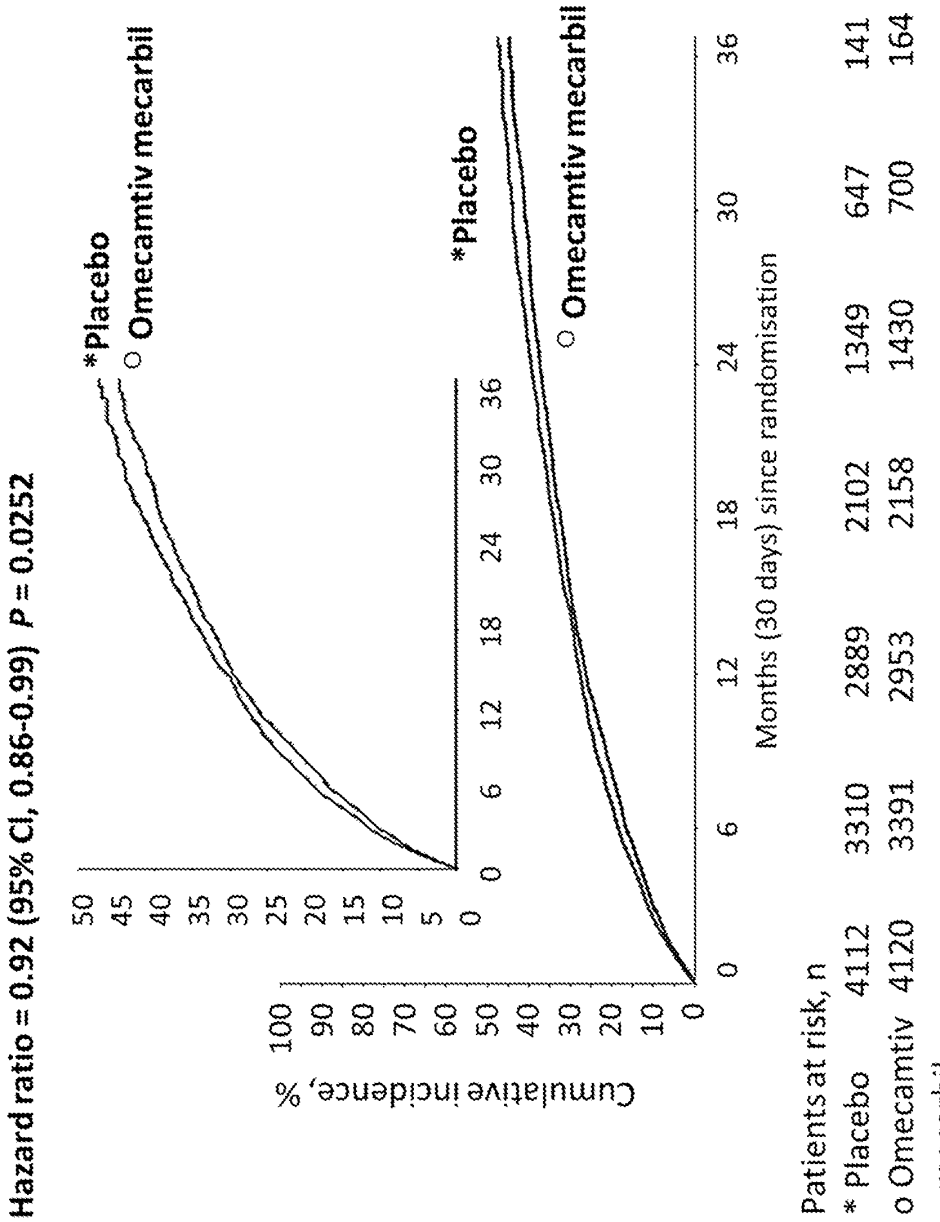

Hazard ratio = 0.92 (95% CI, 0.86-0.99) P = 0.0252
*Placebo
Omecamtiv mecarbil
Cumulative incidence, %
Months (30 days) since randomisation
Patients at risk, n
* Placebo 4112 3310 2889 2102 1349 647 141
o Omecamtiv mecarbil 4120 3391 2953 2158 1430 700 164

FIGURE 1A

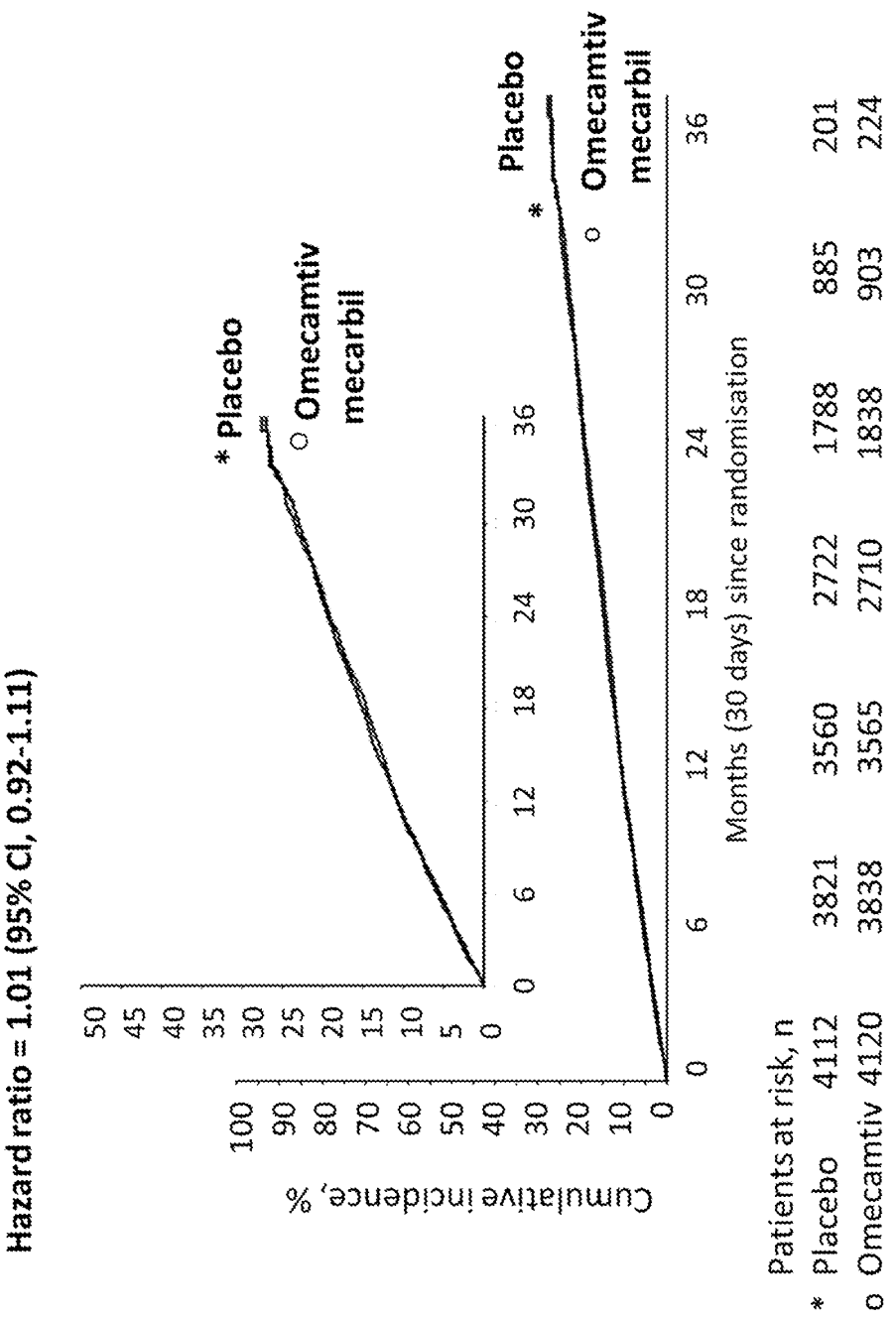

Hazard ratio = 1.01 (95% CI, 0.92-1.11)
Cumulative incidence, %
* Placebo
Omecamtiv mecarbil
Placebo
Omecamtiv mecarbil
Months (30 days) since randomisation
Patients at risk, n
* Placebo 4112 3821 3560 2722 1788 885 201
o Omecamtiv mecarbil 4120 3838 3565 2710 1838 903 224

FIGURE 1B

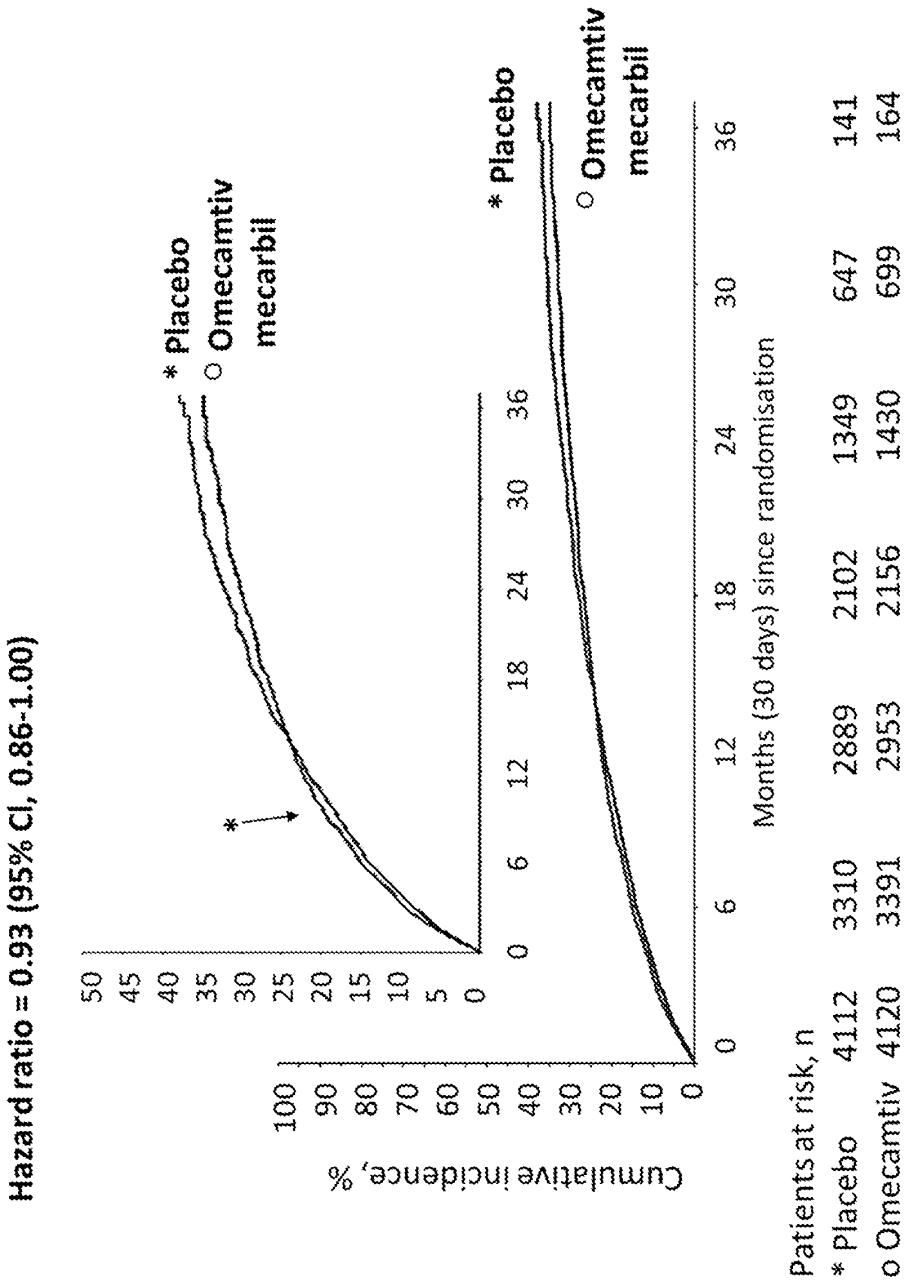

Hazard ratio = 0.93 (95% CI, 0.86-1.00)
* Placebo
Omecamtiv mecarbil
Cumulative incidence, %
Months (30 days) since randomisation
Patients at risk, n
* Placebo 4112 3310 2889 2102 1349 647 141
o Omecamtiv mecarbil 4120 3391 2953 2156 1430 699 164

