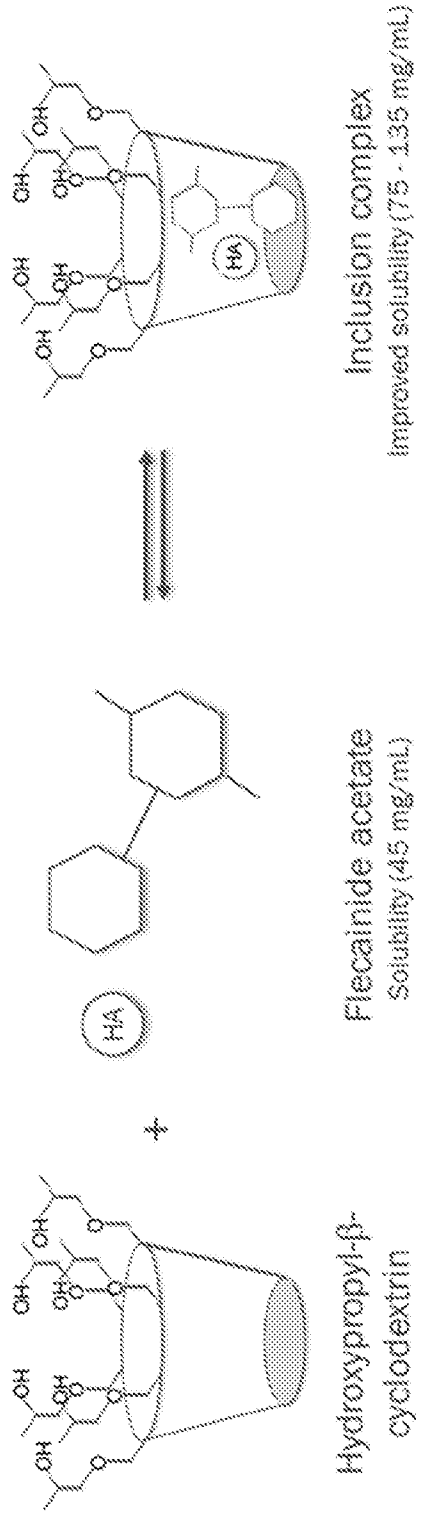
Hydroxypropyl-β-cyclodextrin
+
HA
Flecainide acetate
Solubility (45 mg/mL)
Inclusion complex
Improved solubility (75 - 135 mg/mL)

FIGURE 1

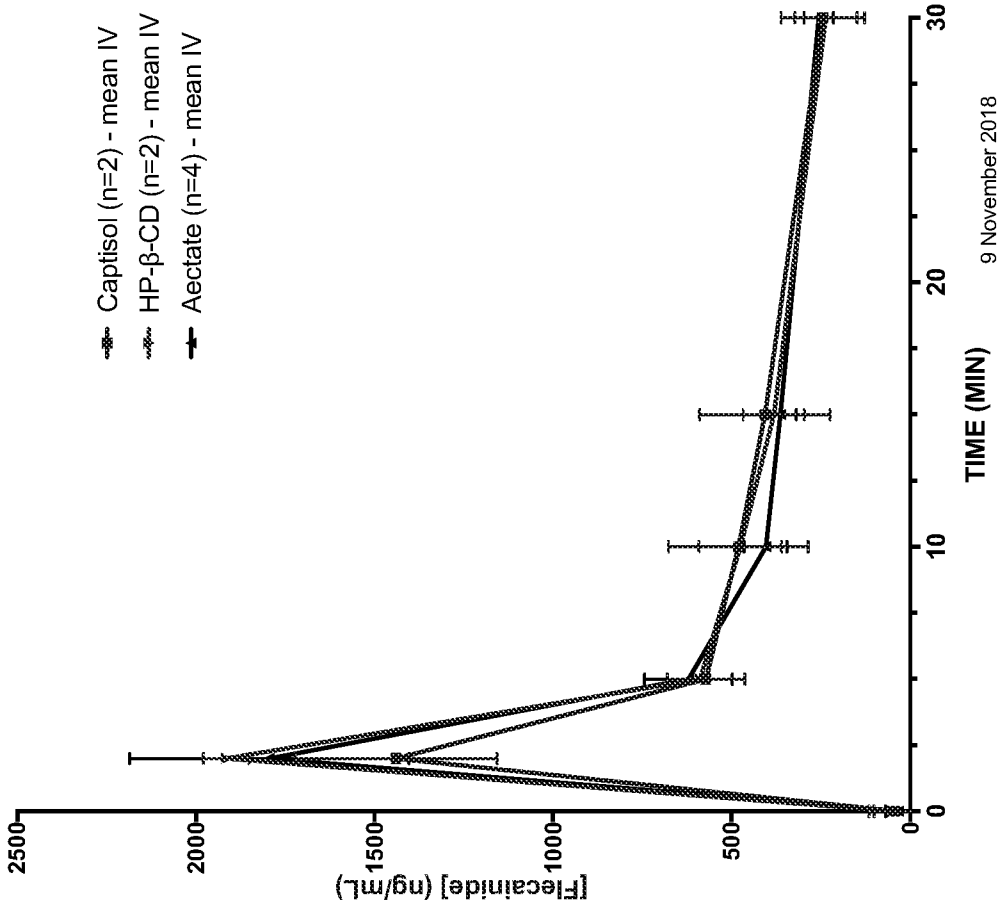
Captisol (n=2) - mean IV
HP-β-CD (n=2) - mean IV
Aectate (n=4) - mean IV
[Flecainide] (ng/mL)
2500
2000
1500
1000
500
0
0
10
20
30
TIME (MIN)
9 November 2018

FIGURE 2

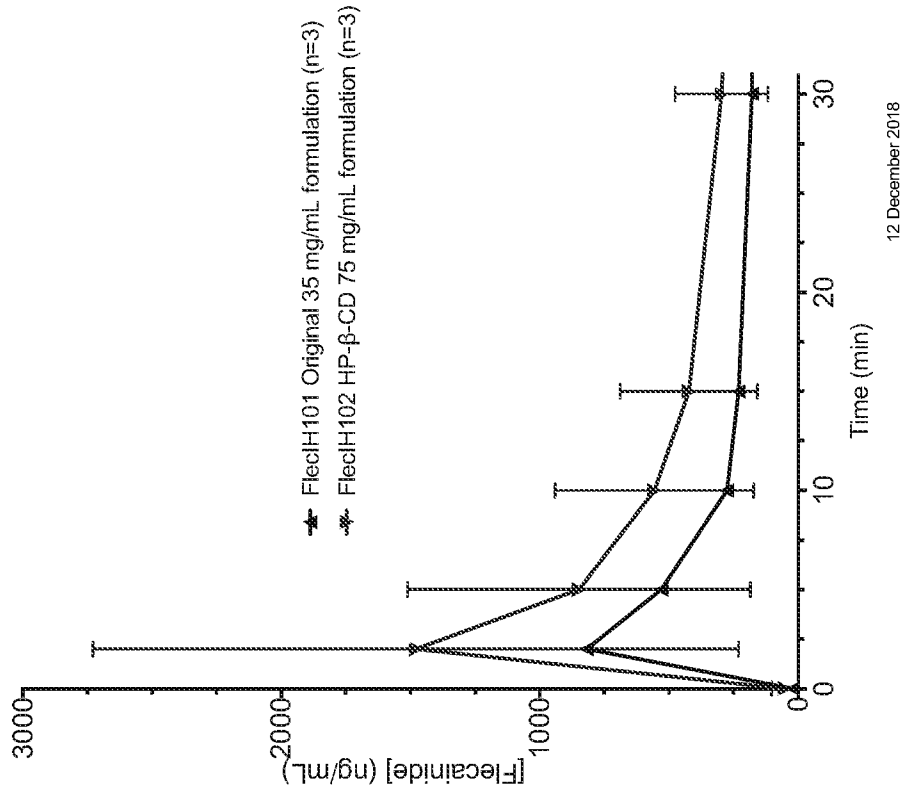
FlecIH101 Original 35 mg/mL formulation (n=3)
FlecIH102 HP-β-CD 75 mg/mL formulation (n=3)
[Flecainide] (ng/mL)
3000
2000
1000
0
0
10
20
30
Time (min)
12 December 2018

FIGURE 3A

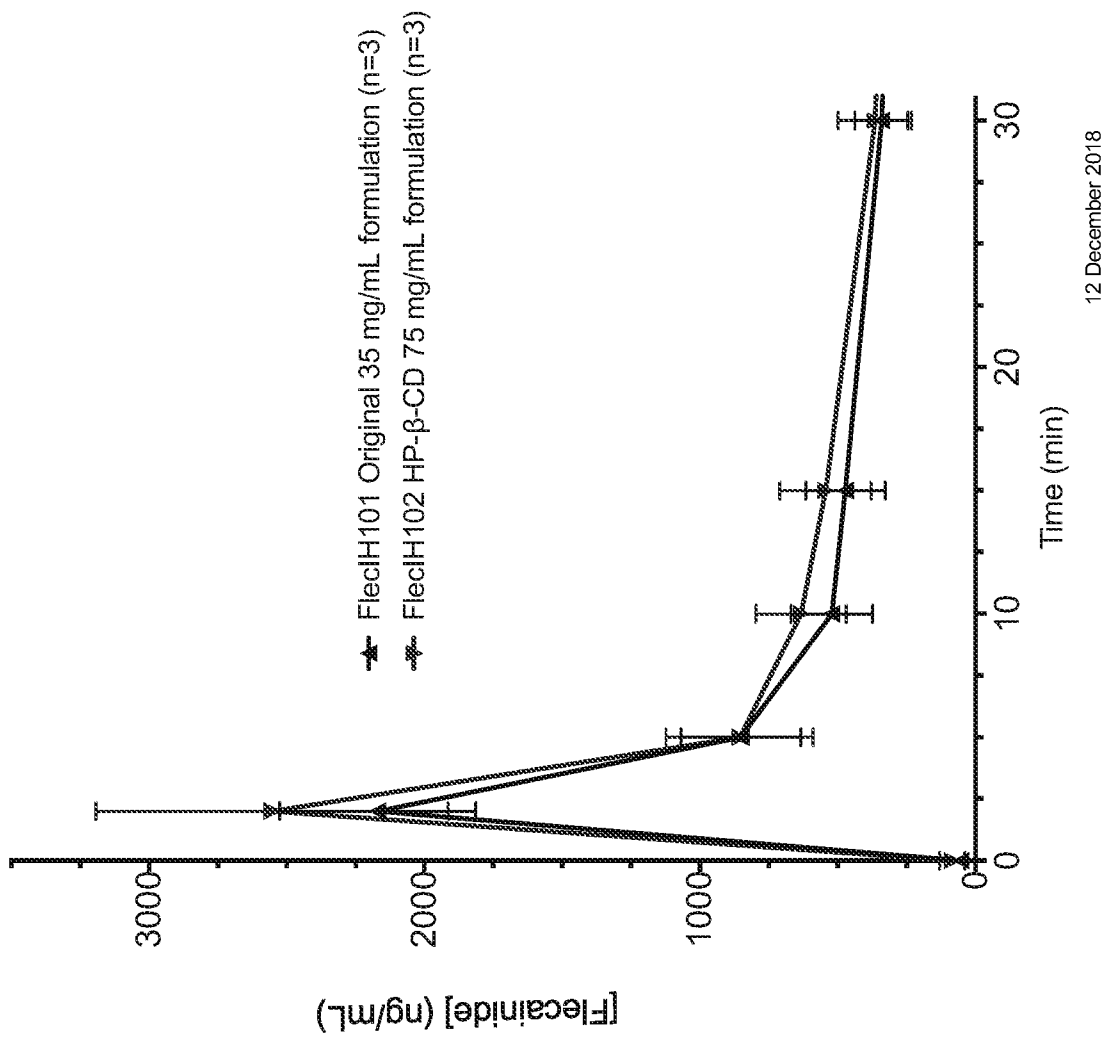
FlecIH101 Original 35 mg/mL formulation (n=3)
FlecIH102 HP-β-CD 75 mg/mL formulation (n=3)
[Flecainide] (ng/mL)
3000
2000
1000
0
0
10
20
30
Time (min)
12 December 2018

FIGURE 3B

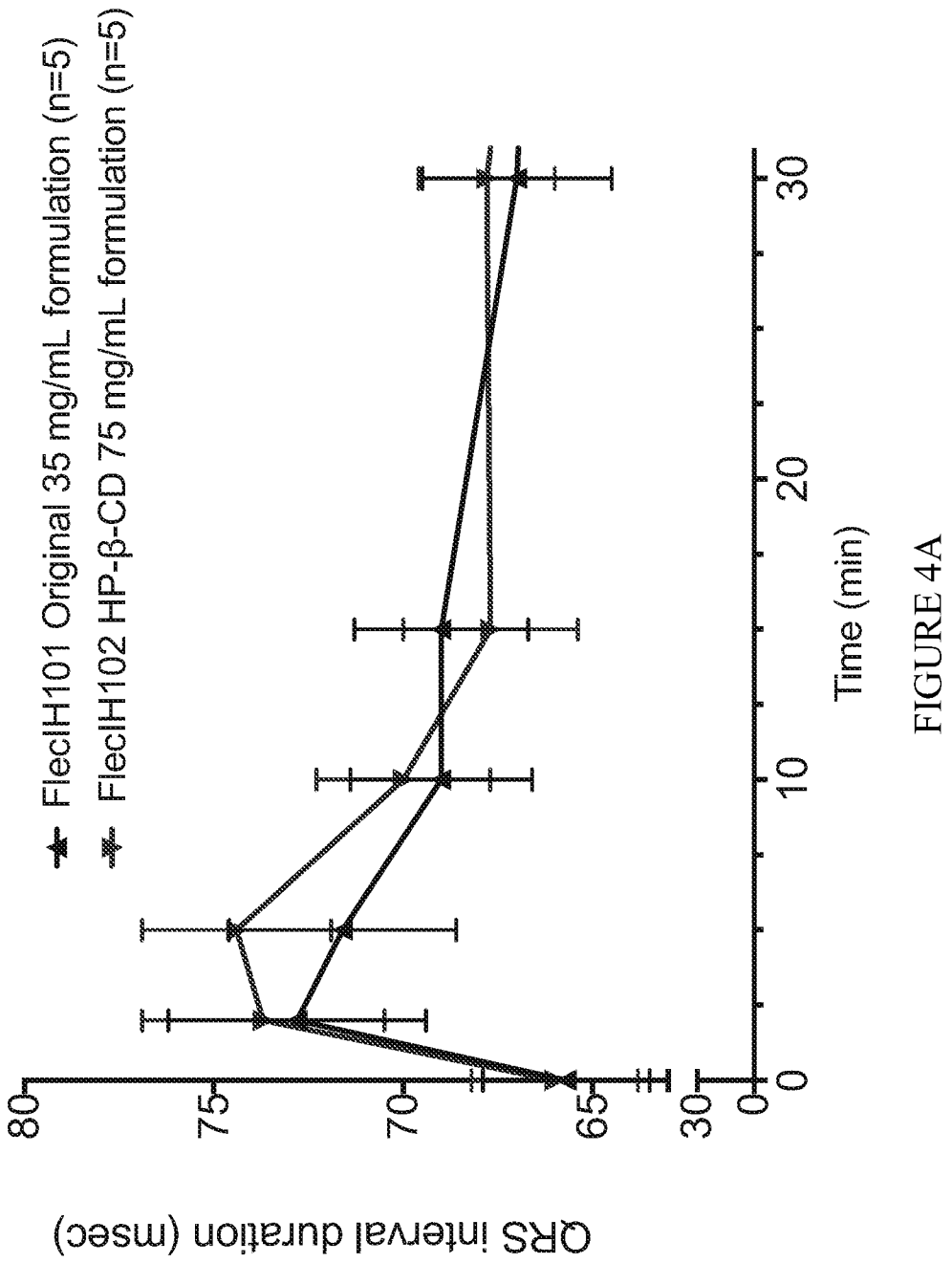
FlecIH101 Original 35 mg/mL formulation (n=5)
FlecIH102 HP-β-CD 75 mg/mL formulation (n=5)
QRS interval duration (msec)
80
75
70
65
30
0
0
10
20
30
Time (min)

