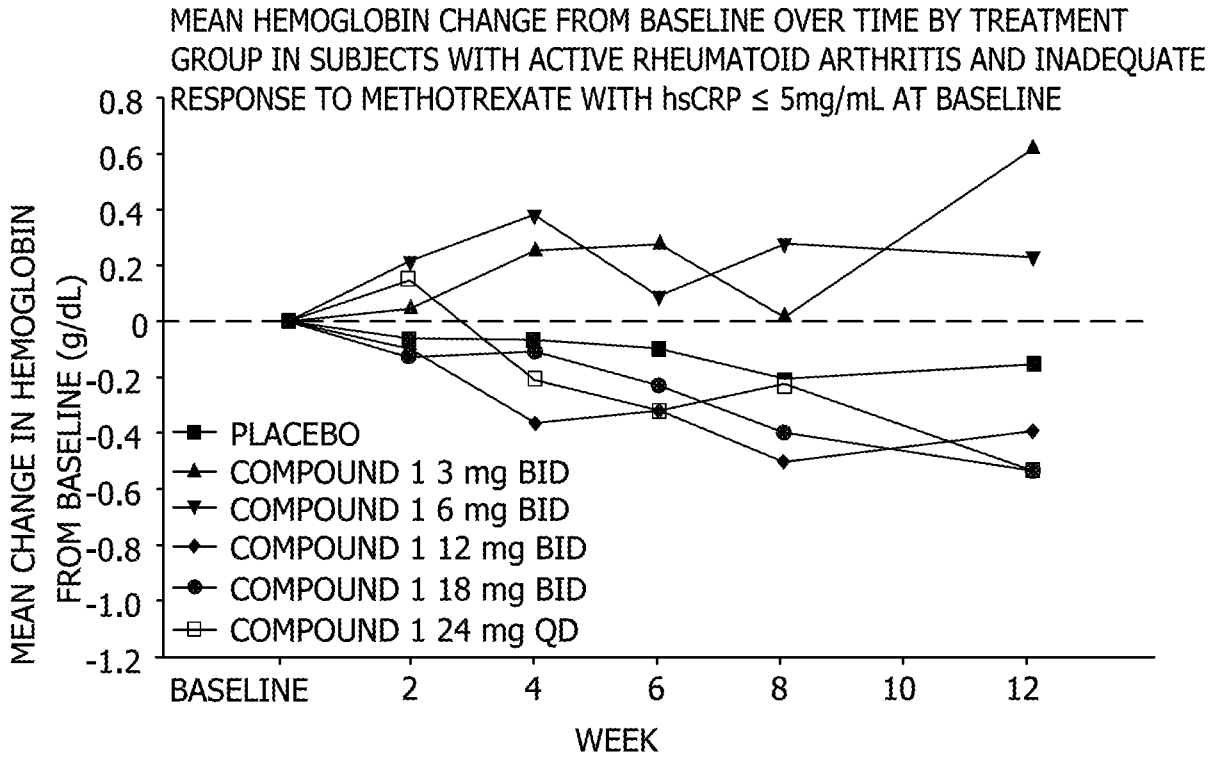
MEAN HEMOGLOBIN CHANGE FROM BASELINE OVER TIME BY TREATMENT GROUP IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE WITH hsCRP ≤ 5mg/mL AT BASELINE
MEAN CHANGE IN HEMOGLOBIN FROM BASELINE (g/dL)
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
PLACEBO
COMPOUND 1 3 mg BID
COMPOUND 1 6 mg BID
COMPOUND 1 12 mg BID
COMPOUND 1 18 mg BID
COMPOUND 1 24 mg QD
BASELINE
2
4
6
8
10
12
WEEK

FIG. 44C