FIGURE 1C

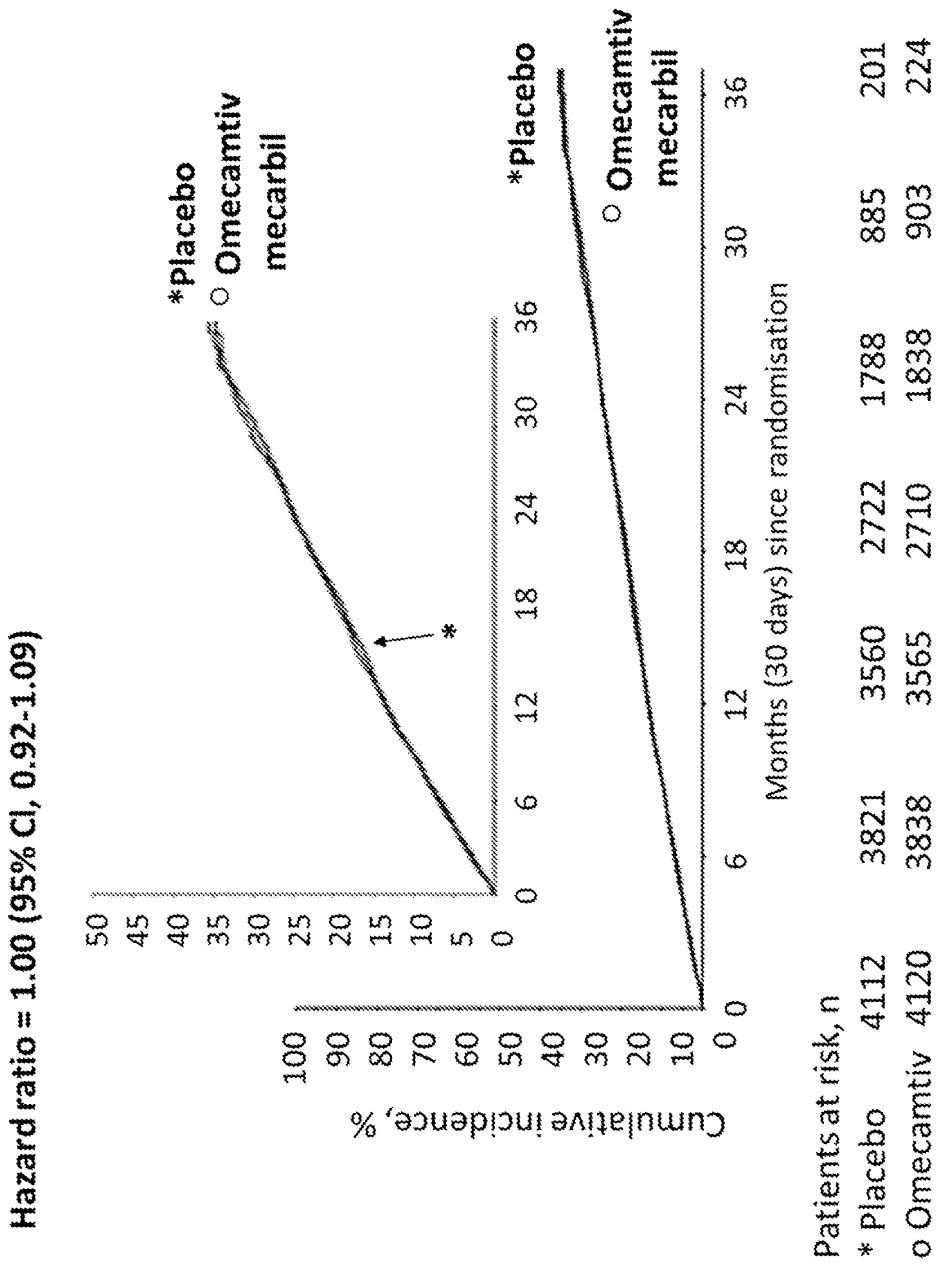

Hazard ratio = 1.00 (95% CI, 0.92-1.09)
*Placebo
○ Omecamtiv mecarbil
*
Cumulative incidence, %
Months (30 days) since randomisation
Patients at risk, n
* Placebo 4112 3821 3560 2722 1788 885 201
o Omecamtiv mecarbil 4120 3838 3565 2710 1838 903 224

FIGURE 1D

Primary Composite
Subgroup
Omecamtiv mecarbil
Placebo
Hazard Ratio
Overall
1523/4120
1607/4112
0.92 (0.86, 0.99)
Randomization Setting
Inpatient
469/1044
497/1040
0.89 (0.78, 1.01)
Outpatient
1054/3076
1110/3072
0.94 (0.86, 1.02)
Region
Asia
100/335
120/335
0.80 (0.61, 1.05)
EEU with Russia
488/1344
517/1337
0.90 (0.80, 1.02)
Latin America
227/787
248/787
0.90 (0.75, 1.07)
US and Canada
306/693
345/693
0.85 (0.73, 0.99)
WEU, SA, and AUS
402/961
377/960
1.07 (0.93, 1.23)
Age
< 65
616/1874
646/1873
0.91 (0.82, 1.02)
>= 65
907/2246
961/2239
0.94 (0.86, 1.03)
Sex
Female
306/875
307/874
0.95 (0.81, 1.12)
Male
1217/3245
1300/3238
0.92 (0.85, 0.99)
Baseline Weight
Q1: <= 68.4 kg
372/1027
423/1032
0.88 (0.77, 1.02)
Q2: (68.4 kg, 80.0 kg]
380/1030
377/1031
0.99 (0.86, 1.15)
Q3: (80.0 kg, 93.9 kg]
348/1018
396/1033
0.85 (0.74, 0.99)
Q4: > 93.9 kg
422/1042
411/1015
0.98 (0.85, 1.12)
Race
Asian
107/355
129/355
0.79 (0.61, 1.02)
Black or African American
124/285
144/277
0.82 (0.64, 1.04)
White
1196/3196
1233/3201
0.95 (0.88, 1.03)
Other
96/284
101/279
0.91 (0.69, 1.21)
Ethnicity
Hispanic or Latino
264/886
290/885
0.90 (0.76, 1.06)
Not Hispanic or Latino
1259/3234
1317/3227
0.93 (0.86, 1.00)

FIGURE 2A

Baseline NYHA Class
II 676/2195 679/2173 0.97 (0.87, 1.08)
III/IV 847/1925 928/1939 0.88 (0.80, 0.97)
Diabetes at baseline
No 805/2434 858/2421 0.91 (0.83, 1.01)
Yes 718/1686 749/1691 0.93 (0.84, 1.03)
Primary cause of HF
Ischemic 877/2193 961/2222 0.90 (0.82, 0.98)
Non-ischemic 646/1927 646/1890 0.96 (0.86, 1.07)
History of MI
No 822/2427 836/2370 0.93 (0.85, 1.03)
Yes 701/1693 769/1742 0.91 (0.83, 1.01)
Presence of Atrial fib/flutter
No 981/2974 1103/3013 0.86 (0.79, 0.94)
Yes 542/1146 504/1099 1.05 (0.93, 1.18)
Baseline LVEF
<= median (28%) 850/2213 971/2243 0.84 (0.77, 0.92)
> median (28%) 673/1907 636/1869 1.04 (0.94, 1.16)
Baseline NT-proBNP (e.xcl. Afib)
Inpatient & <= Median 104/344 100/329 0.97 (0.74, 1.28)
Inpatient & > Median 175/334 201/338 0.75 (0.61, 0.92)
Outpatient & <= Median 223/1131 260/1182 0.88 (0.73, 1.05)
Outpatient & > Median 476/1156 539/1157 0.85 (0.75, 0.97)
Baseline HR
<= Median (71 bpm) 723/2109 767/2105 0.91 (0.82, 1.01)
> Median (71 bpm) 800/2011 840/2007 0.93 (0.85, 1.03)
Baseline SBP
<= Median (116 mmHg) 848/2096 889/2038 0.90 (0.82, 0.99)
> Median (116 mmHg) 675/2024 718/2074 0.95 (0.85, 1.05)
Baseline SBP
< 100 mmHg 281/594 282/533 0.89 (0.76, 1.05)
>= 100 mmHg 1242/3526 1325/3579 0.92 (0.86, 1.00)
Baseline eGFR
<= 60 mL/min/1.73m2 973/2156 984/2165 0.98 (0.89, 1.07)
> 60 mL/min/1.73m2 550/1964 623/1947 0.84 (0.75, 0.94)

FIGURE 2B

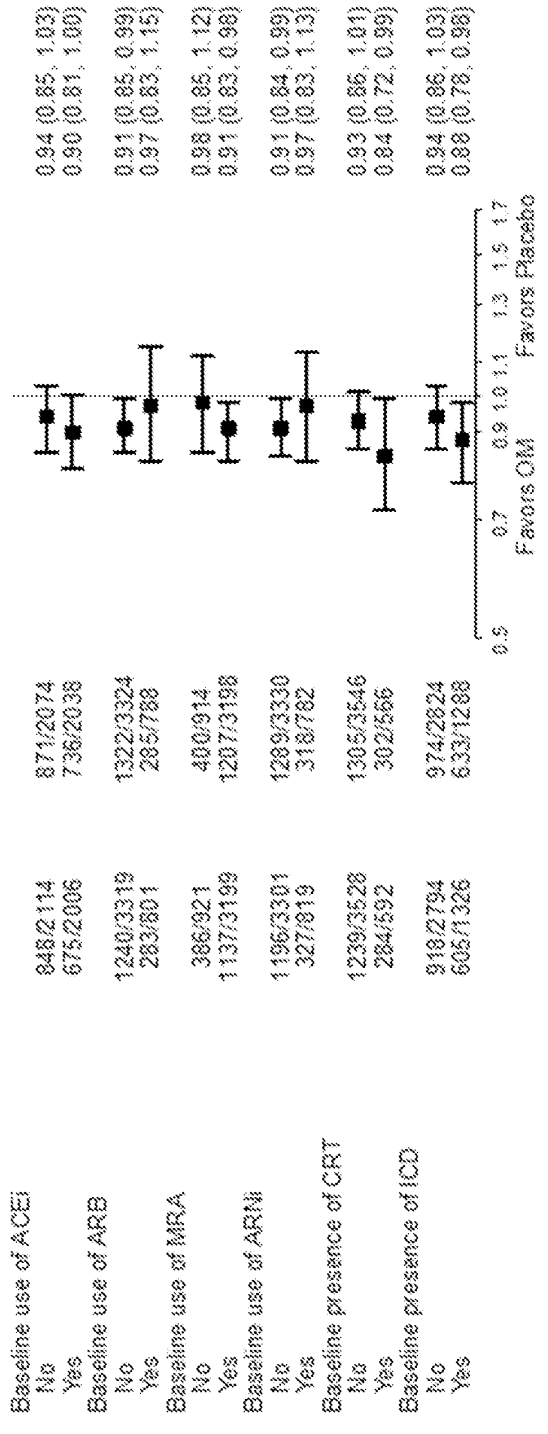
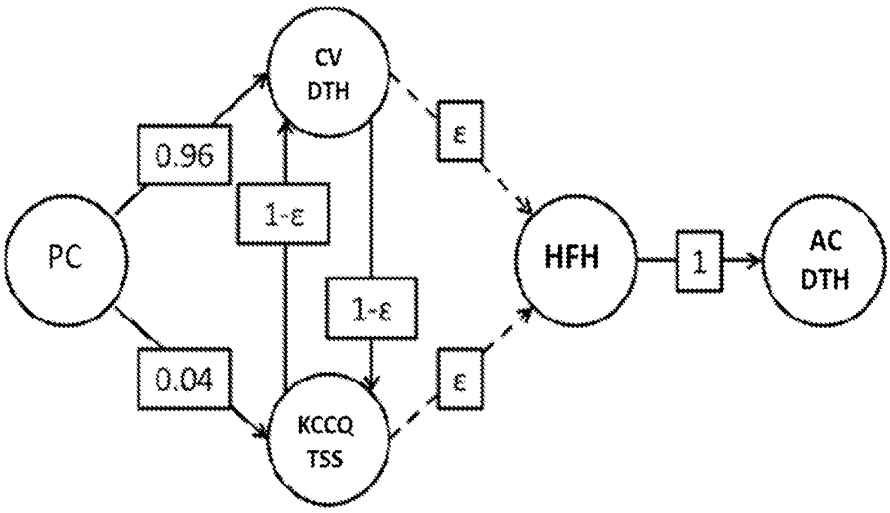

Baseline use of ACEi
No 848/2114 871/2074 0.94 (0.85, 1.03)
Yes 675/2006 736/2036 0.90 (0.81, 1.00)
Baseline use of ARB
No 1240/3319 1322/3324 0.91 (0.85, 0.99)
Yes 283/801 285/788 0.97 (0.83, 1.15)
Baseline use of MRA
No 386/921 400/914 0.98 (0.85, 1.12)
Yes 1137/3199 1207/3198 0.91 (0.83, 0.98)
Baseline use of ARNi
No 1196/3301 1289/3330 0.91 (0.84, 0.99)
Yes 327/819 318/782 0.97 (0.83, 1.13)
Baseline presence of CRT
No 1239/3528 1305/3546 0.93 (0.86, 1.01)
Yes 284/592 302/566 0.84 (0.72, 0.99)
Baseline presence of ICD
No 918/2794 974/2824 0.94 (0.86, 1.03)
Yes 605/1326 633/1288 0.88 (0.78, 0.98)
0.5
0.7
0.9
1.0
1.1
1.3
1.5
1.7
Favors CM
Favors Placebo

FIGURE 2C

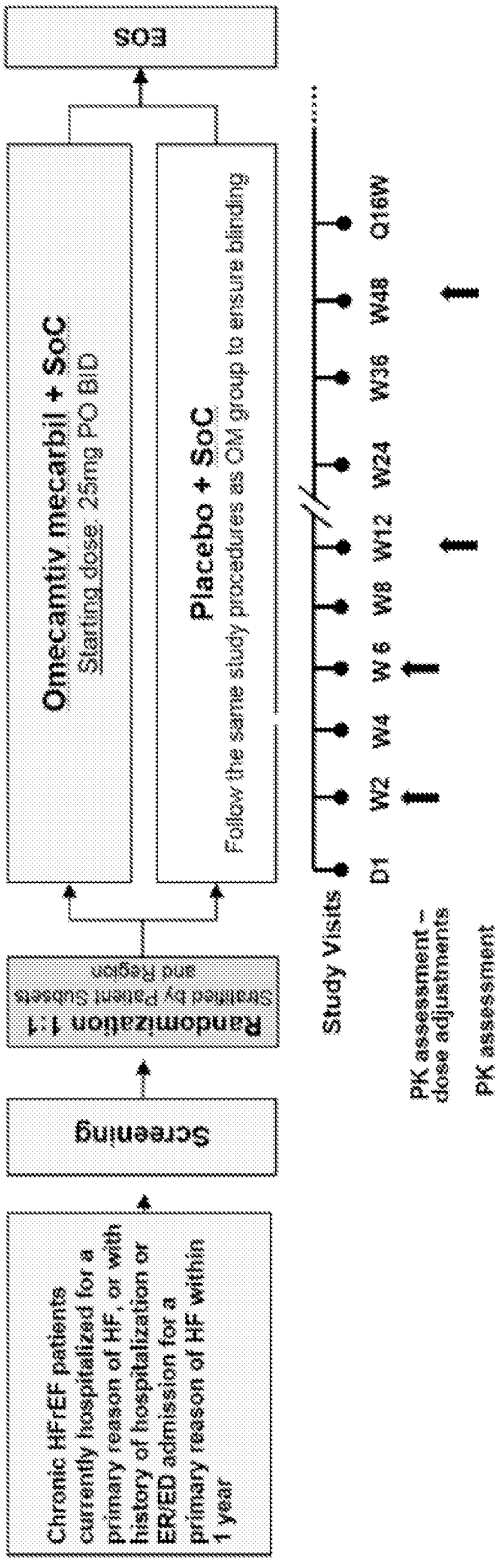


PC = primary composite endpoint; CV DTH = time to CV death; KCCQ TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; HFH = time to first heart failure hospitalization; AC DTH = time to all-cause death.