FIGURE 4A

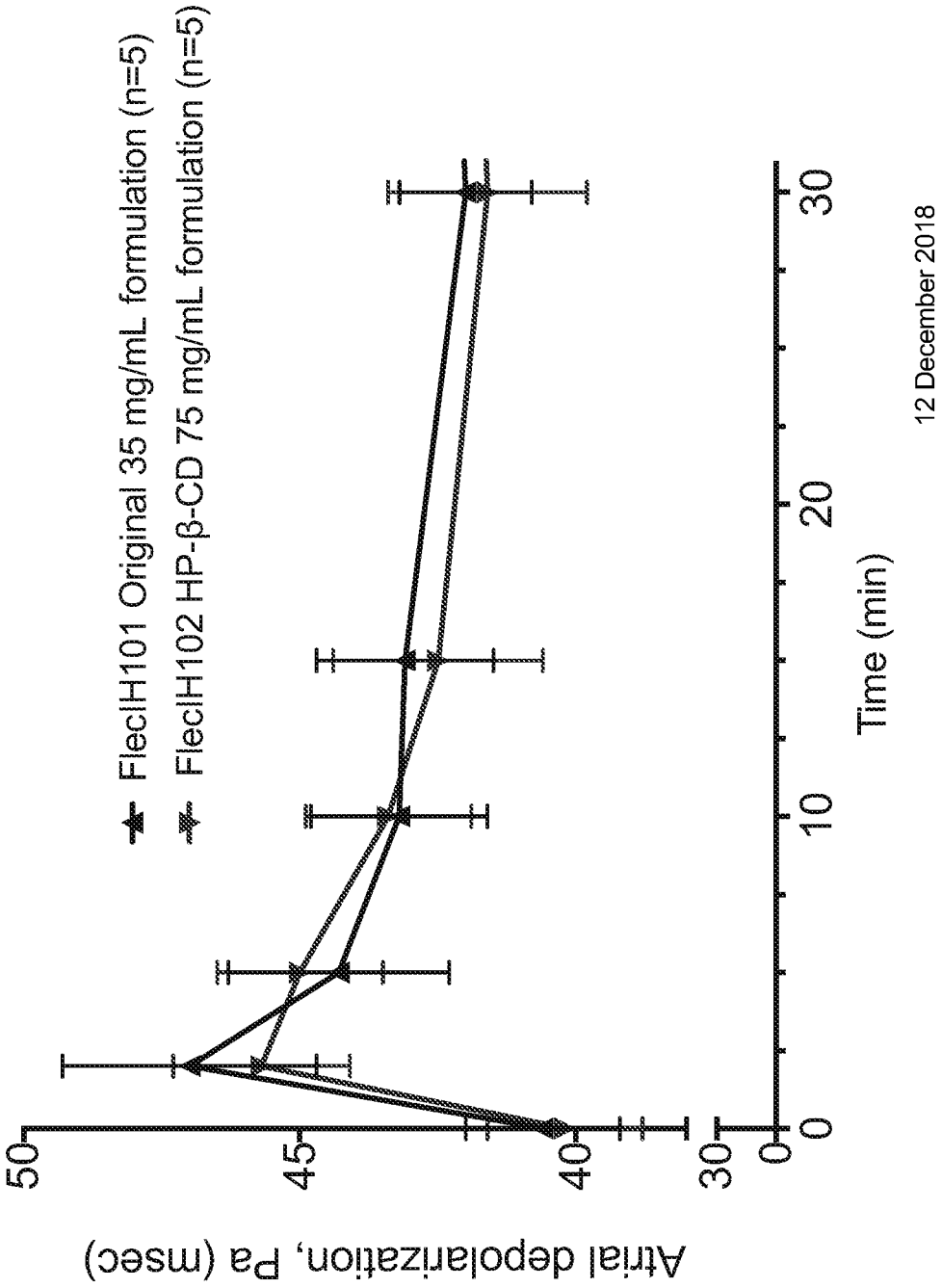
FlecIH101 Original 35 mg/mL formulation (n=5)
FlecIH102 HP-β-CD 75 mg/mL formulation (n=5)
Atrial depolarization, Pa (msec)
50
45
40
30
0
10
20
30
Time (min)
12 December 2018

FIGURE 4B

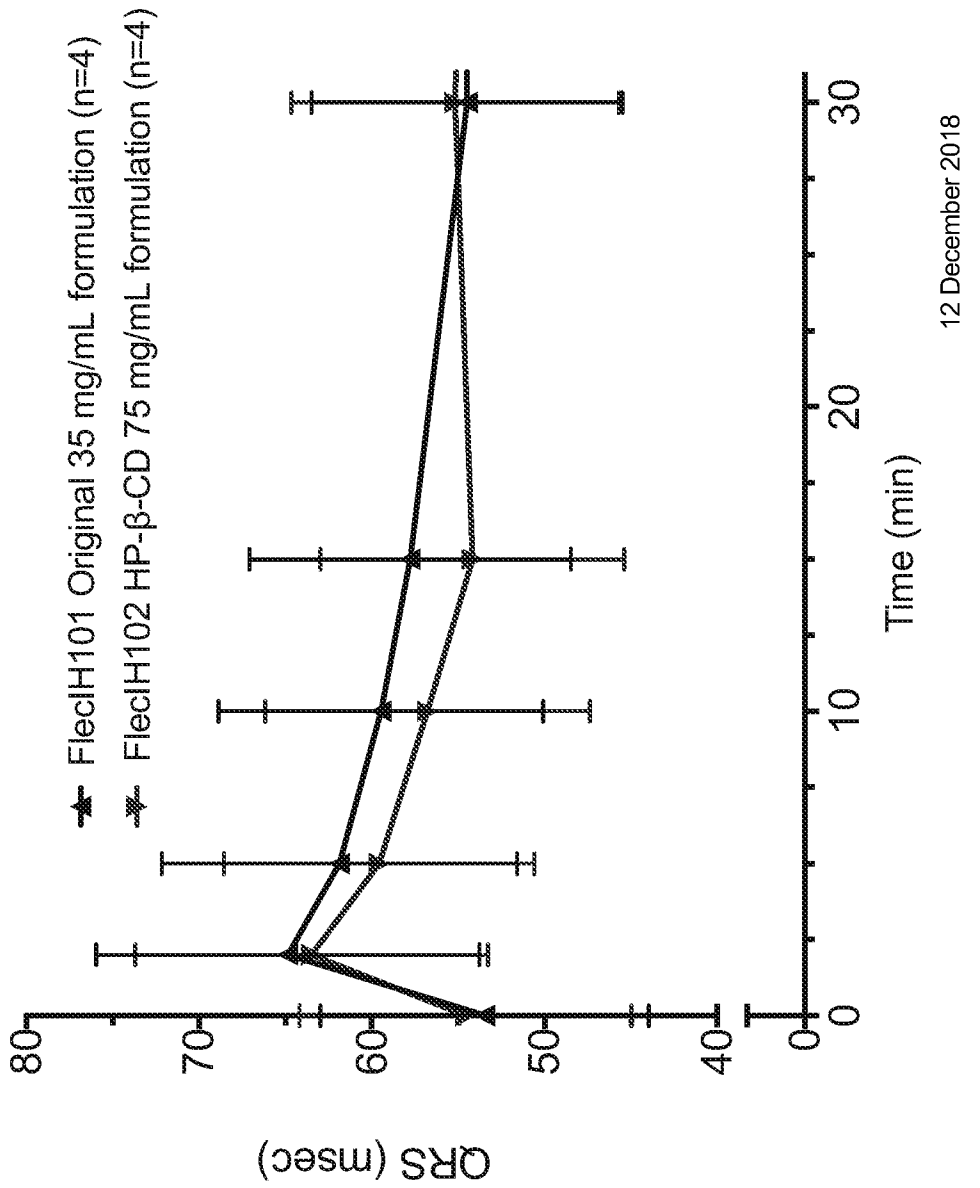
FlecIH101 Original 35 mg/mL formulation (n=4)
FlecIH102 HP-β-CD 75 mg/mL formulation (n=4)
QRS (msec)
80
70
60
50
40
0
10
20
30
Time (min)
12 December 2018

FIGURE 4C

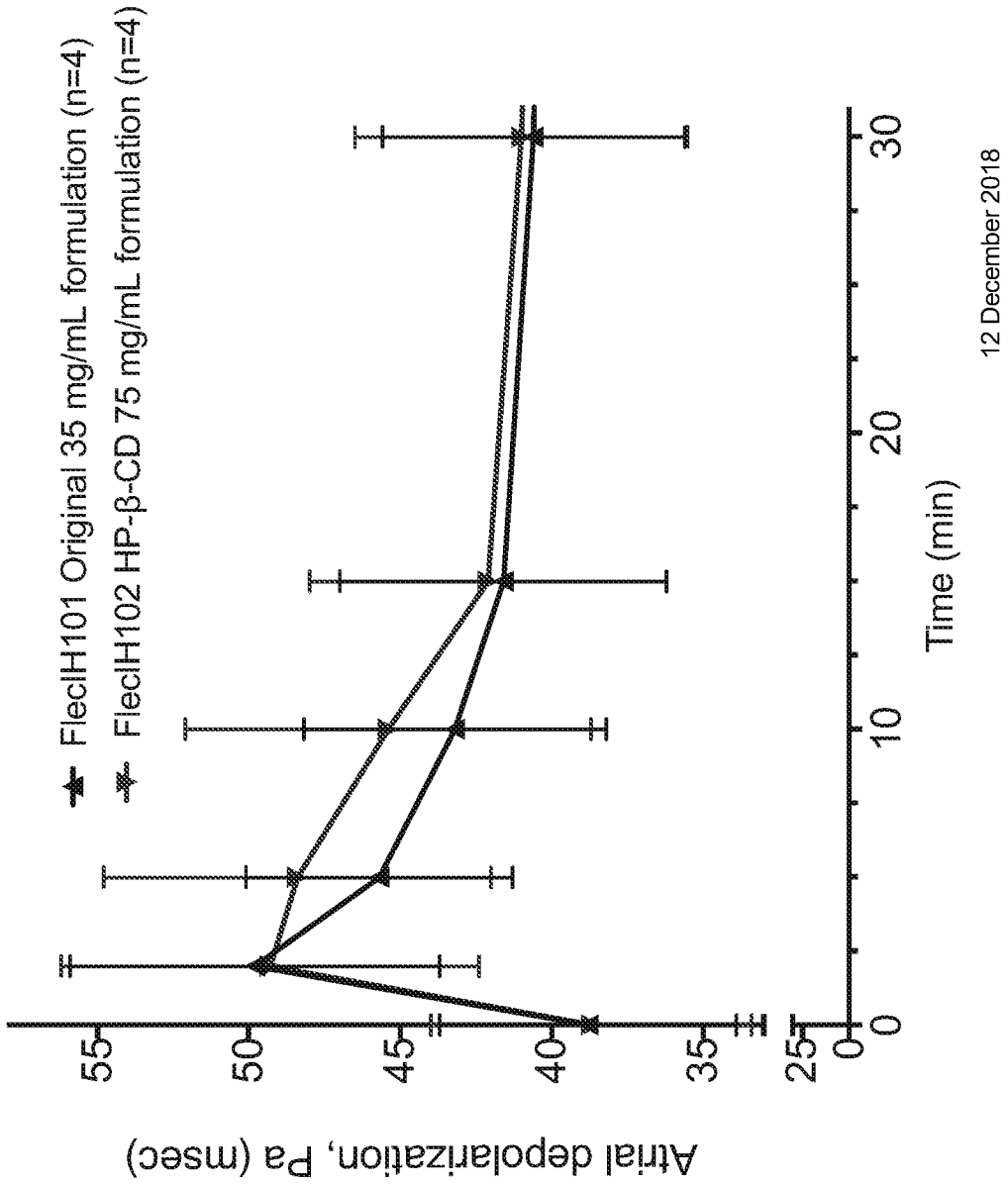
FlecIH101 Original 35 mg/mL formulation (n=4)
FlecIH102 HP-β-CD 75 mg/mL formulation (n=4)
Atrial depolarization, Pa (msec)
55
50
45
40
35
25
0
10
20
30
Time (min)
12 December 2018

FIGURE 4D

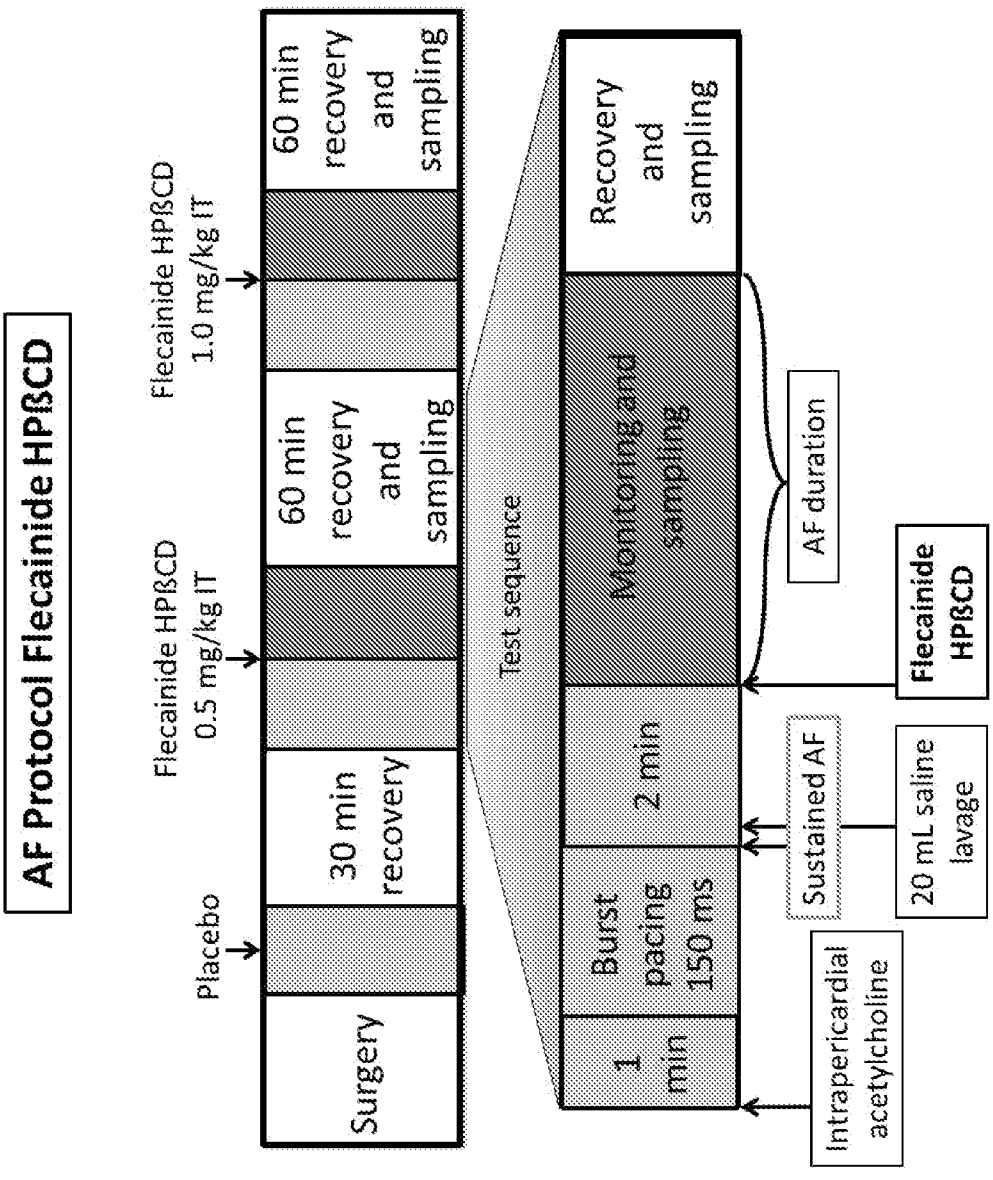
AF Protocol Flecainide HPßCD
Surgery
Placebo
30 min recovery
Flecainide HPßCD 0.5 mg/kg IT
60 min recovery and sampling
Flecainide HPßCD 1.0 mg/kg IT
60 min recovery and sampling
Test sequence
1 min
Burst pacing 150 ms
2 min
Monitoring and sampling
Recovery and sampling
Intrapericardial acetylcholine
Sustained AF
20 mL saline lavage
AF duration
Flecainide HPßCD