Each circle represents a hypothesis test. The values in boxes on the arrows indicate the fraction of α propagated in the direction of the arrow to the next hypothesis test(s). ε = 0.0001, a small value to complete the graph while prioritizing the CV death and KCCQ TSS endpoints over the time to first heart failure hospitalization and all-cause death endpoints. Dashed arrows used to emphasize this prioritization.

No multiplicity adjustment will be made for exploratory or sensitivity analyses.

FIGURE 3



BID = twice a day; ED = emergency department; EOS = end of study; ER = emergency room; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; IP = investigational product; PK = pharmacokinetics; PO = by mouth; Q16W = every 16 weeks; SoC = standard of care;

FIGURE 4

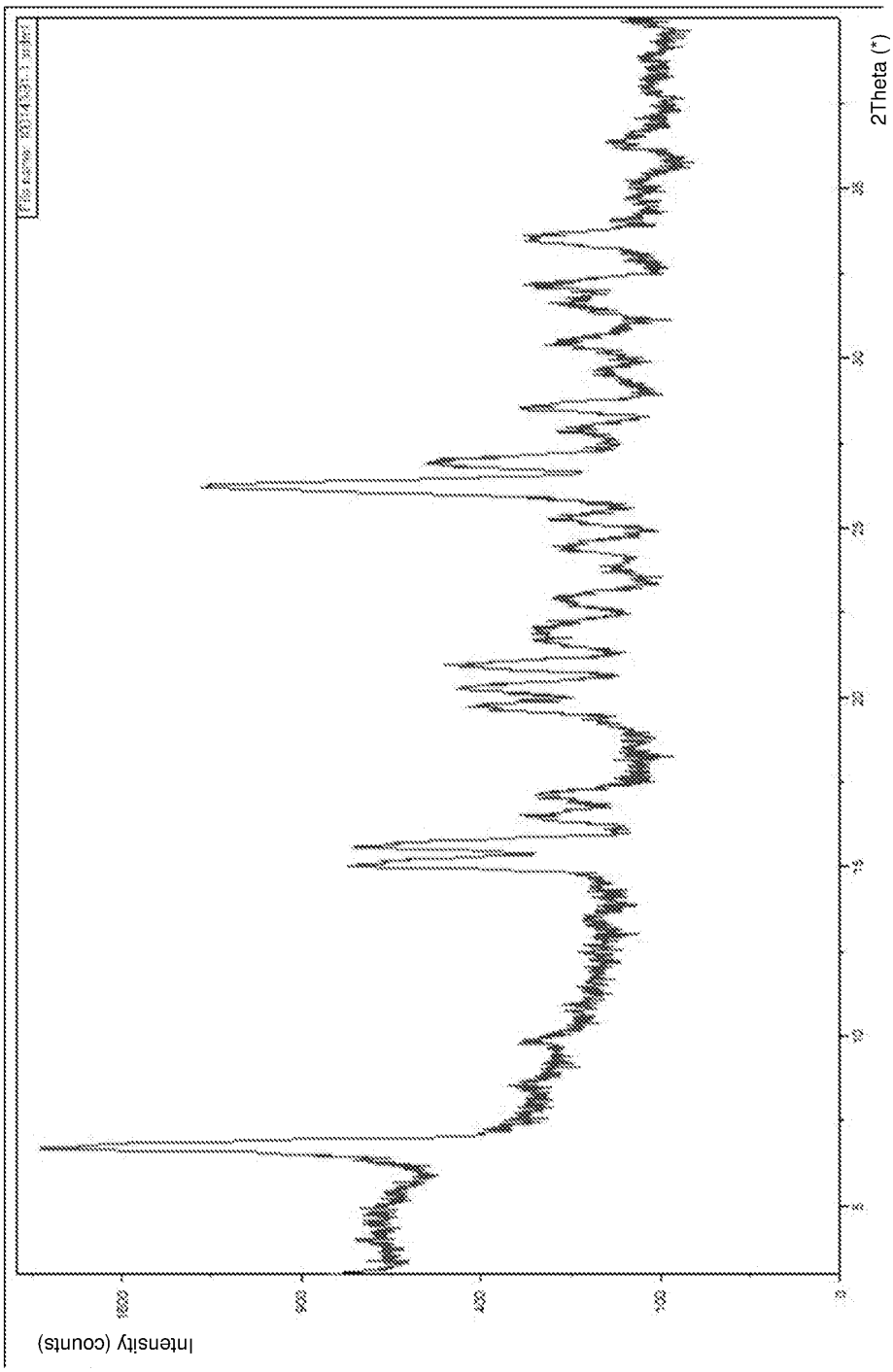


FIGURE 5

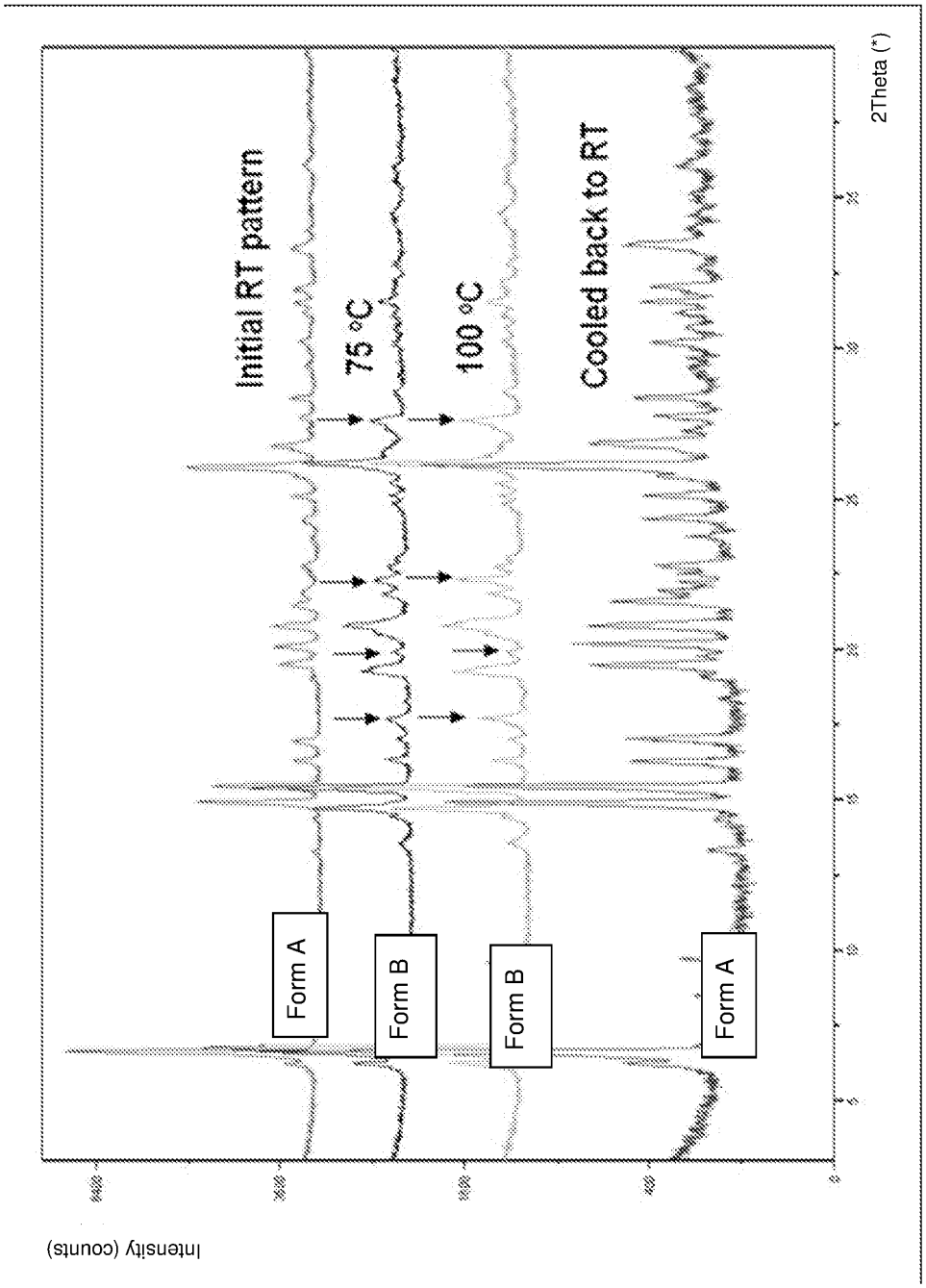

Initial RT pattern
75 °C
100 °C
Cooled back to RT
Form A
Form B
Form B
Form A
Intensity (counts)
2Theta (°)

FIGURE 6

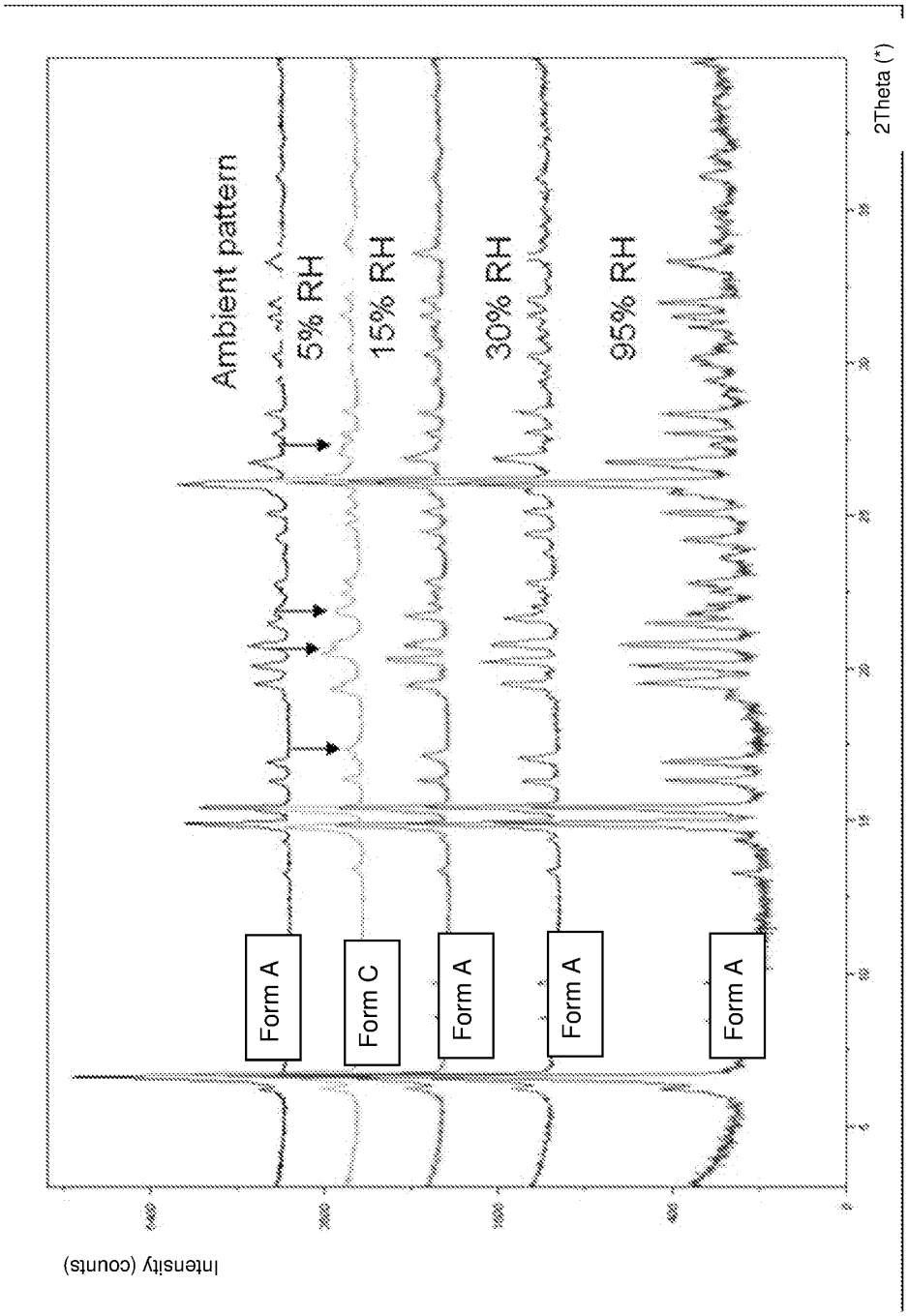

Ambient pattern
5% RH
15% RH
30% RH
95% RH
Form A
Form C
Form A
Form A
Form A
Intensity (counts)
2Theta (°)

FIGURE 7

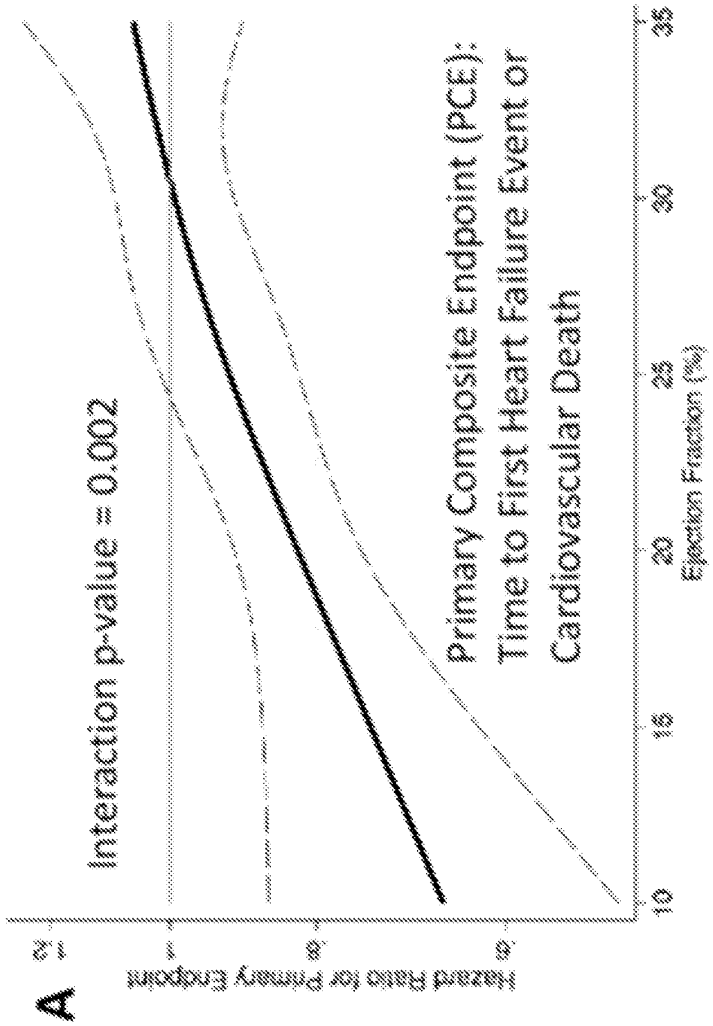

A
Hazard Ratio for Primary Endpoint
1.2
1
.8
.6
Interaction p-value = 0.002
Primary Composite Endpoint (PCE):
Time to First Heart Failure Event or
Cardiovascular Death
10
15
20
25
30
35
Ejection Fraction (%)

FIGURE 8A

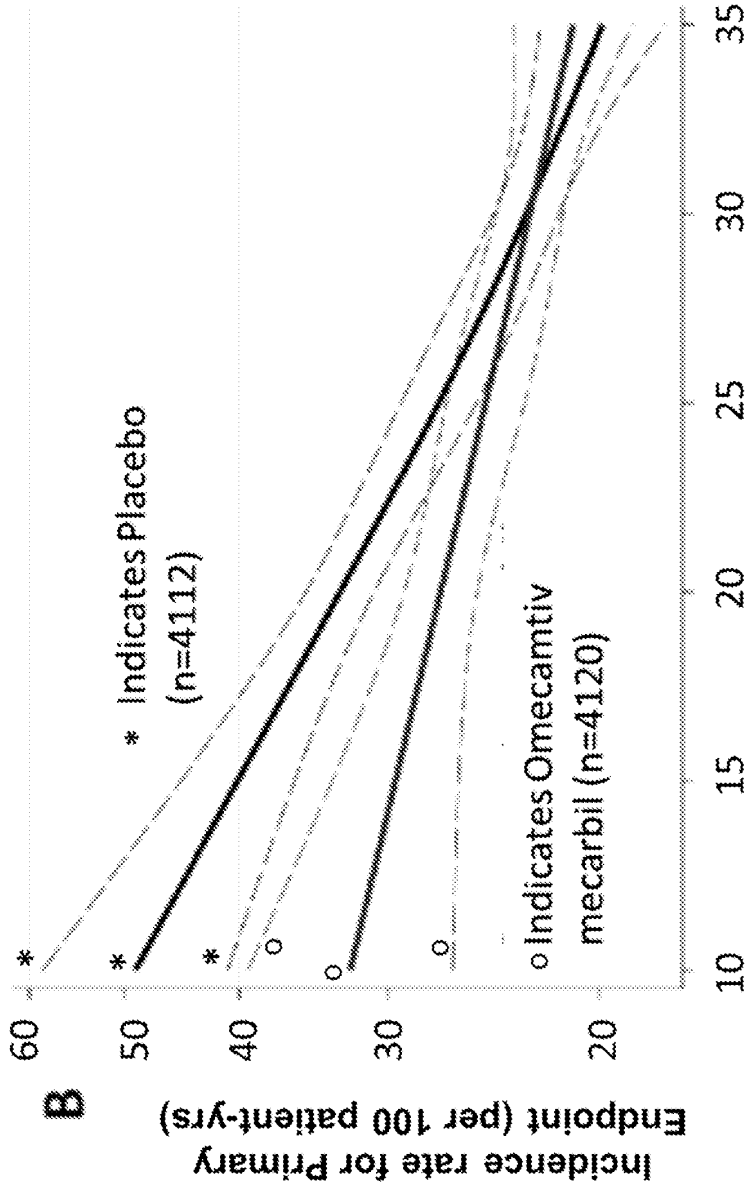

B
Incidence rate for Primary Endpoint (per 100 patient-yrs)
60
50
40
30
20
10
15
20
25
30
35
Ejection Fraction %
* Indicates Placebo (n=4112)
o Indicates Omecamtiv mecarbil (n=4120)

FIGURE 8B

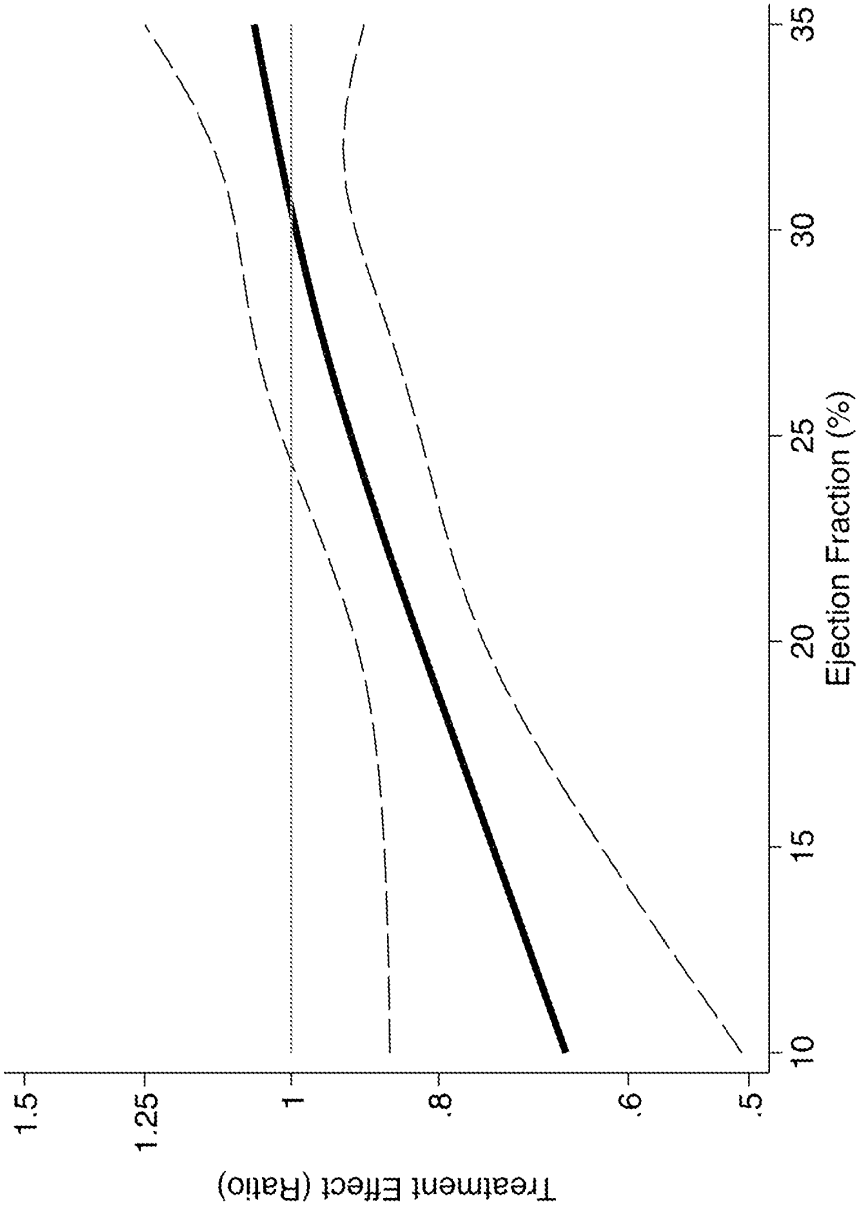

Treatment Effect (Ratio)
1.5
1.25
1
.8
.6
.5
10
15
20
25
30
35
Ejection Fraction (%)

FIGURE 9

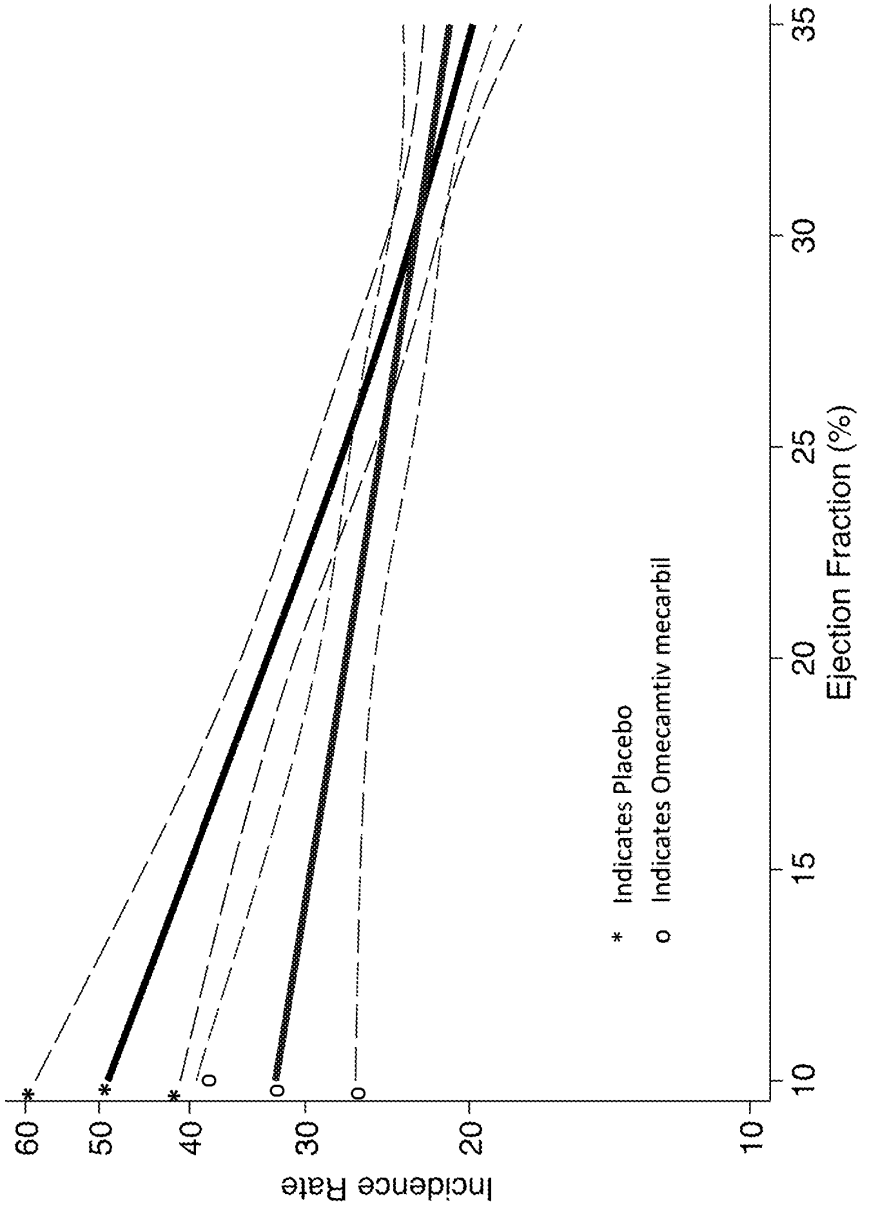

Incidence Rate
60
50
40
30
20
10
10
15
20
25
30
35
Ejection Fraction (%)
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 10A