FIGURE 5

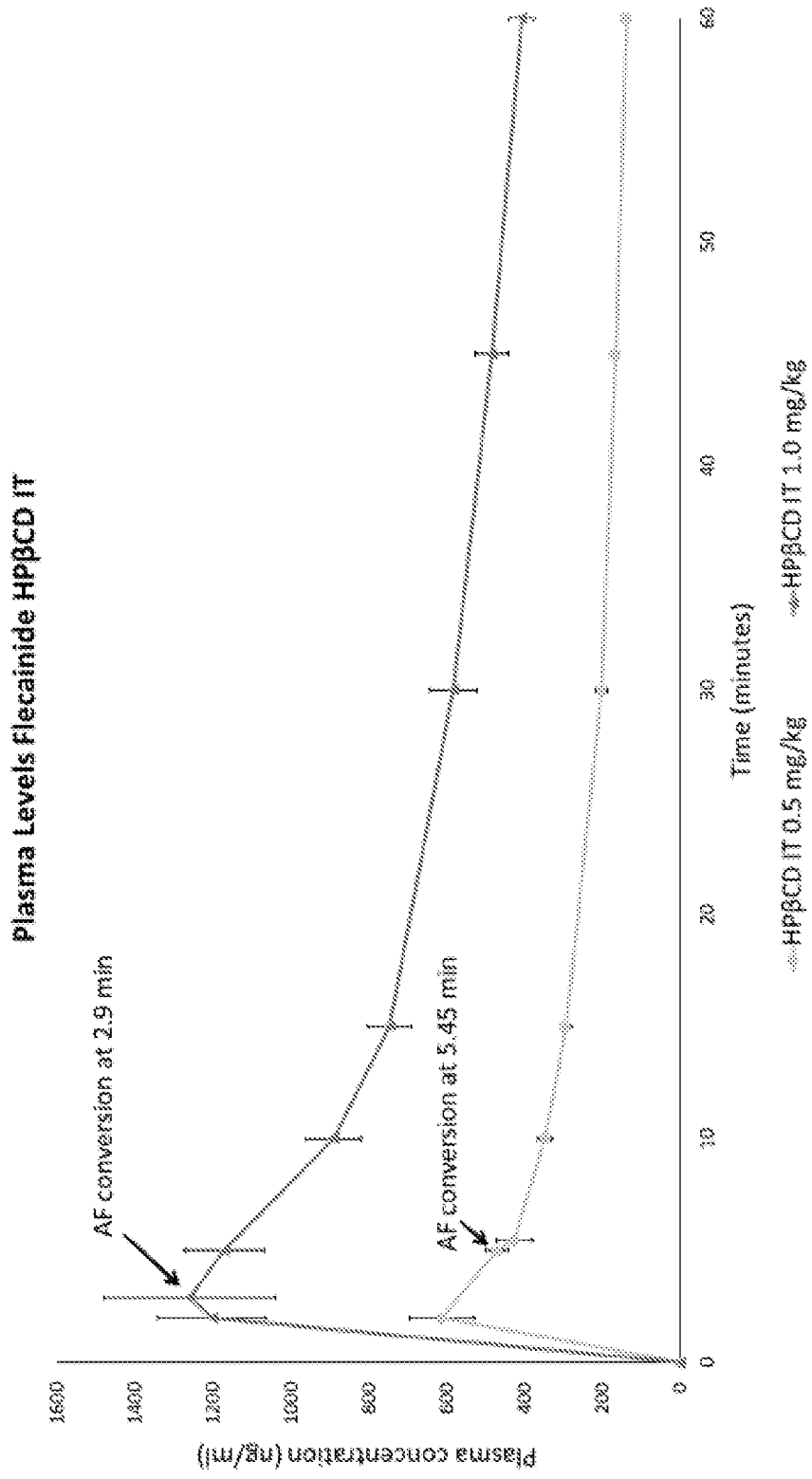
Plasma Levels Flecainide HPβCD IT
AF conversion at 2.9 min
AF conversion at 5.45 min
Plasma concentration (ng/ml)
Time (minutes)
HPβCD IT 0.5 mg/kg
HPβCD IT 1.0 mg/kg

FIGURE 6

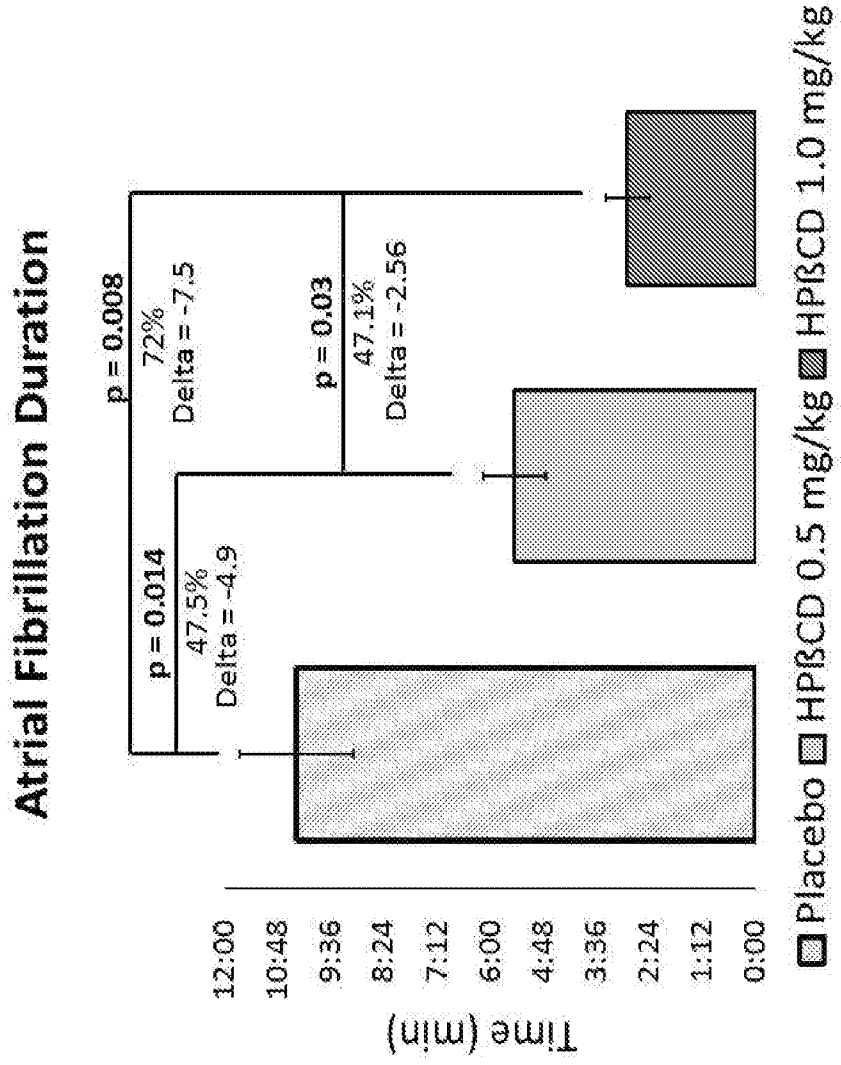
Atrial Fibrillation Duration
p = 0.008
72%
Delta = -7.5
p = 0.014
47.5%
Delta = -4.9
p = 0.03
47.1%
Delta = -2.56
Time (min)
12:00
10:48
9:36
8:24
7:12
6:00
4:48
3:36
2:24
1:12
0:00
Placebo
HPßCD 0.5 mg/kg
HPßCD 1.0 mg/kg

FIGURE 7

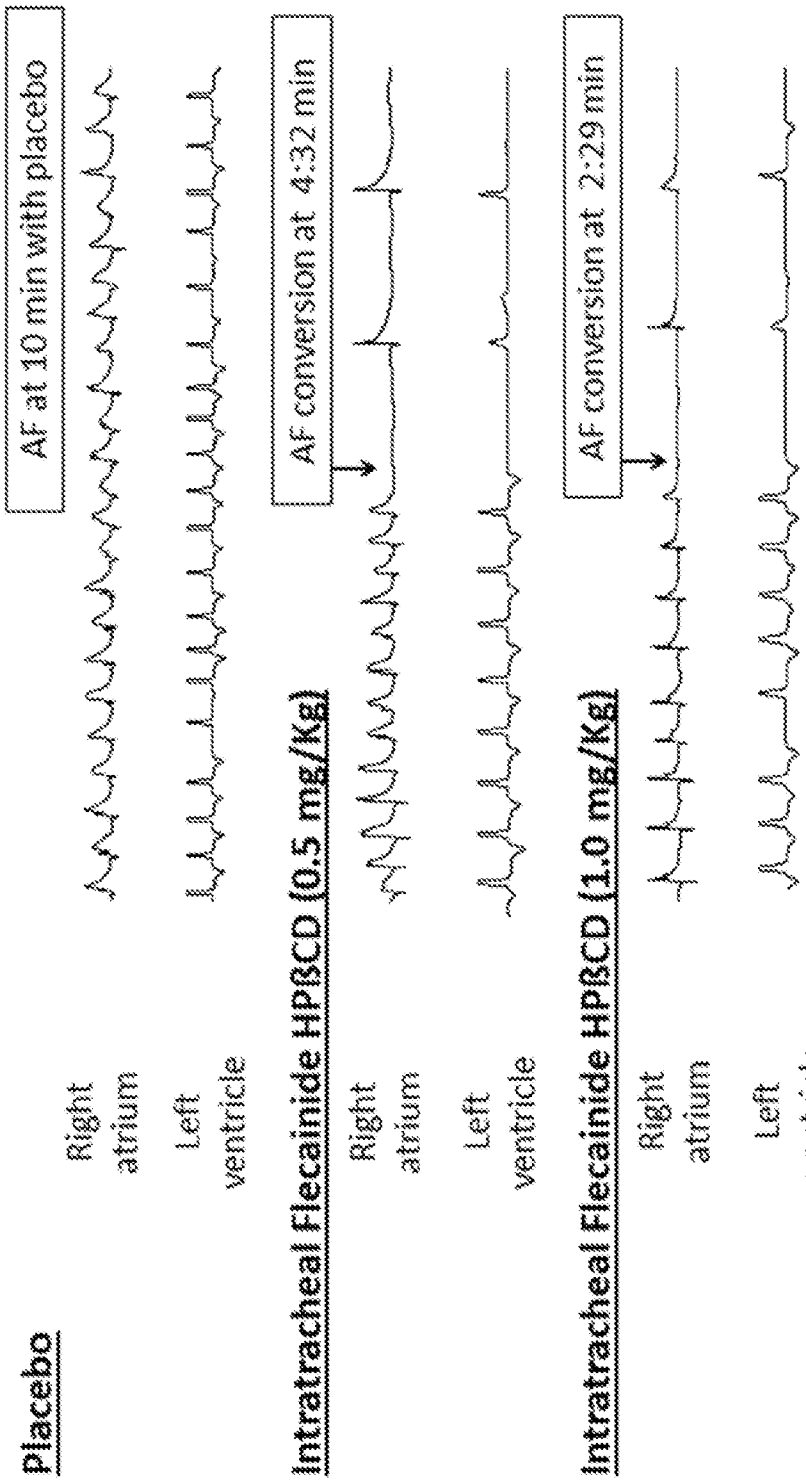
Placebo
AF at 10 min with placebo
Right atrium
Left ventricle
Intratracheal Flecainide HPβCD (0.5 mg/Kg)
AF conversion at 4:32 min
Right atrium
Left ventricle
Intratracheal Flecainide HPβCD (1.0 mg/Kg)
AF conversion at 2:29 min
Right atrium
Left ventricle

FIGURE 8

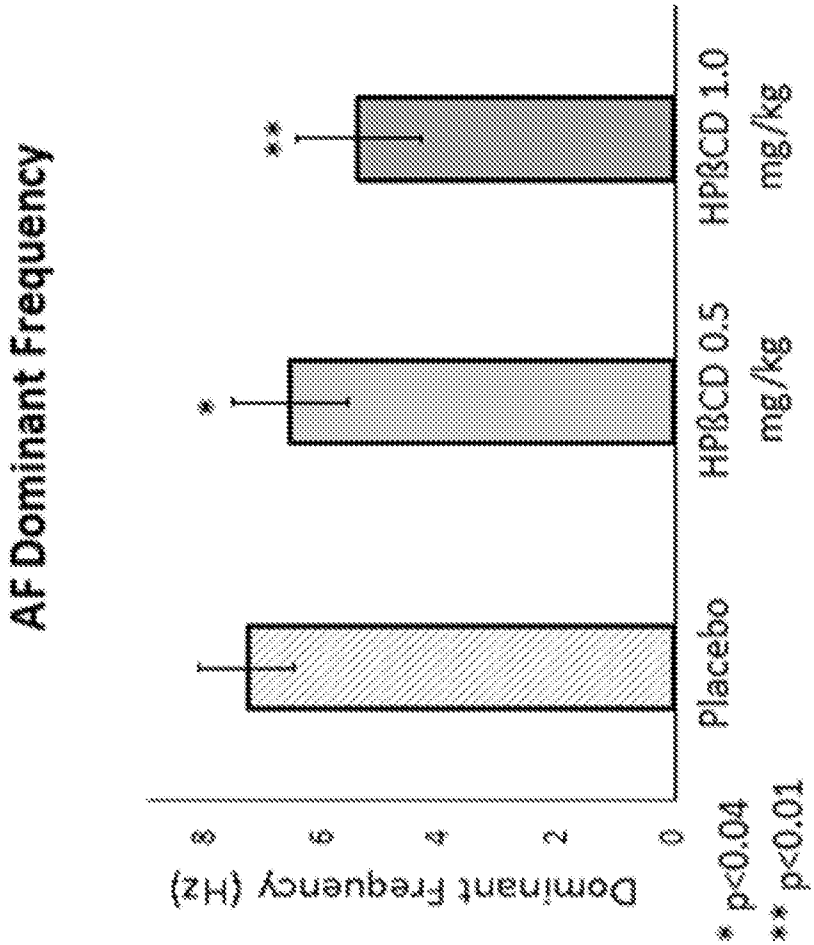
AF Dominant Frequency
Dominant Frequency (Hz)
0
2
4
6
8
*
**
Placebo
HPβCD 0.5 mg/kg
HPβCD 1.0 mg/kg
* p<0.04
** p<0.01