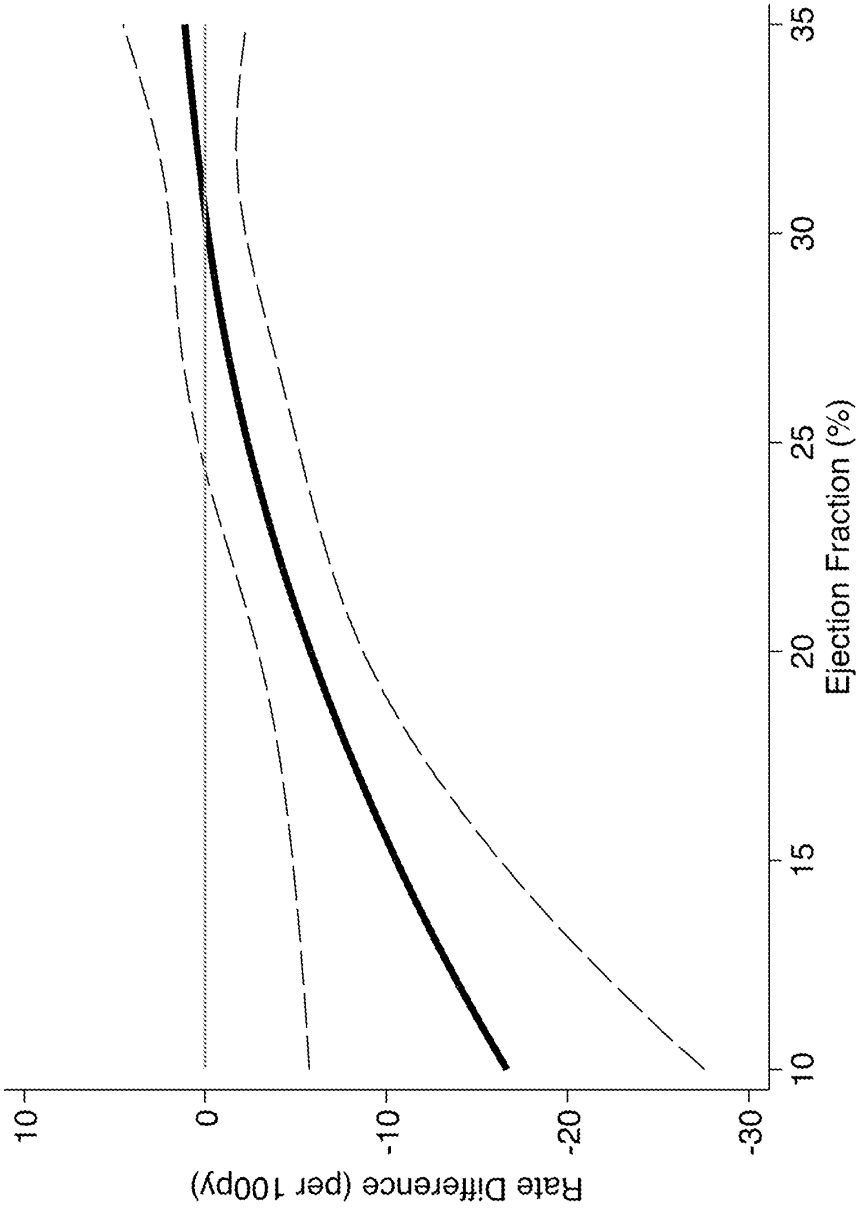

Rate Difference (per 100py)
10
0
-10
-20
-30
10
15
20
25
30
35
Ejection Fraction (%)

FIGURE 10B

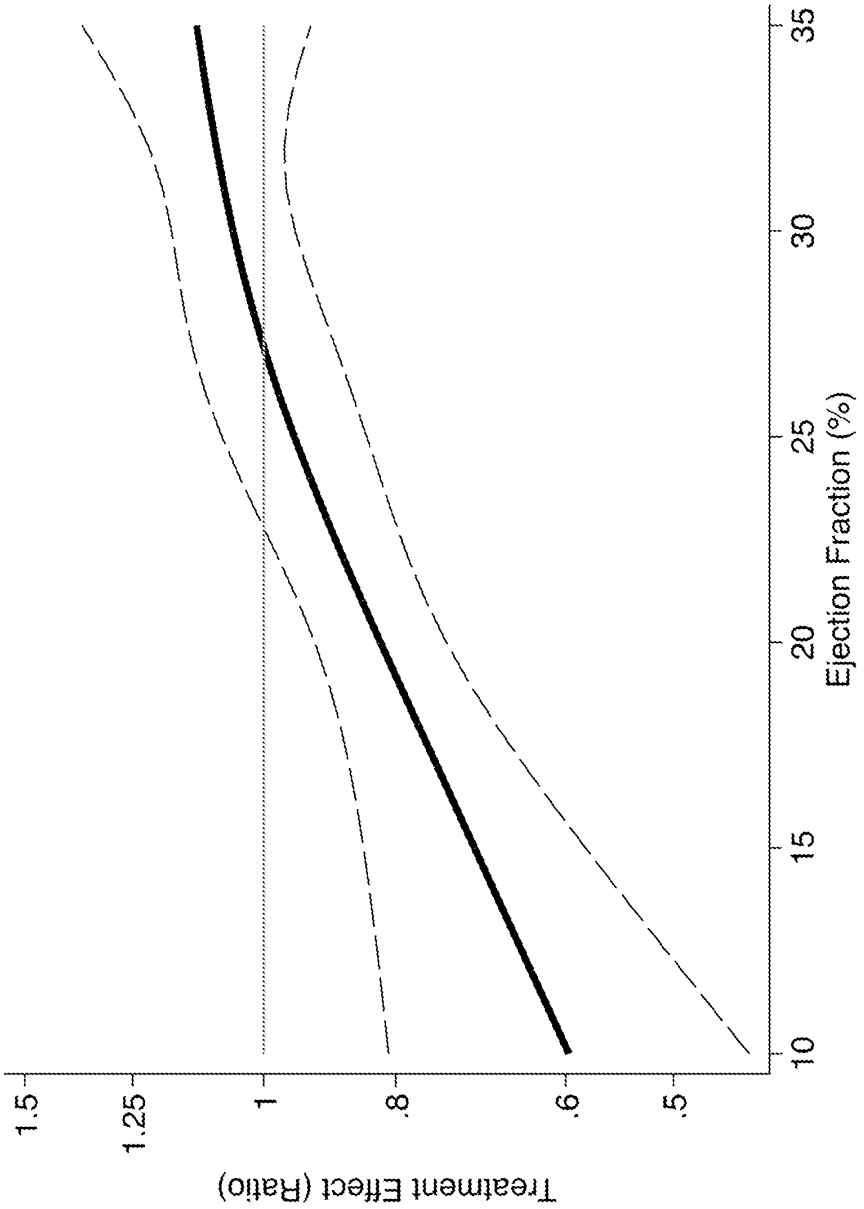

Treatment Effect (Ratio)
1.5
1.25
1
.8
.6
.5
10
15
20
25
30
35
Ejection Fraction (%)

FIGURE 11A

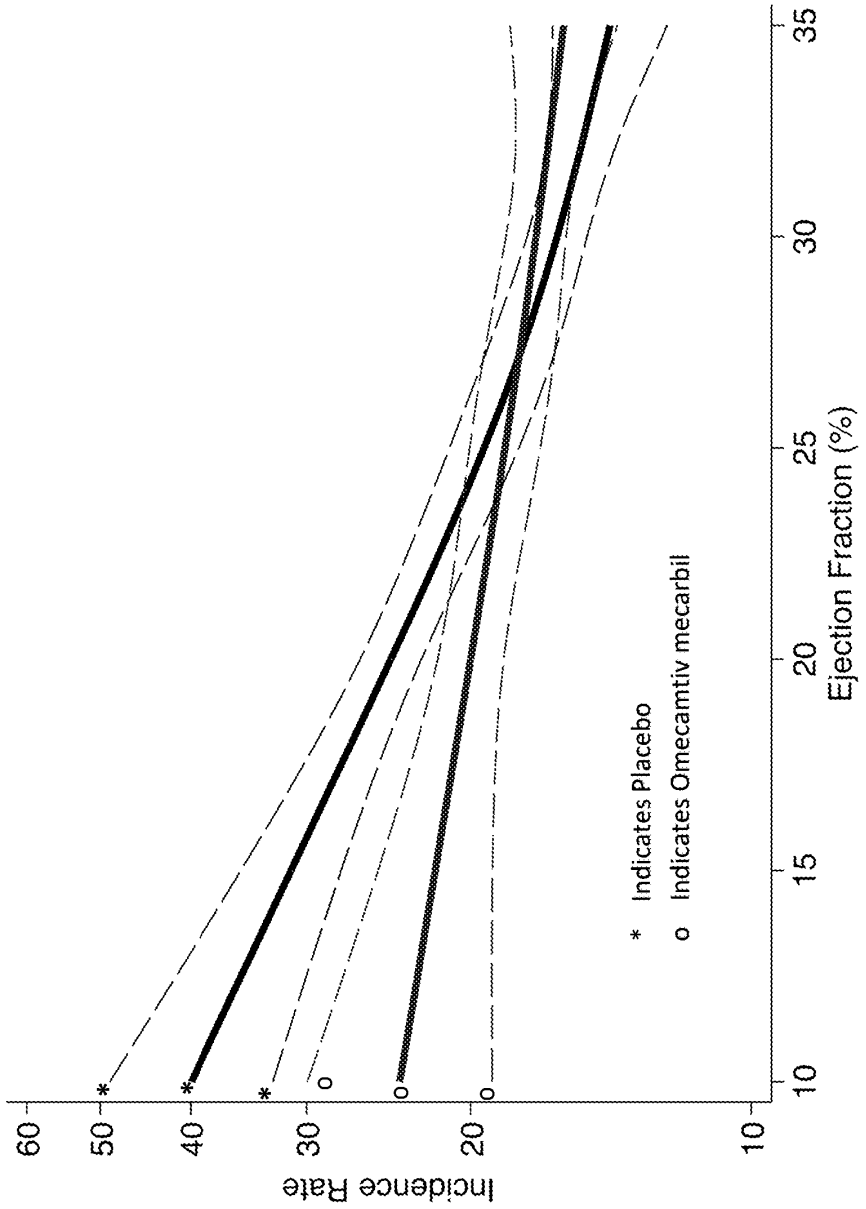

Incidence Rate
60
50
40
30
20
10
10
15
20
25
30
35
Ejection Fraction (%)
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 11B

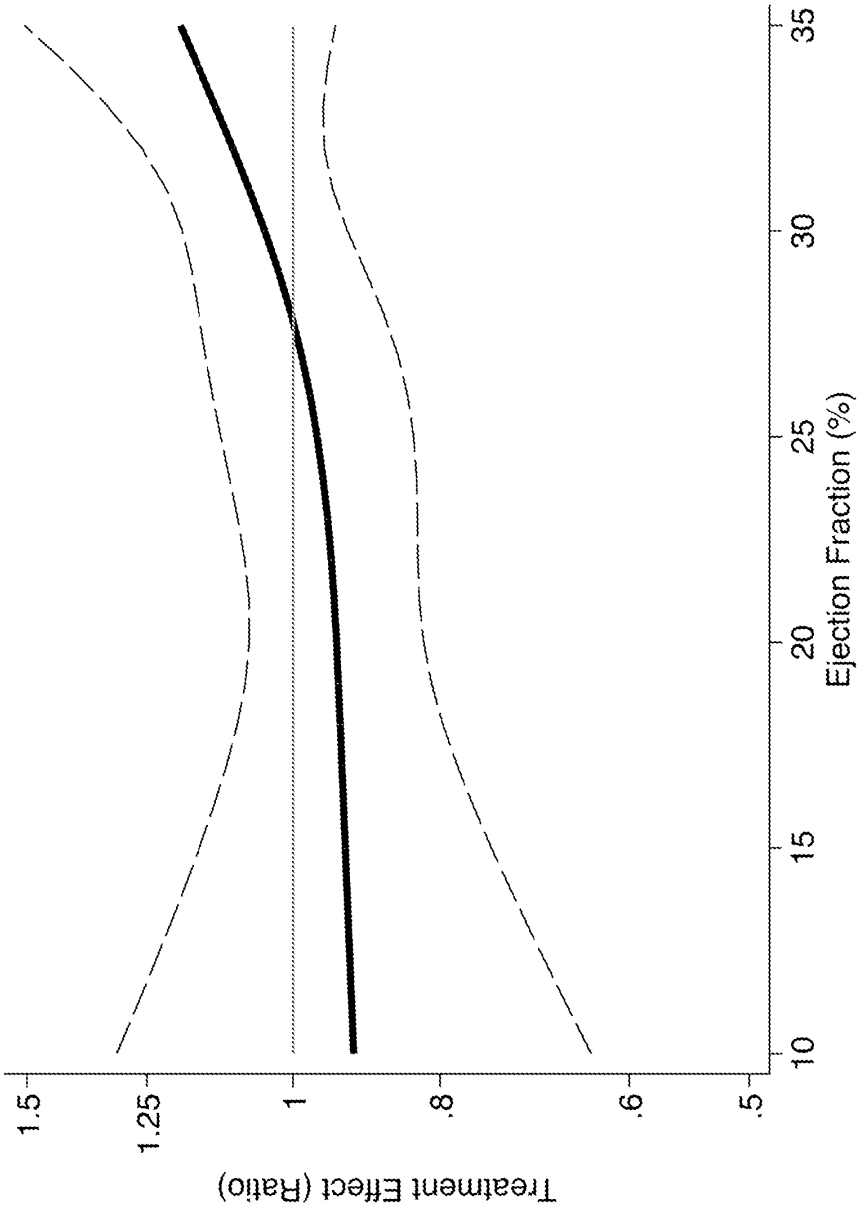

Treatment Effect (Ratio)
1.5
1.25
1
.8
.6
.5
10
15
20
25
30
35
Ejection Fraction (%)

FIGURE 12A

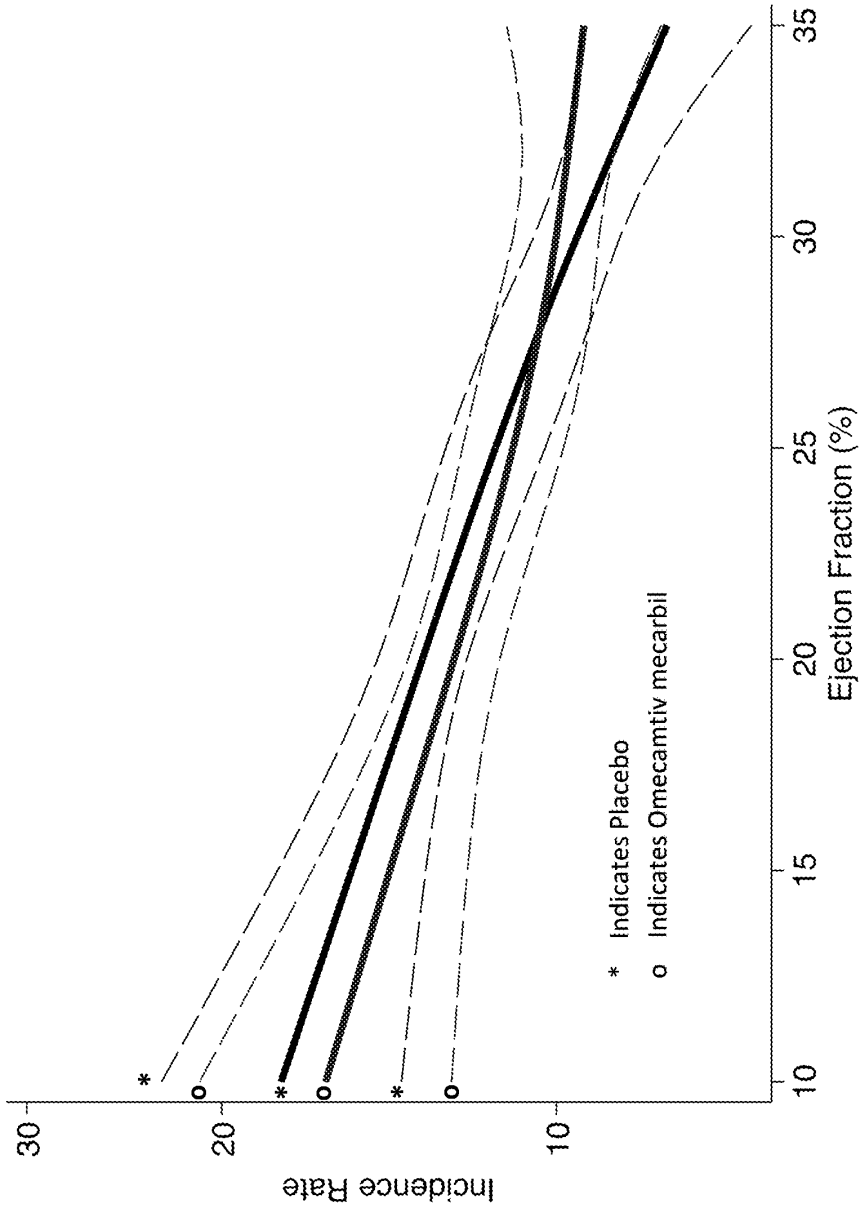

Incidence Rate
30
20
10
10
15
20
25
30
35
Ejection Fraction (%)
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 12B

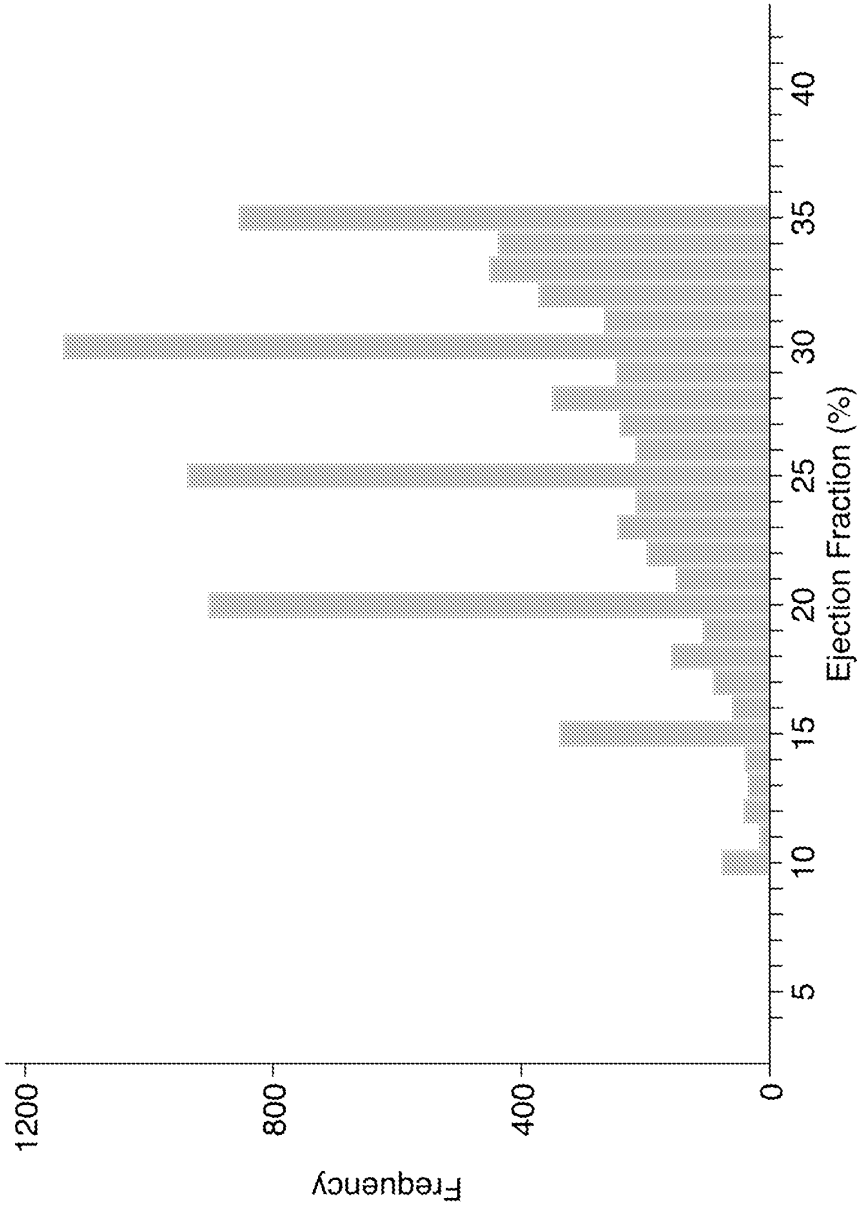

Frequency
0
400
800
1200
5
10
15
20
25
30
35
40
Ejection Fraction (%)

FIGURE 13A

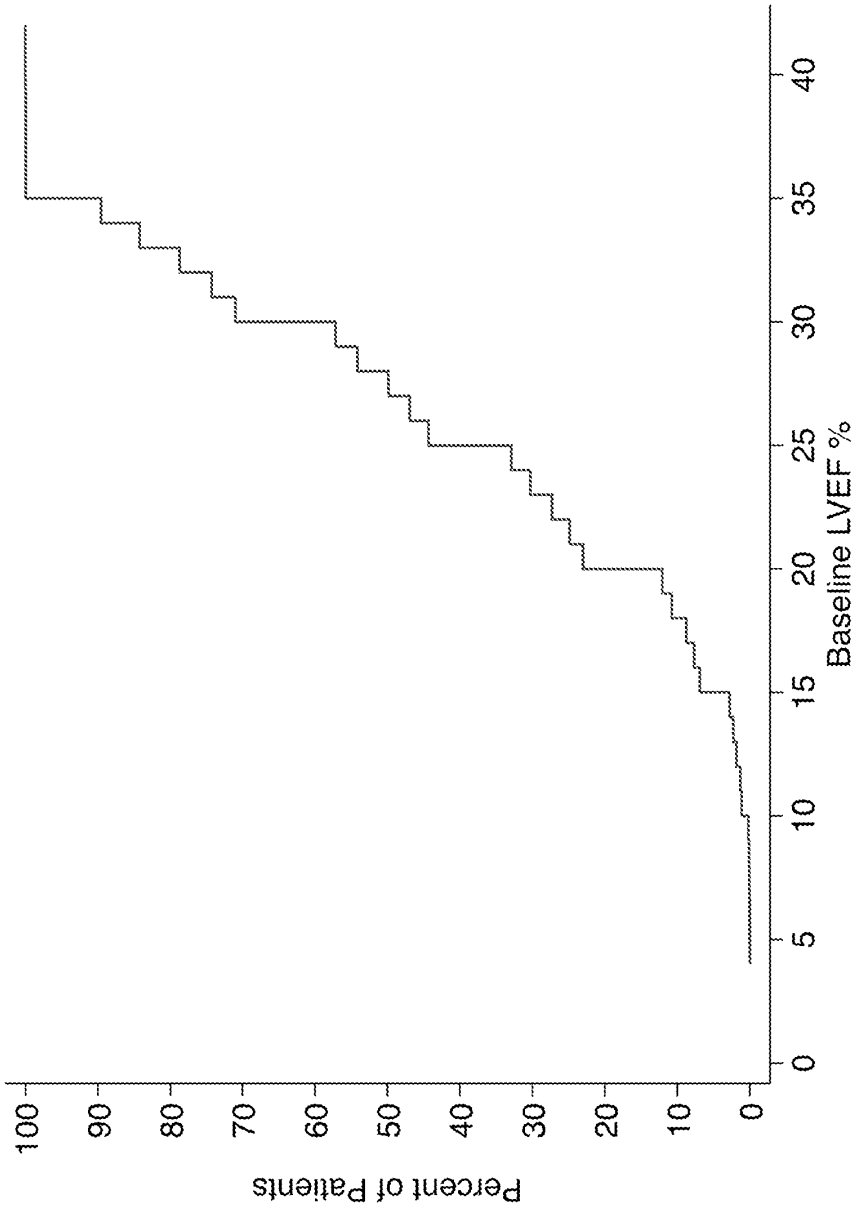

Percent of Patients
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Baseline LVEF %

FIGURE 13B

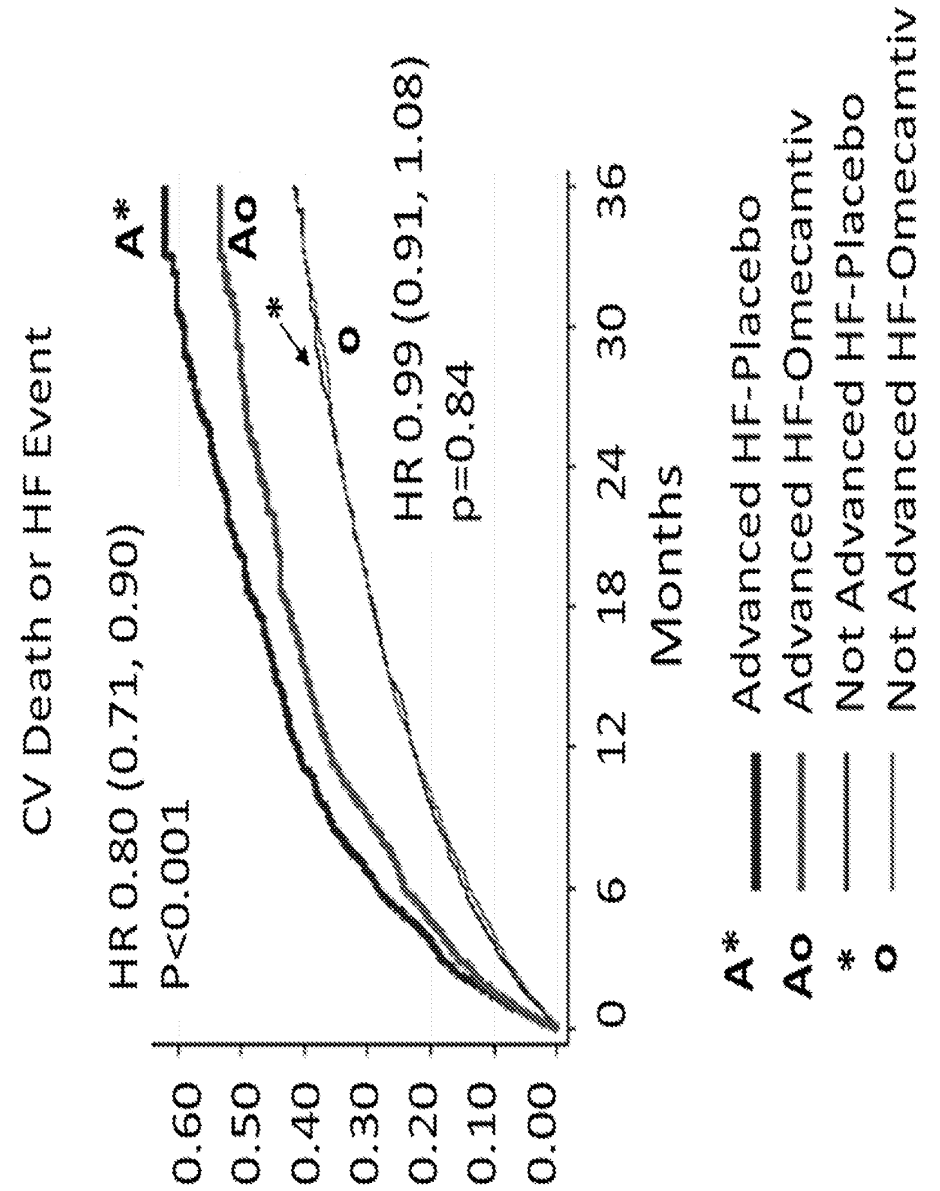

CV Death or HF Event
HR 0.80 (0.71, 0.90)
P<0.001
HR 0.99 (0.91, 1.08)
p=0.84
A*
Ao
*
o
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
6
12
18
24
30
36
Months
A* Advanced HF-Placebo
Ao Advanced HF-Omecamtiv
* Not Advanced HF-Placebo
o Not Advanced HF-Omecamtiv