FIGURE 9

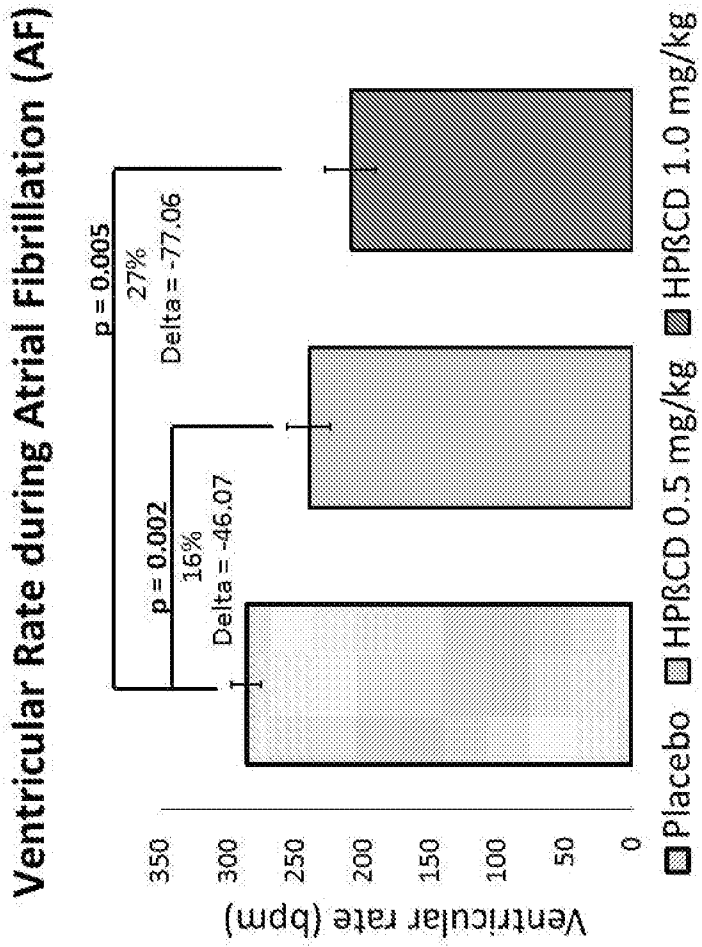
Ventricular Rate during Atrial Fibrillation (AF)
p = 0.005
27%
Delta = -77.06
p = 0.002
16%
Delta = -46.07
Ventricular rate (bpm)
350
300
250
200
150
100
50
0
Placebo
HPßCD 0.5 mg/kg
HPßCD 1.0 mg/kg

FIGURE 10

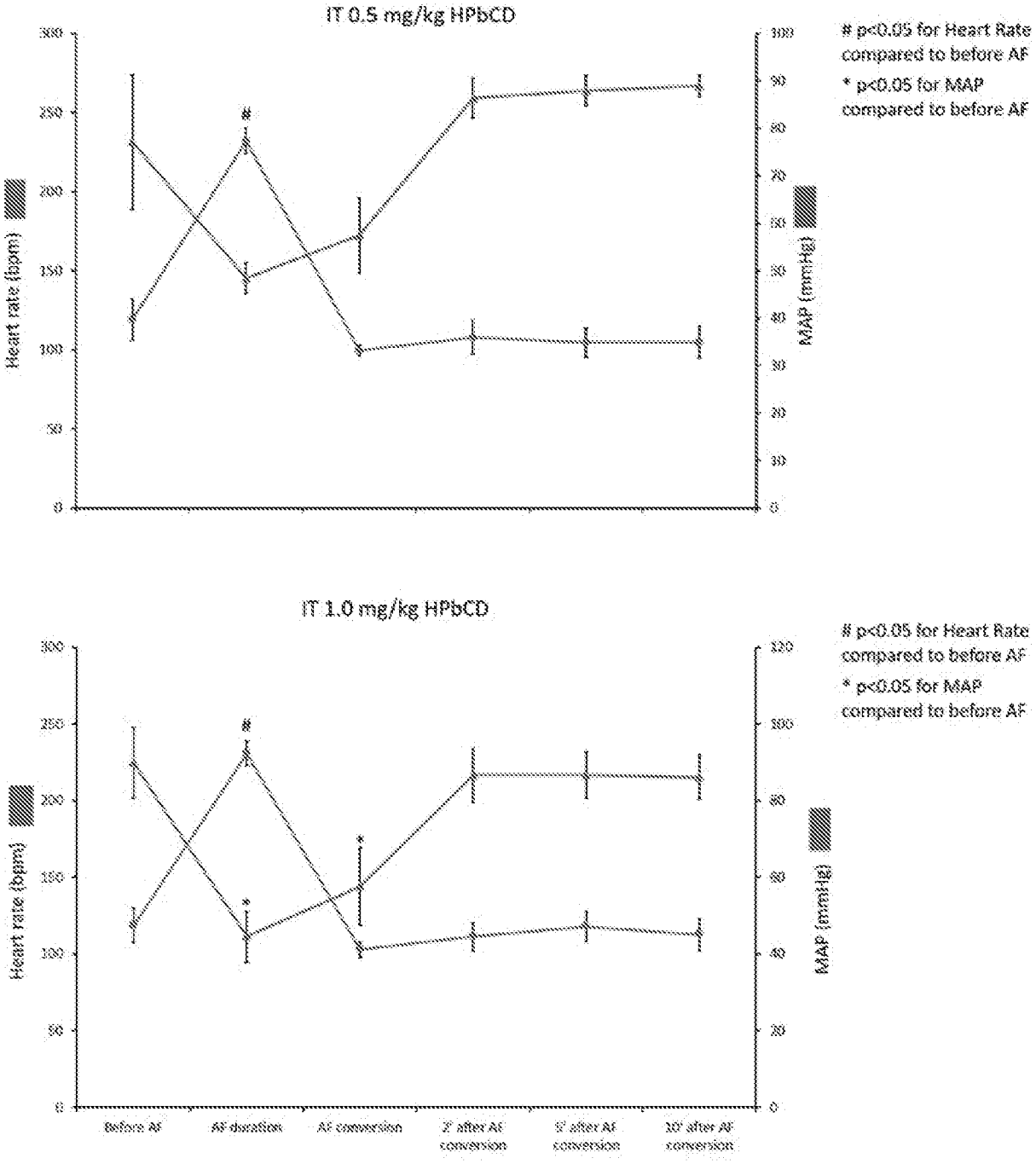
IT 0.5 mg/kg HPbCD
# p<0.05 for Heart Rate compared to before AF
* p<0.05 for MAP compared to before AF
Heart rate (bpm)
MAP (mmHg)
IT 1.0 mg/kg HPbCD
# p<0.05 for Heart Rate compared to before AF
* p<0.05 for MAP compared to before AF
Heart rate (bpm)
MAP (mmHg)
Before AF
AF duration
AF conversion
2' after AF conversion
5' after AF conversion
10' after AF conversion

FIGURE 11

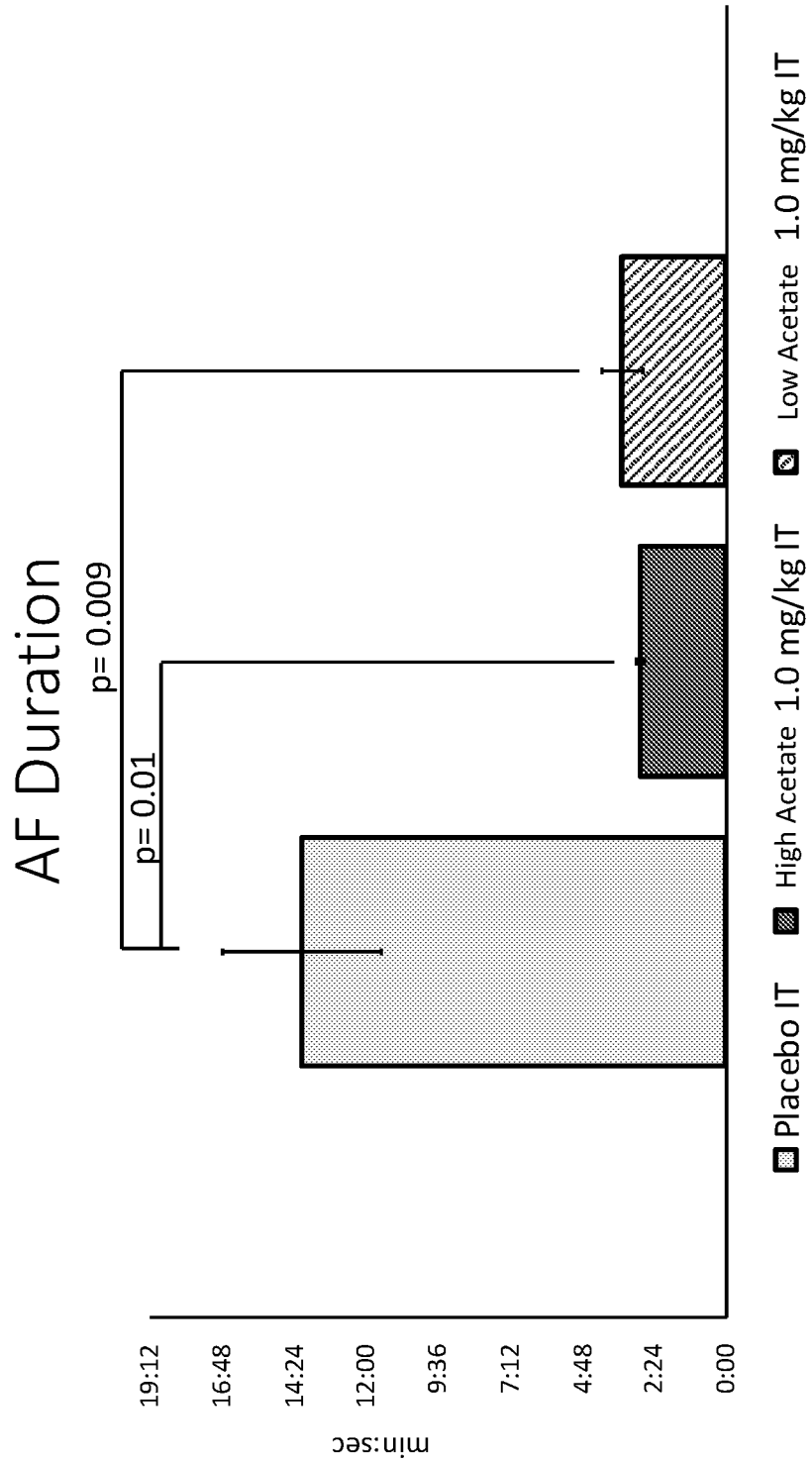
AF Duration
p= 0.009
p= 0.01
min:sec
19:12
16:48
14:24
12:00
9:36
7:12
4:48
2:24
0:00
Placebo IT
High Acetate 1.0 mg/kg IT
Low Acetate 1.0 mg/kg IT

FIGURE 12

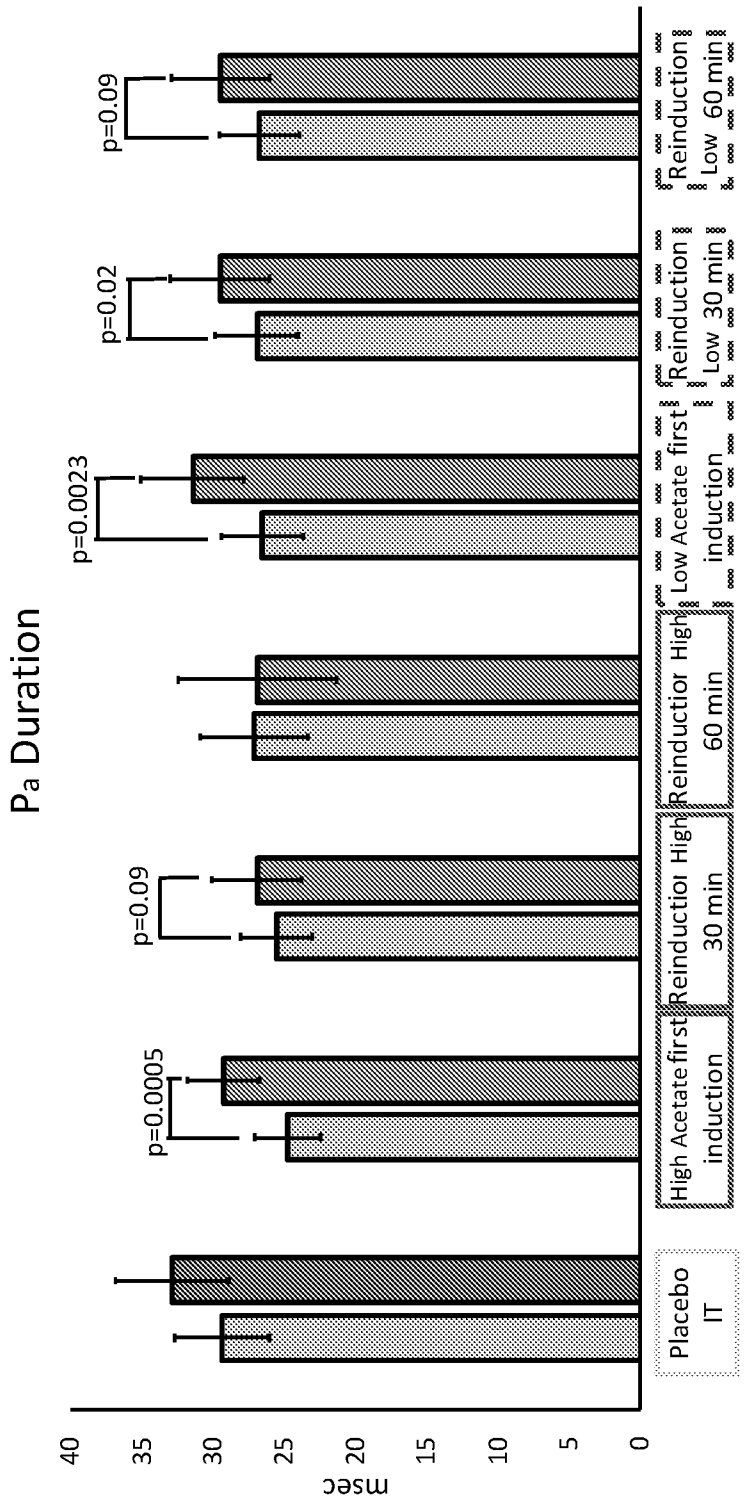
Pa Duration
msec
40
35
30
25
20
15
10
5
0
p=0.0005
p=0.09
p=0.0023
p=0.02
p=0.09
Placebo
IT
High Acetate first induction
High Reinduction 30 min
High Reinduction 60 min
Low Acetate first induction
Low Reinduction 30 min
Low Reinduction 60 min
before af
AF conversion