FIGURE 14A

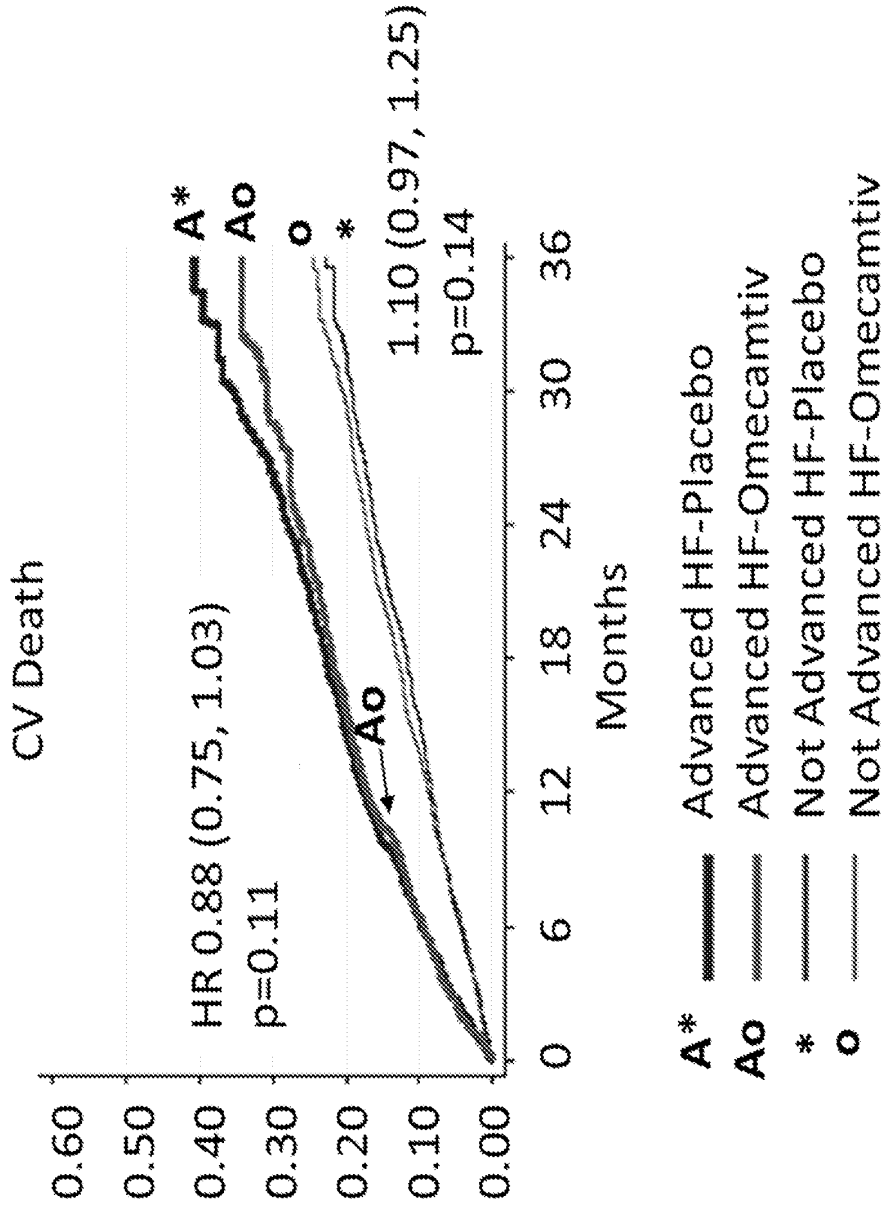

CV Death
HR 0.88 (0.75, 1.03)
p=0.11
1.10 (0.97, 1.25)
p=0.14
A*
Ao
o
*
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
6
12
18
24
30
36
Months
A* Advanced HF-Placebo
Ao Advanced HF-Omecamtiv
* Not Advanced HF-Placebo
o Not Advanced HF-Omecamtiv

FIGURE 14B

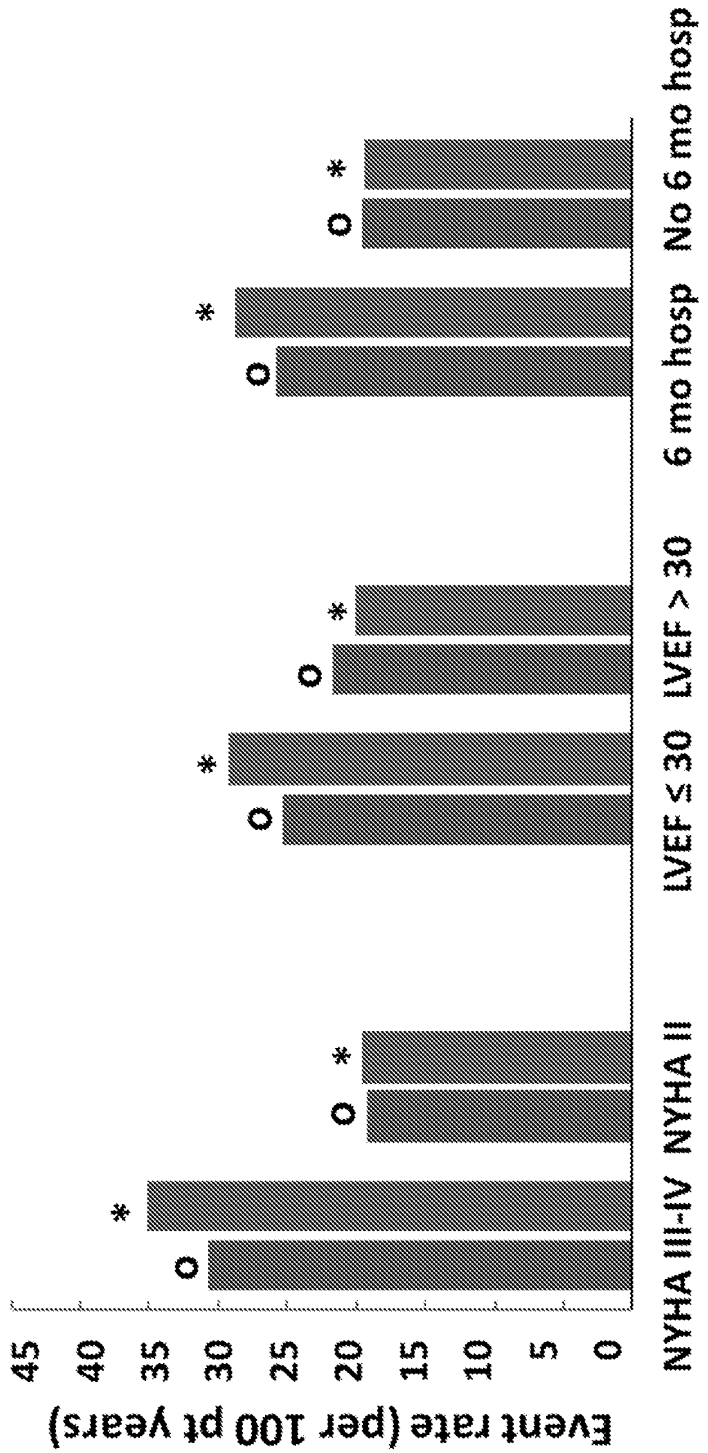

Event rate (per 100 pt years)
45
40
35
30
25
20
15
10
5
0
NYHA III-IV
NYHA II
LVEF ≤ 30
LVEF > 30
6 mo hosp
No 6 mo hosp
o Omecamtiv mecarbil
*Placebo

FIGURE 15A

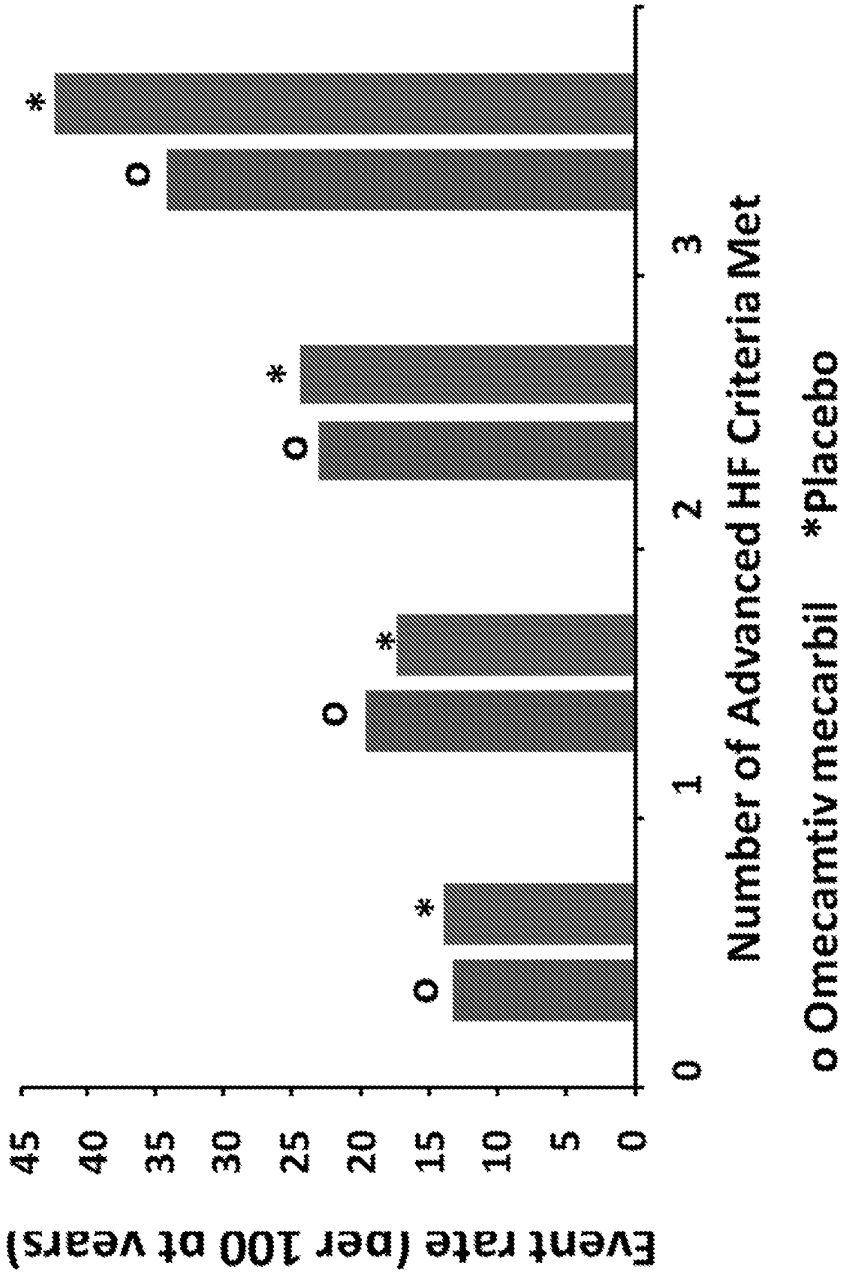

Event rate (per 100 pt years)
45
40
35
30
25
20
15
10
5
0
o
*
o
*
o
*
o
*
0
1
2
3
Number of Advanced HF Criteria Met
o Omecamtiv mecarbil *Placebo

FIGURE 15B

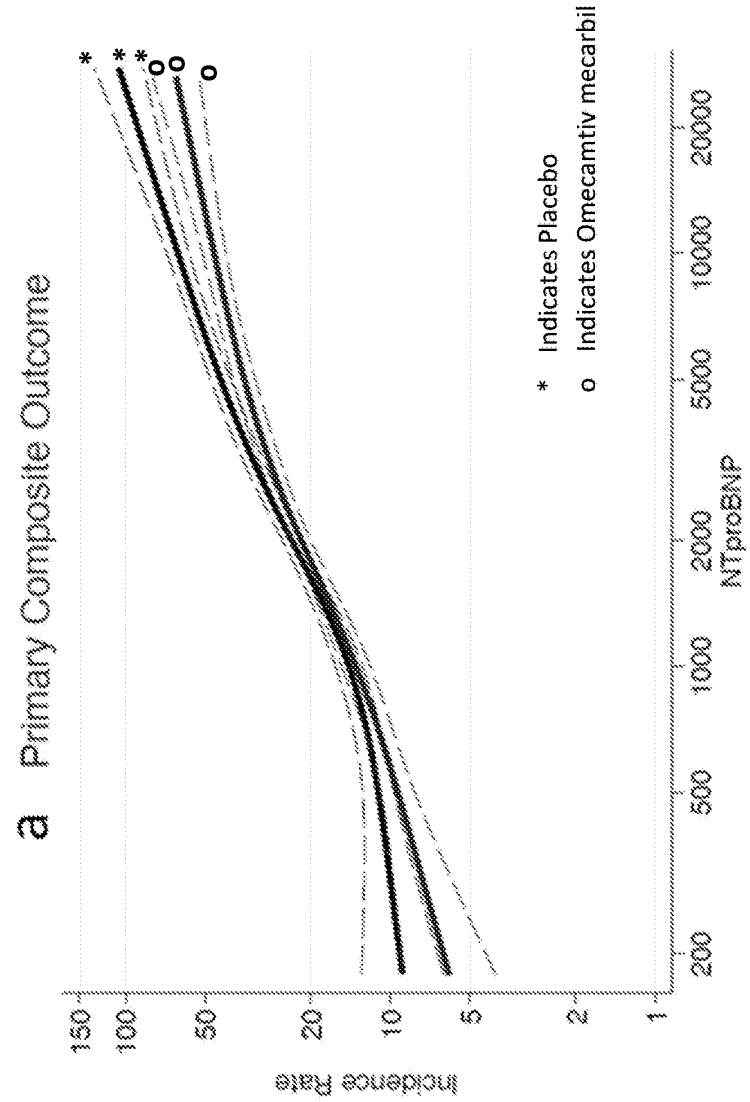

a Primary Composite Outcome
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 16A