FIGURE 13

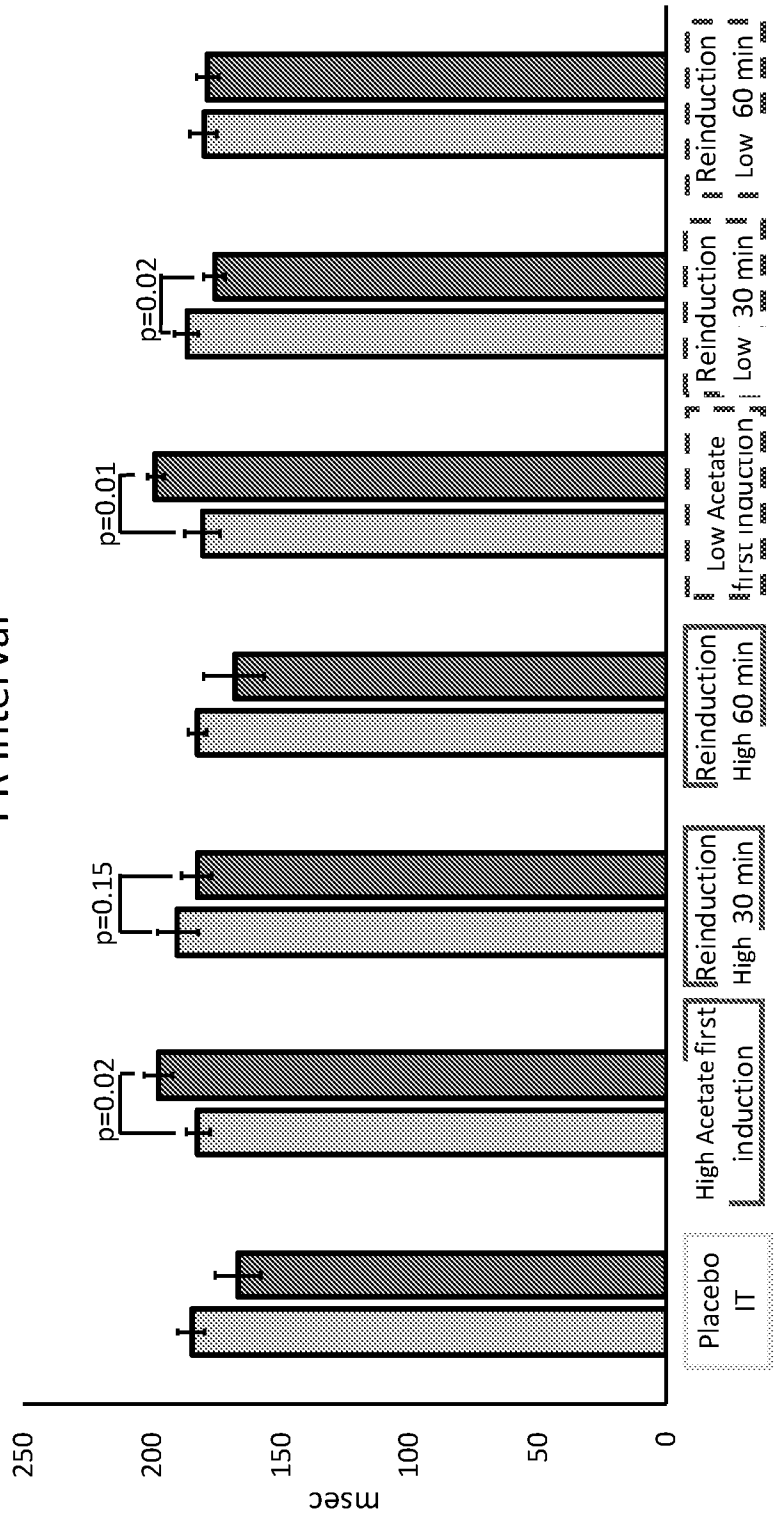
PR Interval
msec
250
200
150
100
50
0
p=0.02
p=0.15
p=0.01
p=0.02
Placebo IT
High Acetate first induction
Reinduction High 30 min
Reinduction High 60 min
Low Acetate first induction
Reinduction Low 30 min
Reinduction Low 60 min
Before AF
AF conversion

FIGURE 14

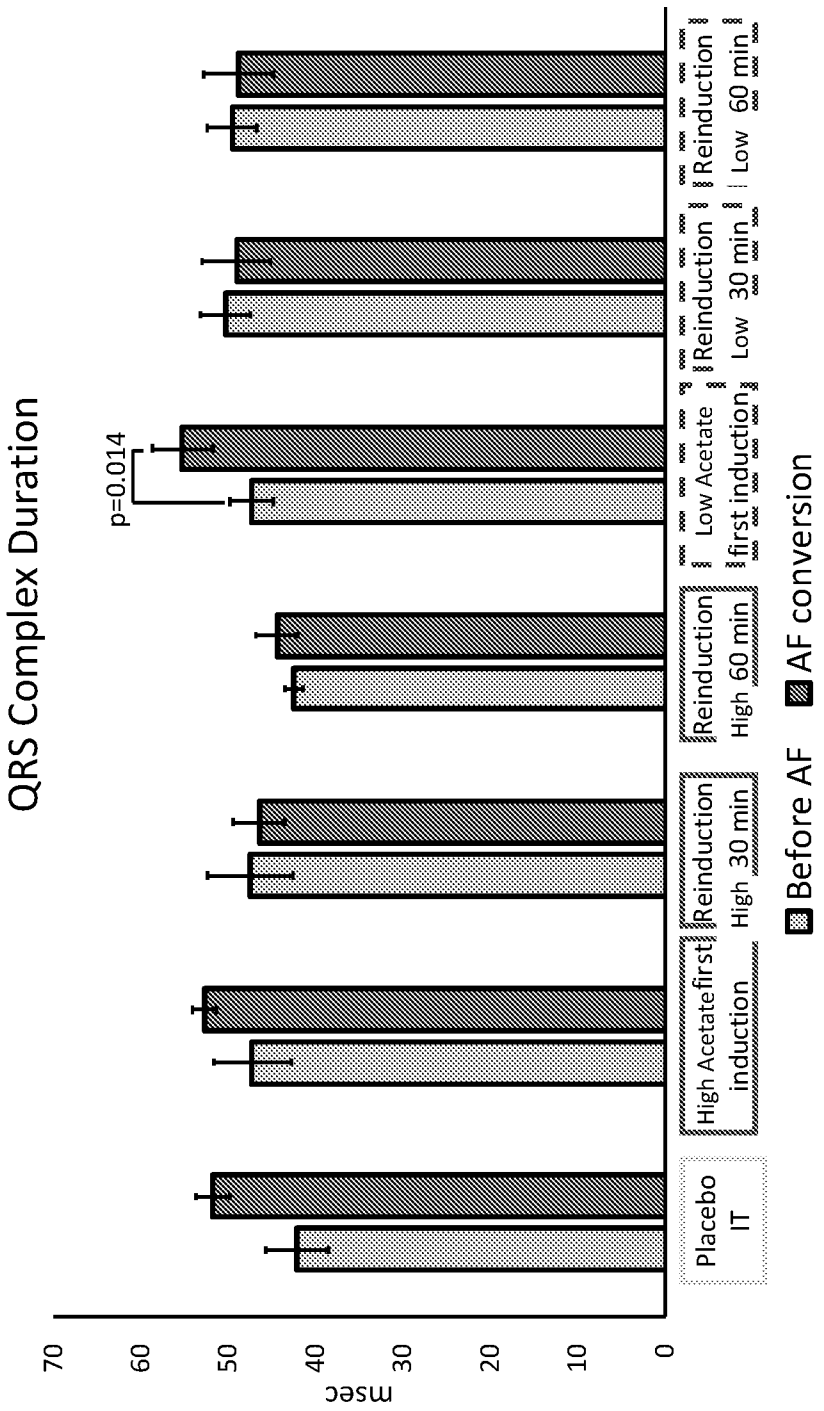
QRS Complex Duration
msec
70
60
50
40
30
20
10
0
p=0.014
Placebo
IT
High Acetate first induction
Reinduction High 30 min
Reinduction High 60 min
Low Acetate first induction
Reinduction Low 30 min
Reinduction Low 60 min
Before AF
AF conversion

FIGURE 15

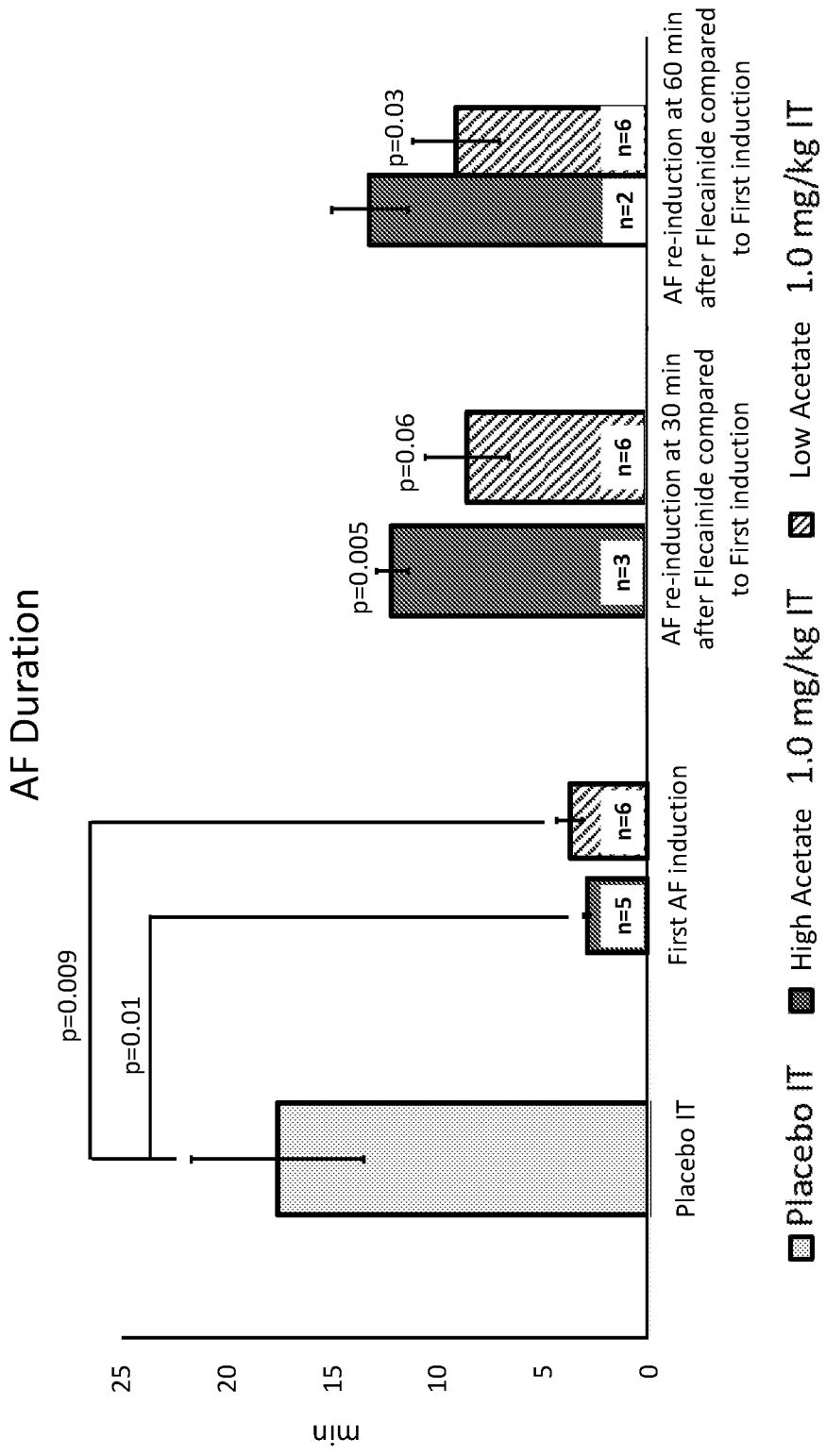
AF Duration
min
25
20
15
10
5
0
p=0.009
p=0.01
p=0.005
p=0.06
p=0.03
n=5
n=6
n=3
n=6
n=2
n=6
Placebo IT
First AF induction
AF re-induction at 30 min after Flecainide compared to First induction
AF re-induction at 60 min after Flecainide compared to First induction
Placebo IT
High Acetate 1.0 mg/kg IT
Low Acetate 1.0 mg/kg IT

FIGURE 16

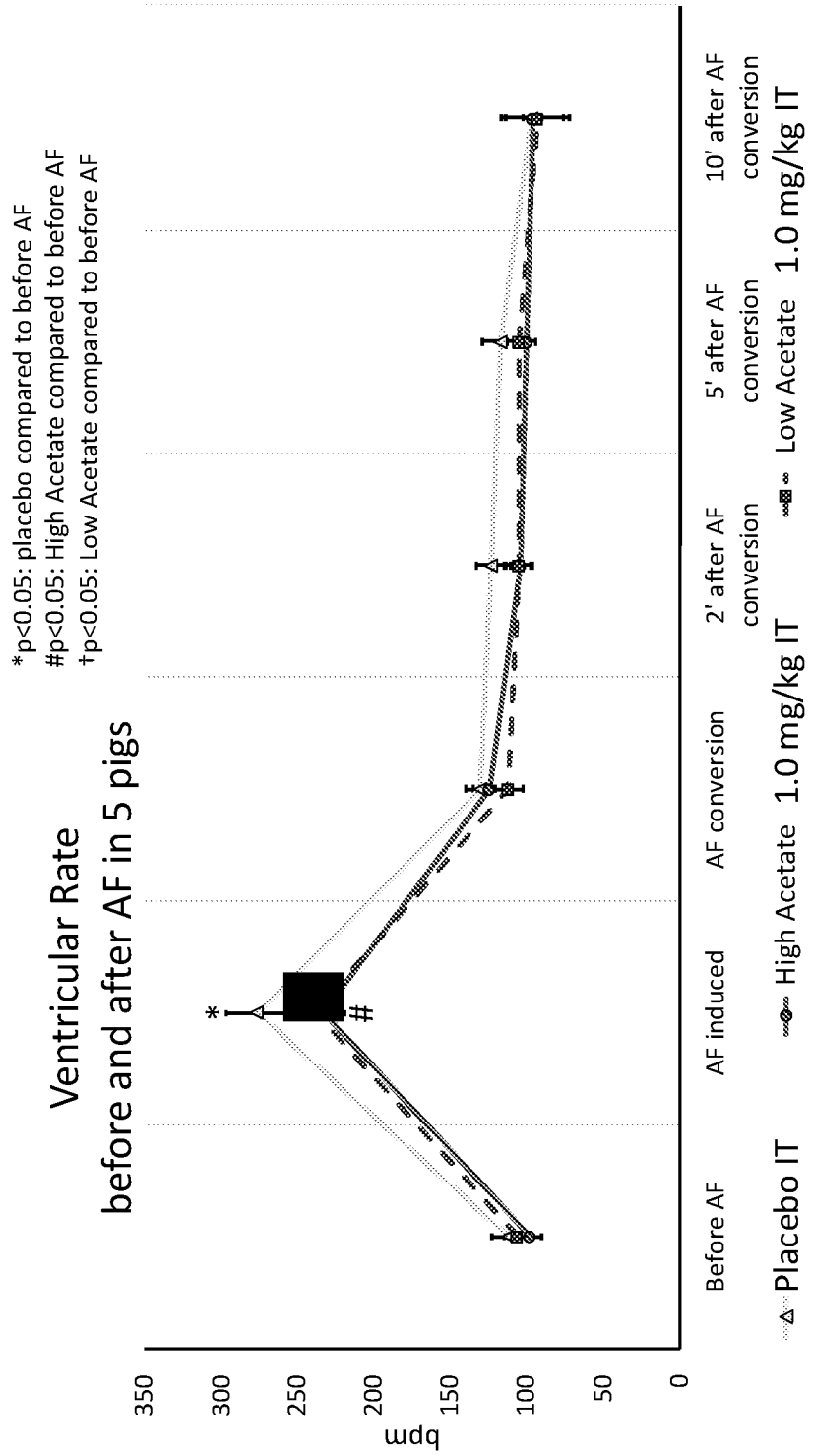
*p<0.05: placebo compared to before AF
#p<0.05: High Acetate compared to before AF
†p<0.05: Low Acetate compared to before AF
Ventricular Rate
before and after AF in 5 pigs
bpm
350
300
250
200
150
100
50
0
*
#
Before AF
AF induced
AF conversion
2' after AF conversion
5' after AF conversion
10' after AF conversion
Placebo IT
High Acetate 1.0 mg/kg IT
Low Acetate 1.0 mg/kg IT

FIGURE 17

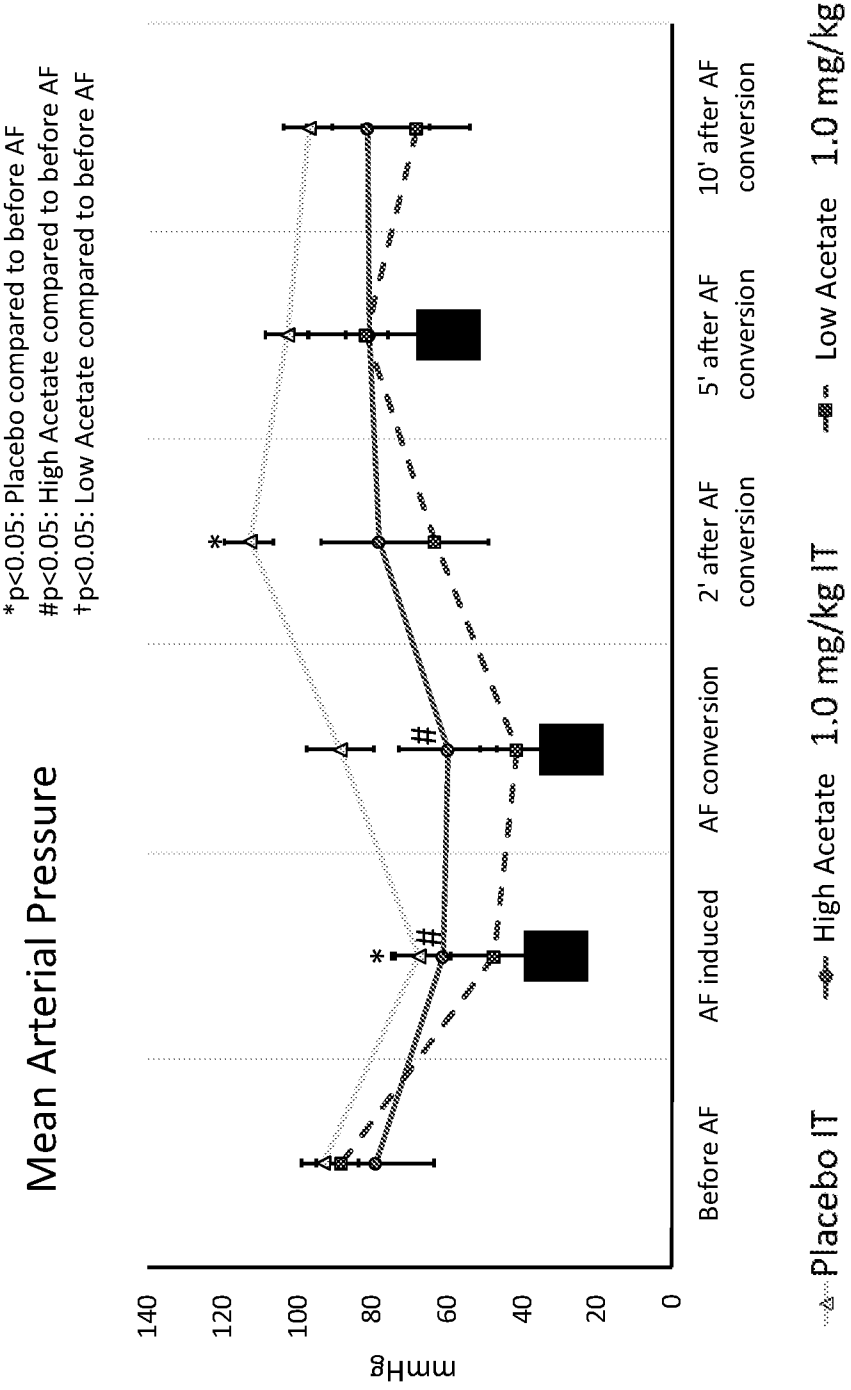
Mean Arterial Pressure
*p<0.05: Placebo compared to before AF
#p<0.05: High Acetate compared to before AF
†p<0.05: Low Acetate compared to before AF
mmHg
140
120
100
80
60
40
20
0
Before AF
AF induced
AF conversion
2' after AF conversion
5' after AF conversion
10' after AF conversion
Placebo IT
High Acetate 1,0 mg/kg IT
Low Acetate 1.0 mg/kg IT

FIGURE 18

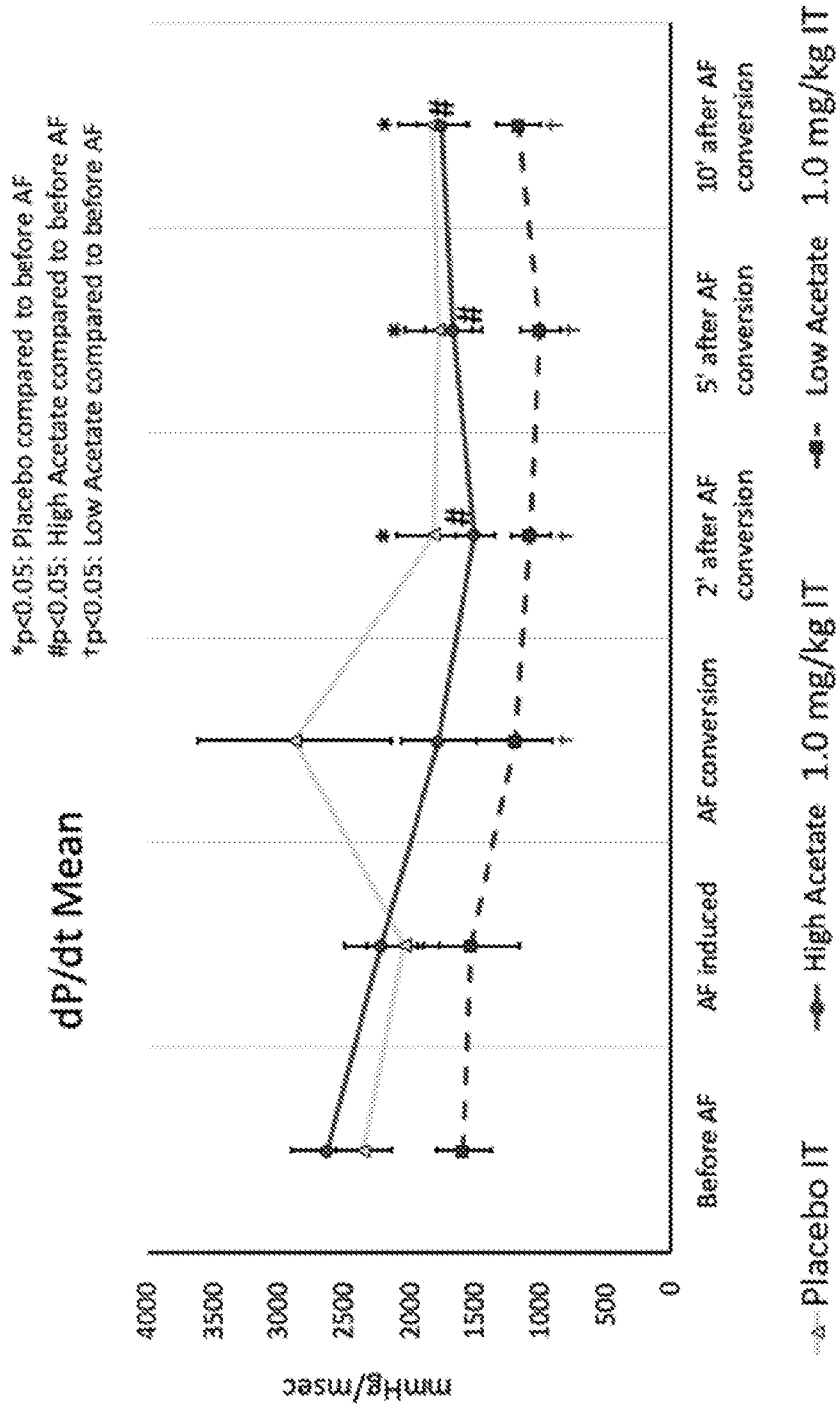
dP/dt Mean
*p<0.05: Placebo compared to before AF
#p<0.05: High Acetate compared to before AF
†p<0.05: Low Acetate compared to before AF
mmHg/msec
4000
3500
3000
2500
2000
1500
1000
500
0
Before AF
AF induced
AF conversion
2' after AF conversion
5' after AF conversion
10' after AF conversion
Placebo IT
High Acetate 1.0 mg/kg IT
Low Acetate 1.0 mg/kg IT

FIGURE 19

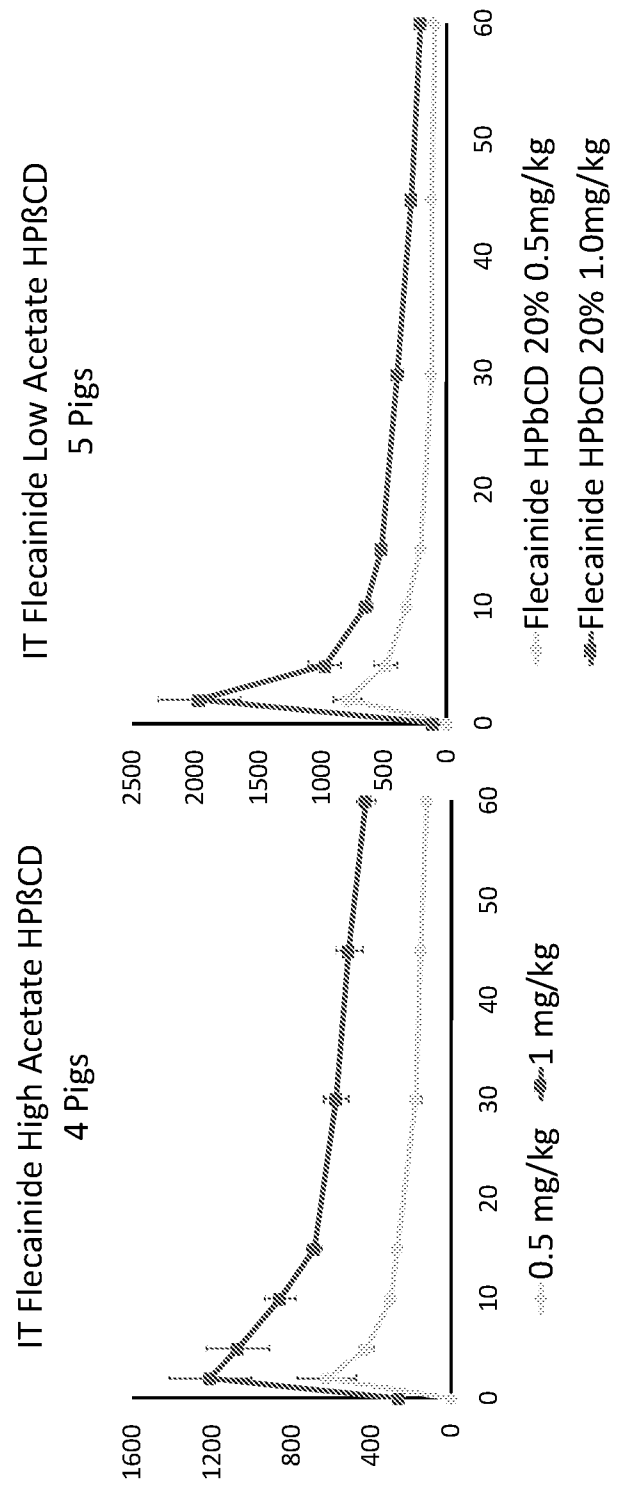
IT Flecainide High Acetate HPßCD
4 Pigs
IT Flecainide Low Acetate HPßCD
5 Pigs
1600
1200
800
400
0
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
0.5 mg/kg
1 mg/kg
Flecainide HPbCD 20% 0.5mg/kg
Flecainide HPbCD 20% 1.0mg/kg

FIGURE 20

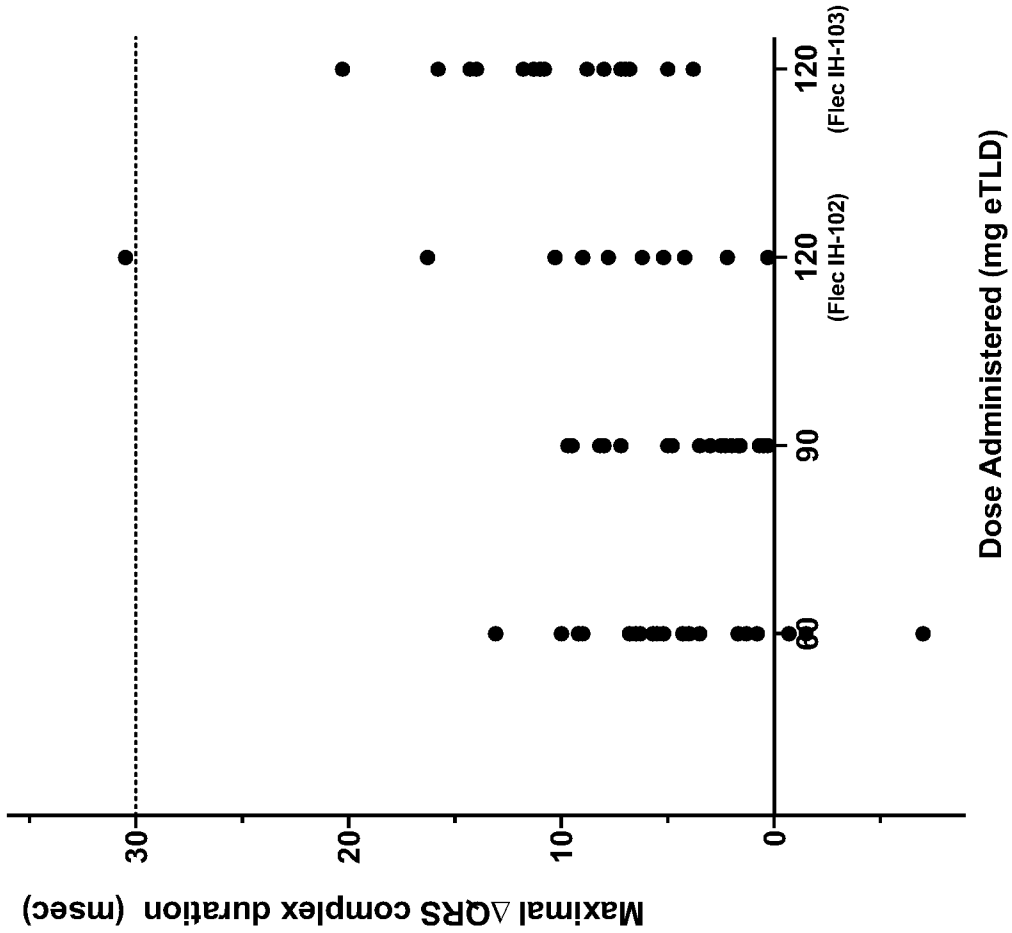
Maximal ΔQRS complex duration (msec)
30
20
10
0
60
90
120
(Flec IH-102)
120
(Flec IH-103)
Dose Administered (mg eTLD)

FIGURE 21

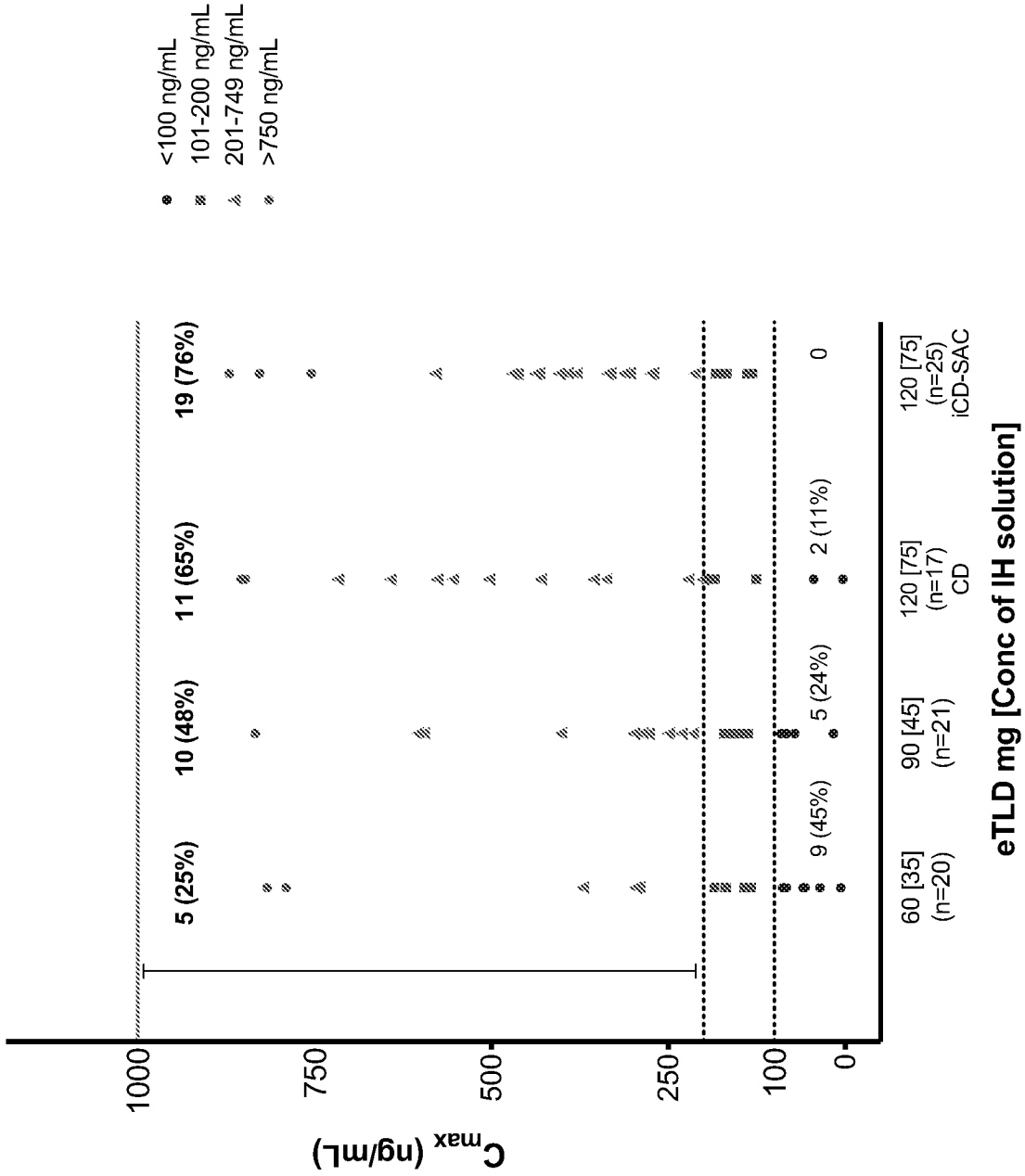
● <100 ng/mL
▨ 101-200 ng/mL
▨ 201-749 ng/mL
▨ >750 ng/mL
1000
750
500
250
100
0
C_{max} (ng/mL)
5 (25%)
10 (48%)
11 (65%)
19 (76%)
9 (45%)
5 (24%)
2 (11%)
0
60 [35] (n=20)
90 [45] (n=21)
120 [75] (n=17) CD
120 [75] (n=25) iCD-SAC
eTLD mg [Conc of IH solution]

FIGURE 22A

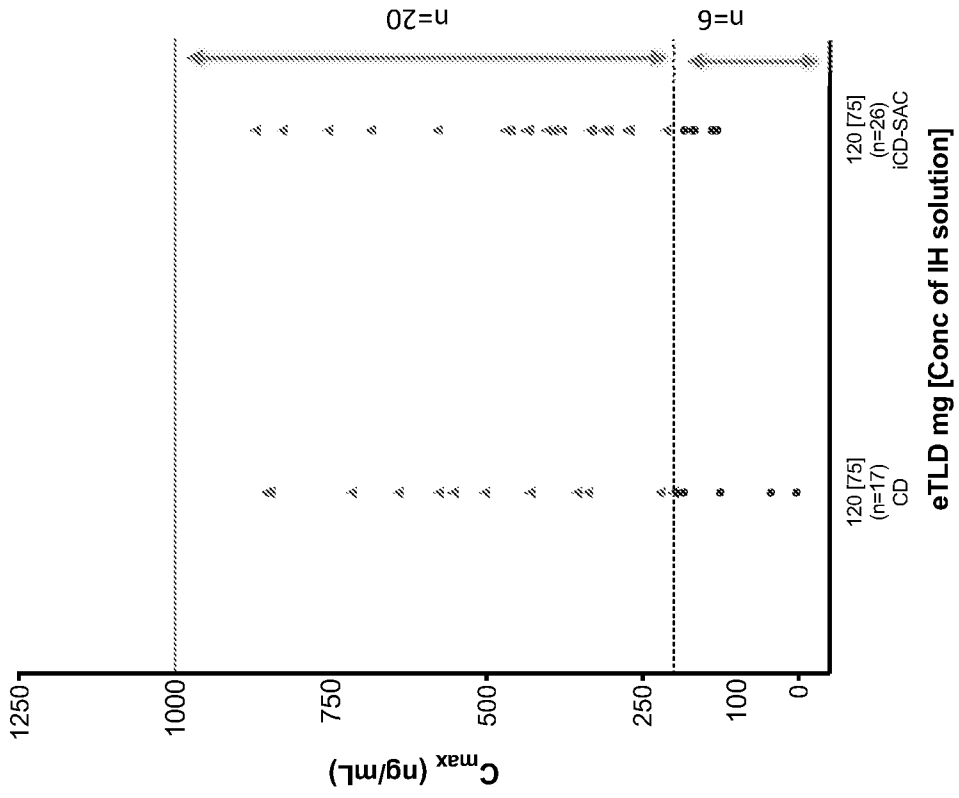
1250
1000
750
500
250
100
0
C_{max} (ng/mL)
n=20
n=6
120 [75] (n=17) CD
120 [75] (n=26) iCD-SAC
eTLD mg [Conc of IH solution]

FIGURE 22B

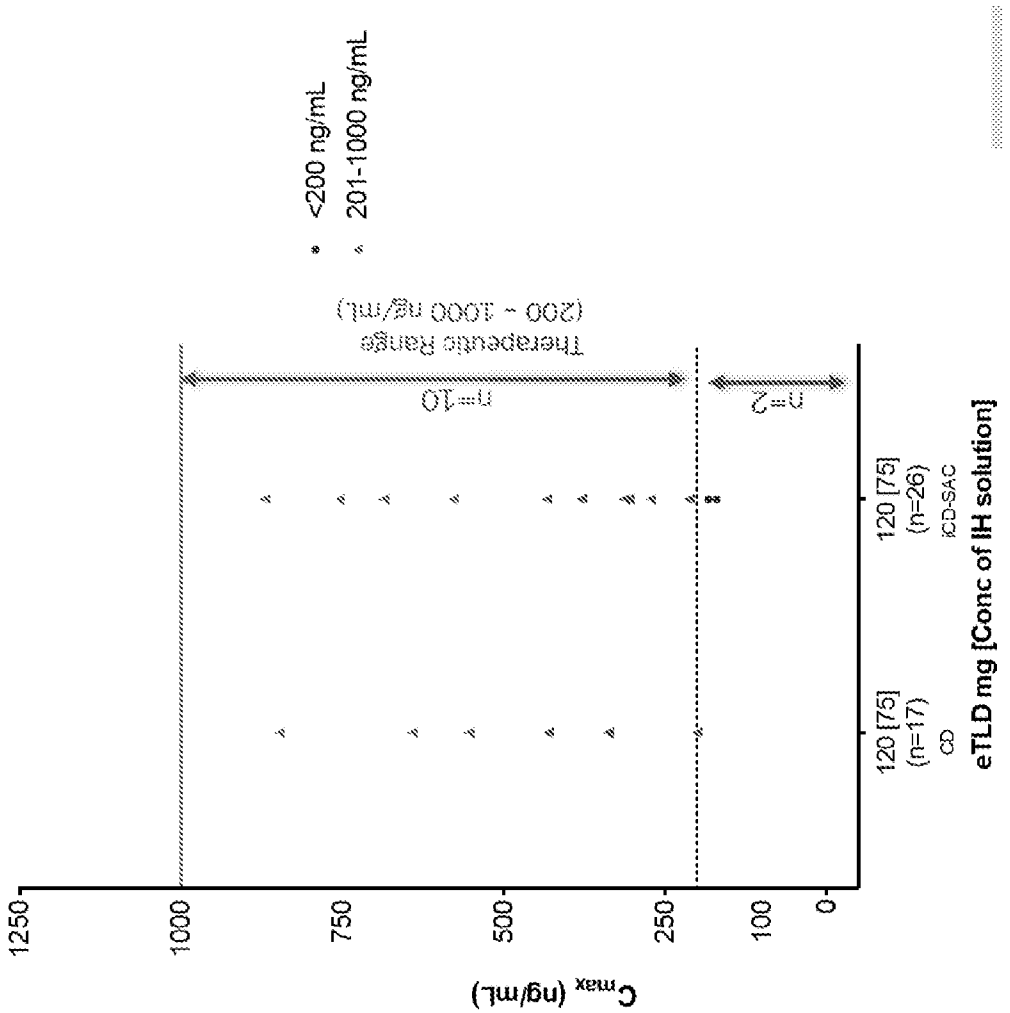
1250
1000
750
500
250
100
0
C_{max} (ng/mL)
<200 ng/mL
201-1000 ng/mL
Therapeutic Range
(200 ~ 1000 ng/mL)
n=10
n=2
120 [75]
(n=17)
CD
120 [75]
(n=26)
iCD-SAC
eTLD mg [Conc of IH solution]

FIGURE 22C

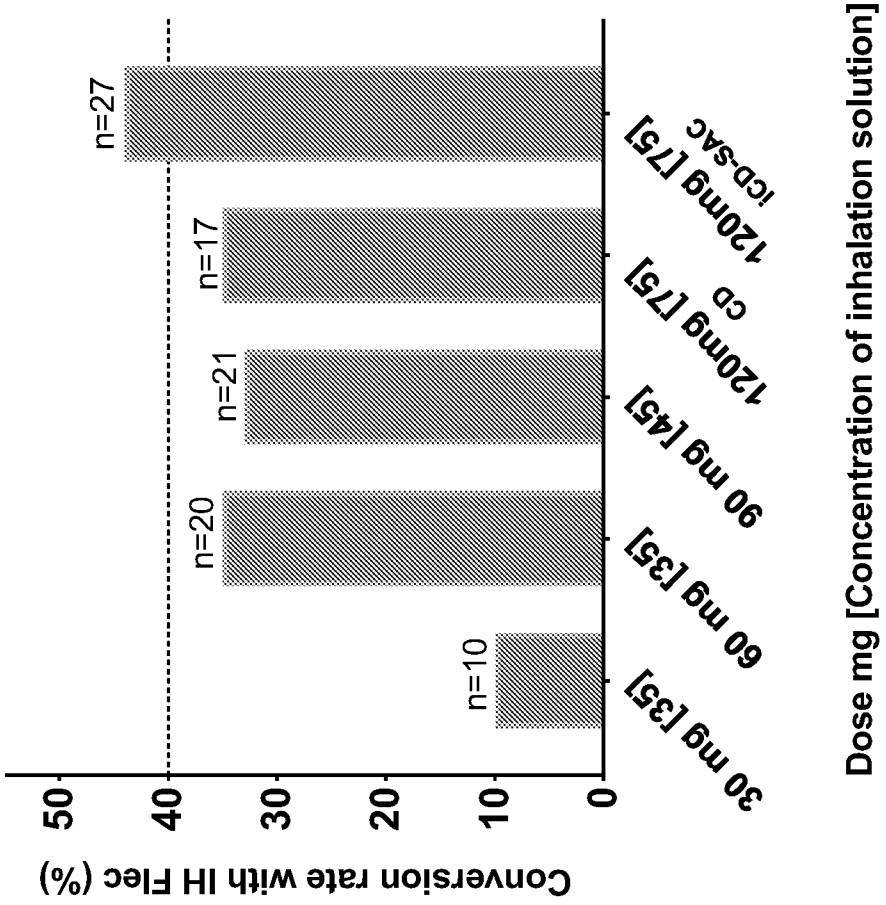
Conversion rate with IH Flec (%)
0
10
20
30
40
50
n=10
n=20
n=21
n=17
n=27
30 mg [35]
60 mg [35]
90 mg [45]
120mg [75] CD
120mg [75] iCD-SAC
Dose mg [Concentration of inhalation solution]

FIGURE 23A

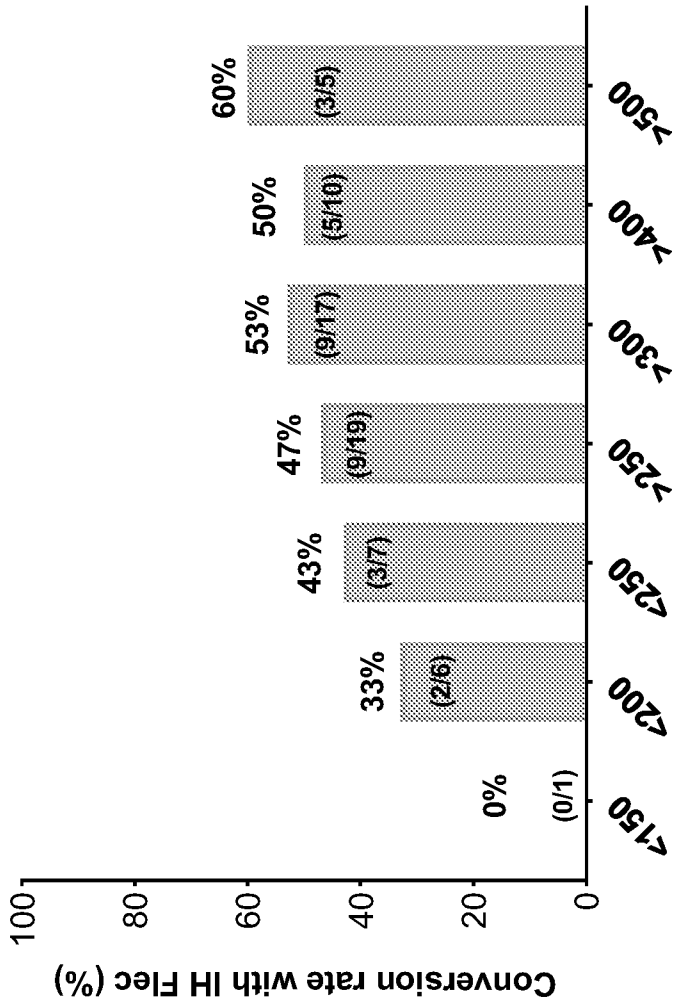
Conversion rate with IH Flec (%)
100
80
60
40
20
0
0%
(0/1)
33%
(2/6)
43%
(3/7)
47%
(9/19)
53%
(9/17)
50%
(5/10)
60%
(3/5)
≤150
≤200
≤250
≤250
≤300
≤400
≤500
Cmax cut-off (ng/mL)

FIGURE 23B

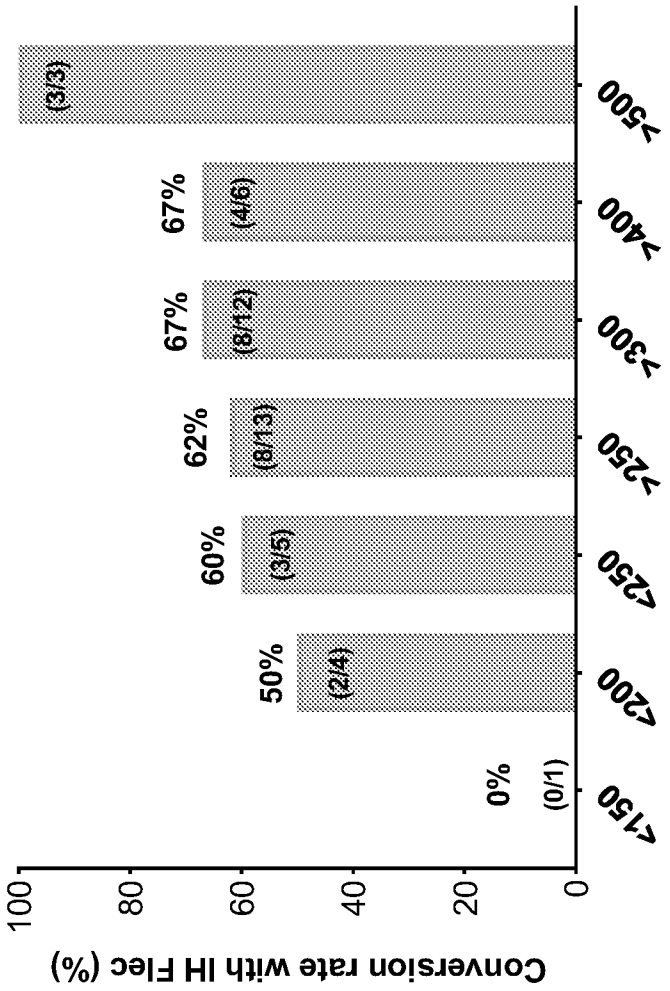
Conversion rate with IH Flec (%)
100
80
60
40
20
0
0%
(0/1)
50%
(2/4)
60%
(3/5)
62%
(8/13)
67%
(8/12)
67%
(4/6)
100%
(3/3)
≤150
200
250
≥250
≥300
≥400
≥500
Cmax cut-off (ng/mL)

FIGURE 23C

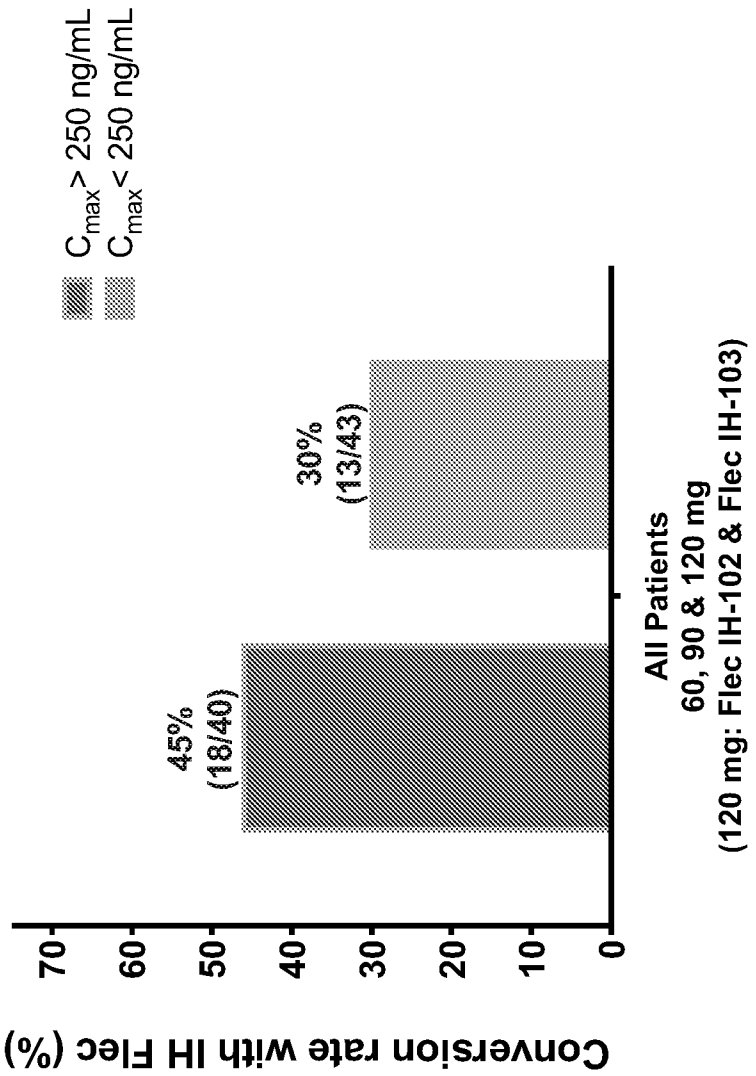
C_{max} > 250 ng/mL
C_{max} < 250 ng/mL
Conversion rate with IH Flec (%)
70
60
50
40
30
20
10
0
45%
(18/40)
30%
(13/43)
All Patients
60, 90 & 120 mg
(120 mg: Flec IH-102 & Flec IH-103)

FIGURE 23D

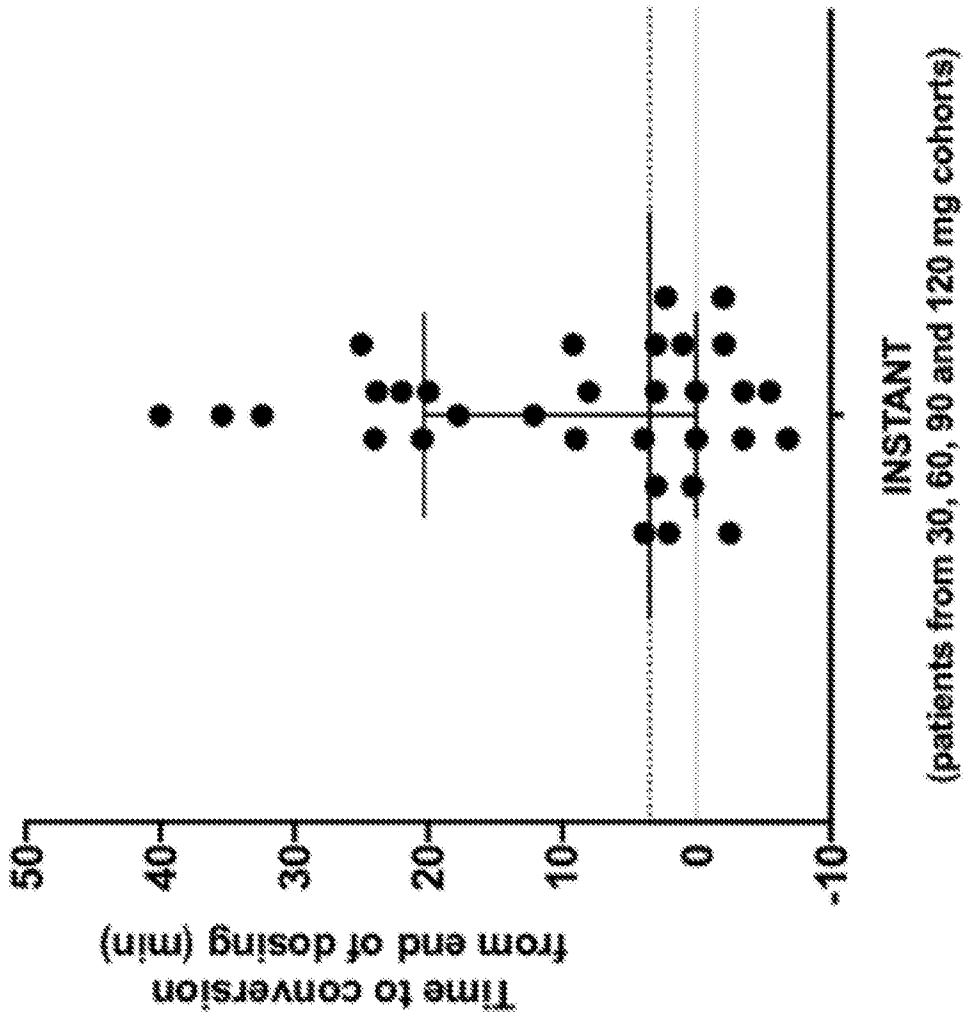
Time to conversion
from end of dosing (min)
50
40
30
20
10
0
-10
INSTANT
(patients from 30, 60, 90 and 120 mg cohorts)

FIGURE 24

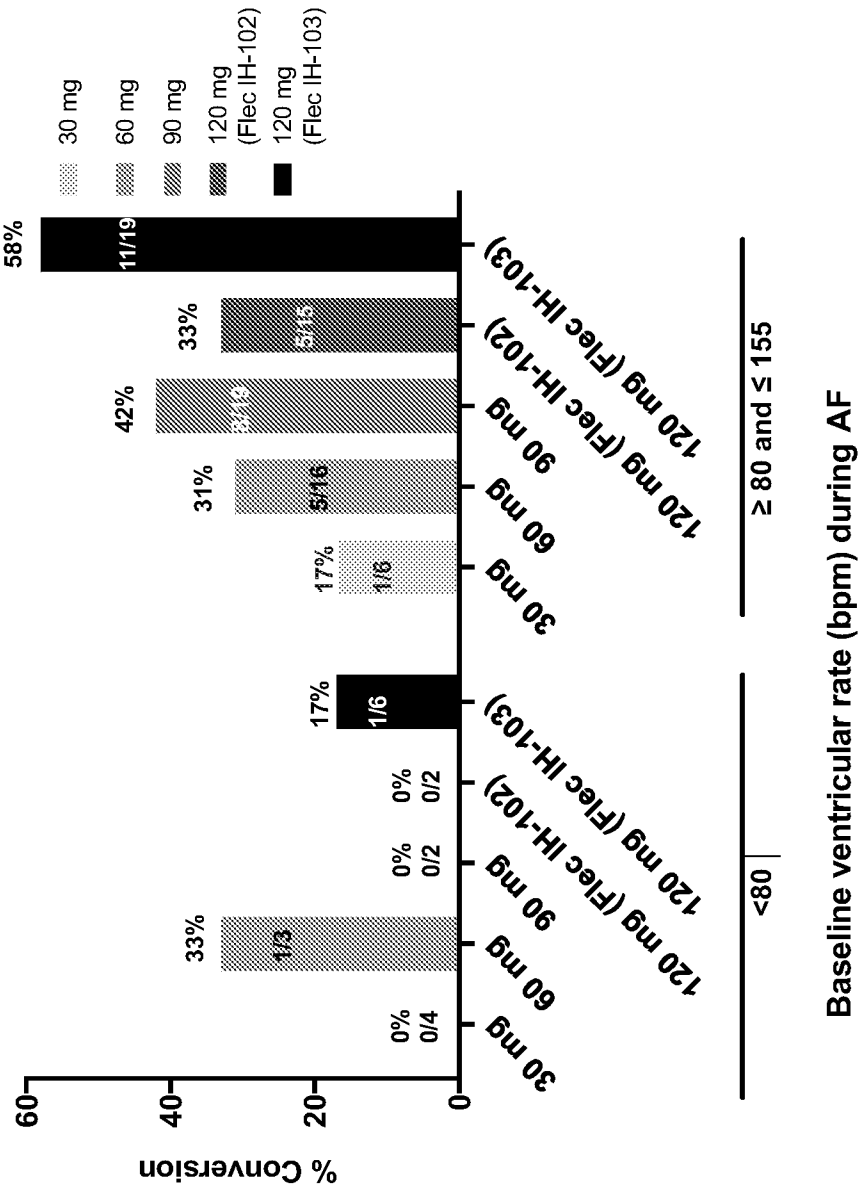
30 mg
60 mg
90 mg
120 mg (Flec IH-102)
120 mg (Flec IH-103)
% Conversion
60
40
20
0
58%
11/19
33%
5/15
42%
3/7
31%
5/16
17%
1/6
17%
1/6
0%
0/2
0%
0/2
33%
1/3
0%
0/4
30 mg
60 mg
90 mg
120 mg (Flec IH-102)
120 mg (Flec IH-103)
30 mg
60 mg
90 mg
120 mg (Flec IH-102)
120 mg (Flec IH-103)
<80
≥ 80 and ≤ 155
Baseline ventricular rate (bpm) during AF

FIGURE 25

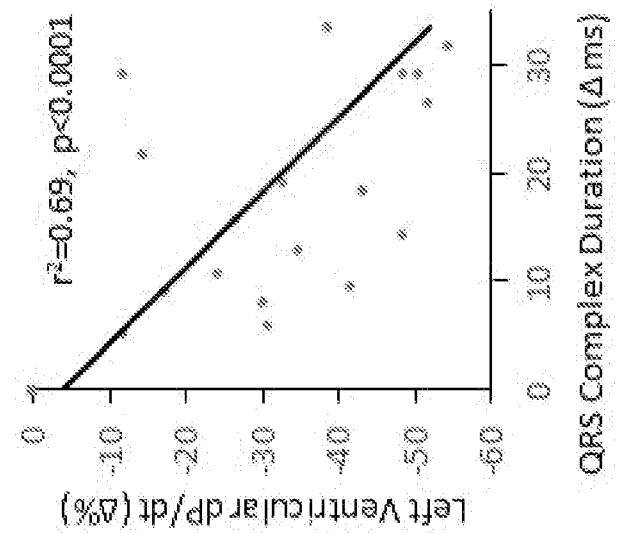

FIGURE 26B

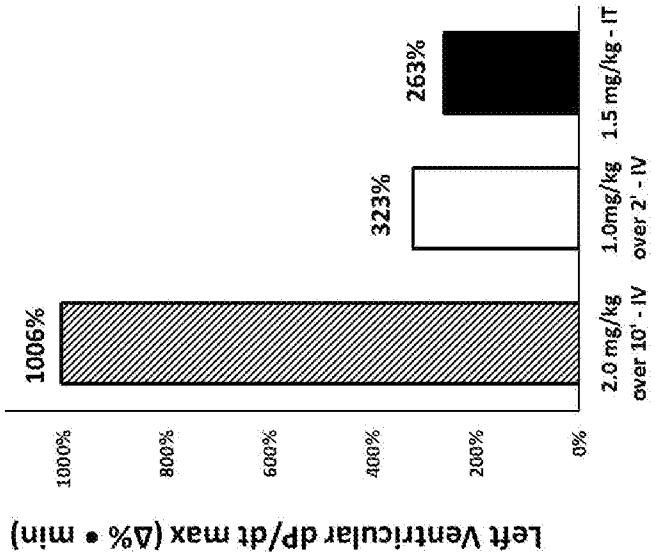

FIGURE 26A