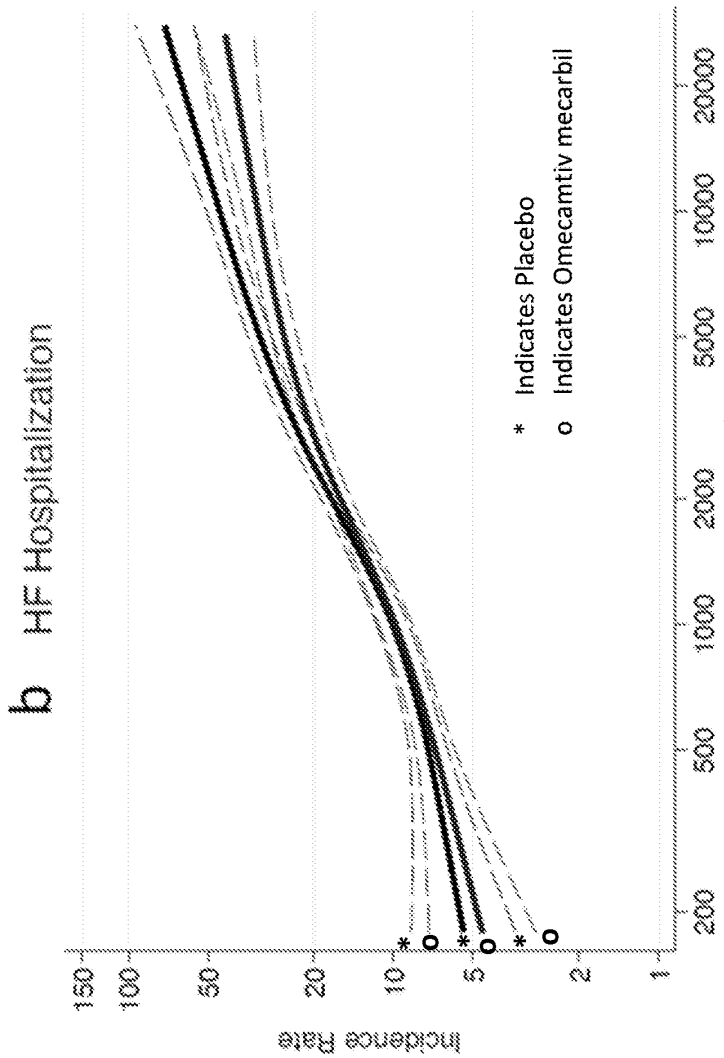

b HF Hospitalization
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 16B

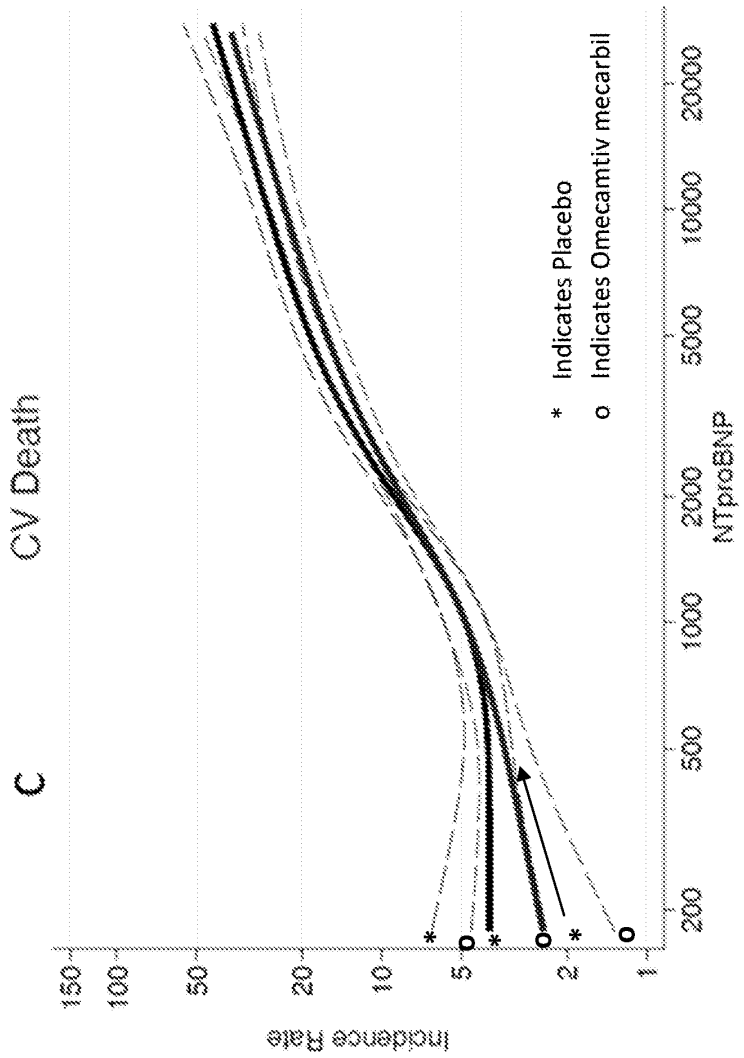

C
CV Death
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 16C

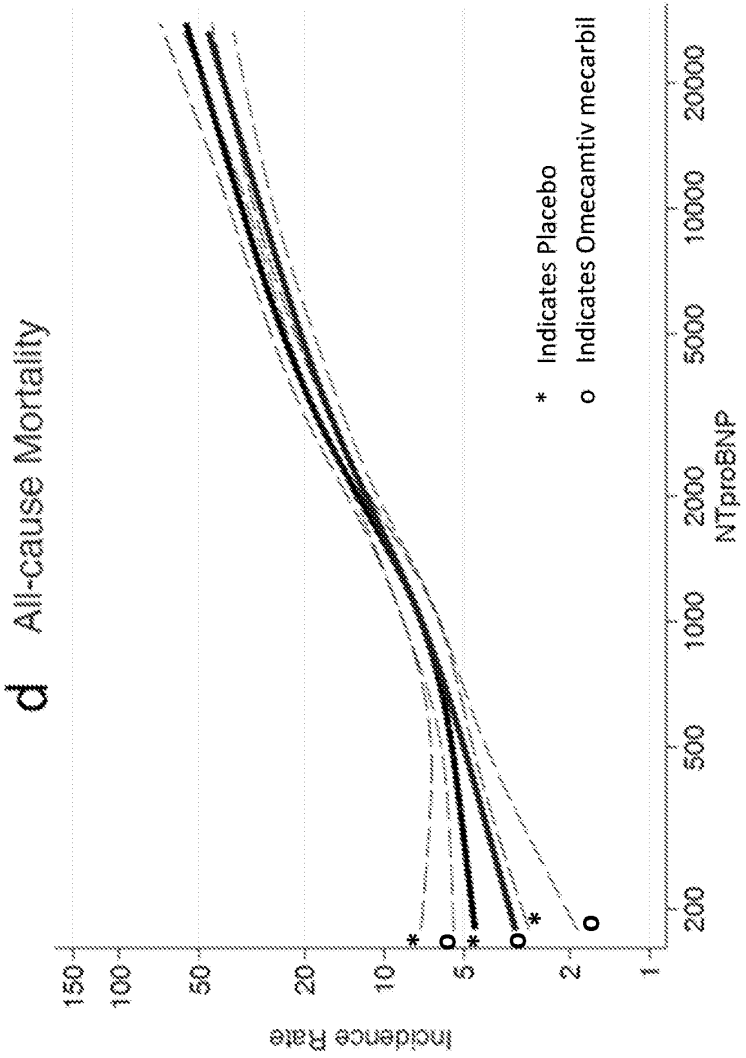

d All-cause Mortality
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 16D

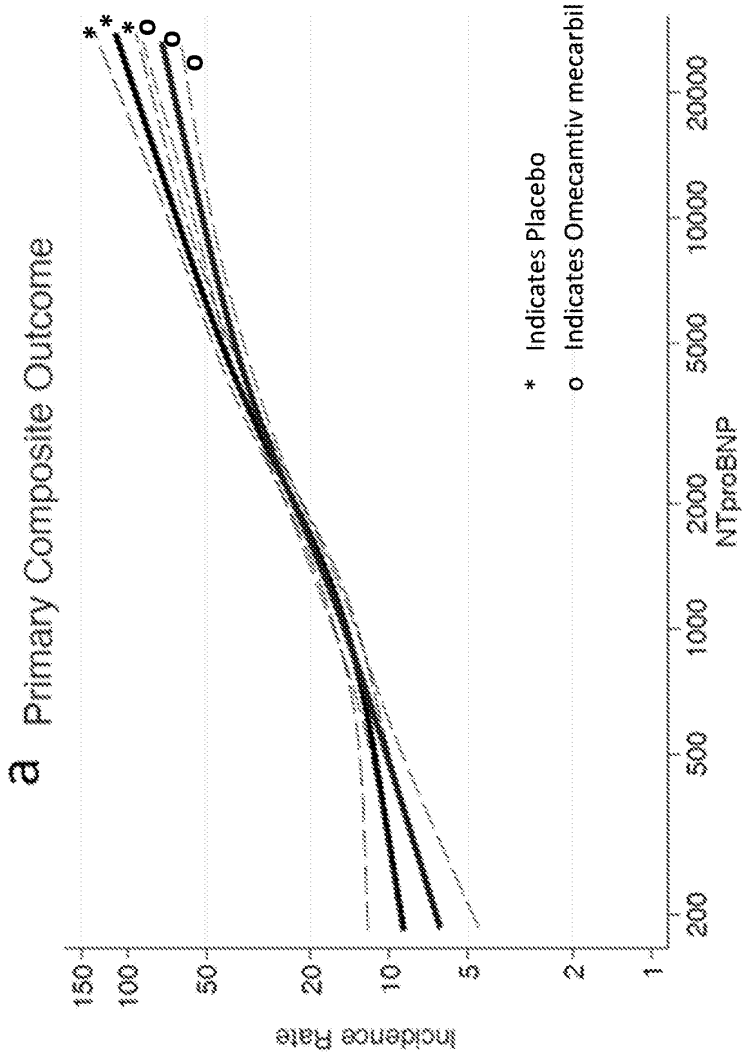

a Primary Composite Outcome
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 17A

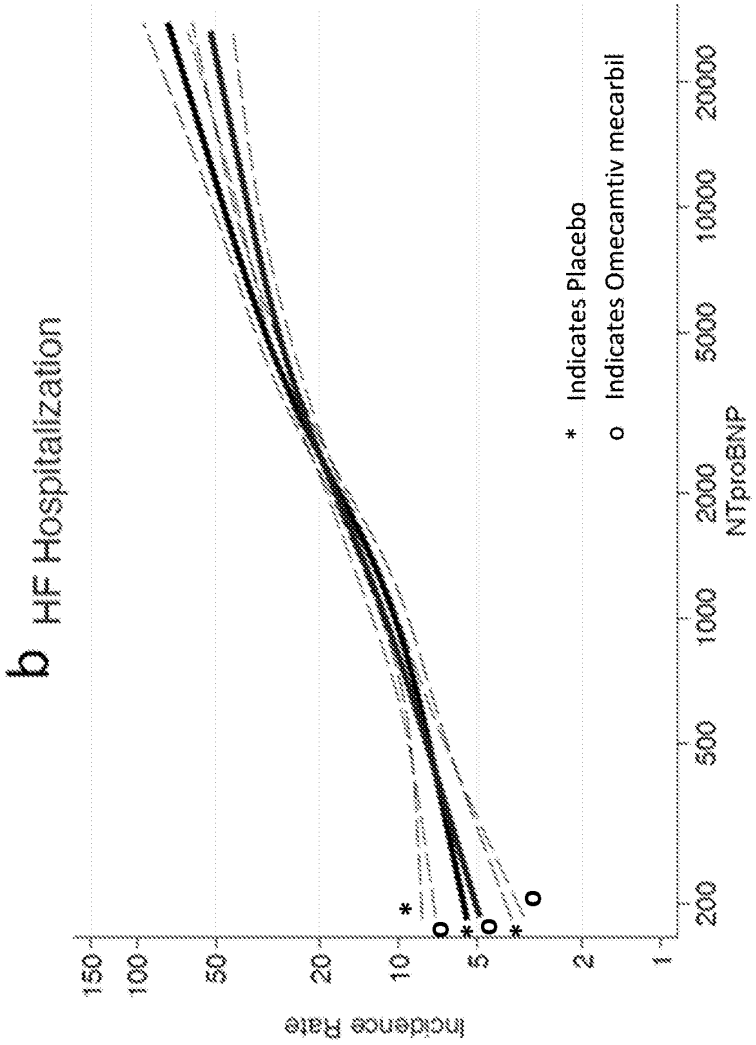

b HF Hospitalization
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 17B

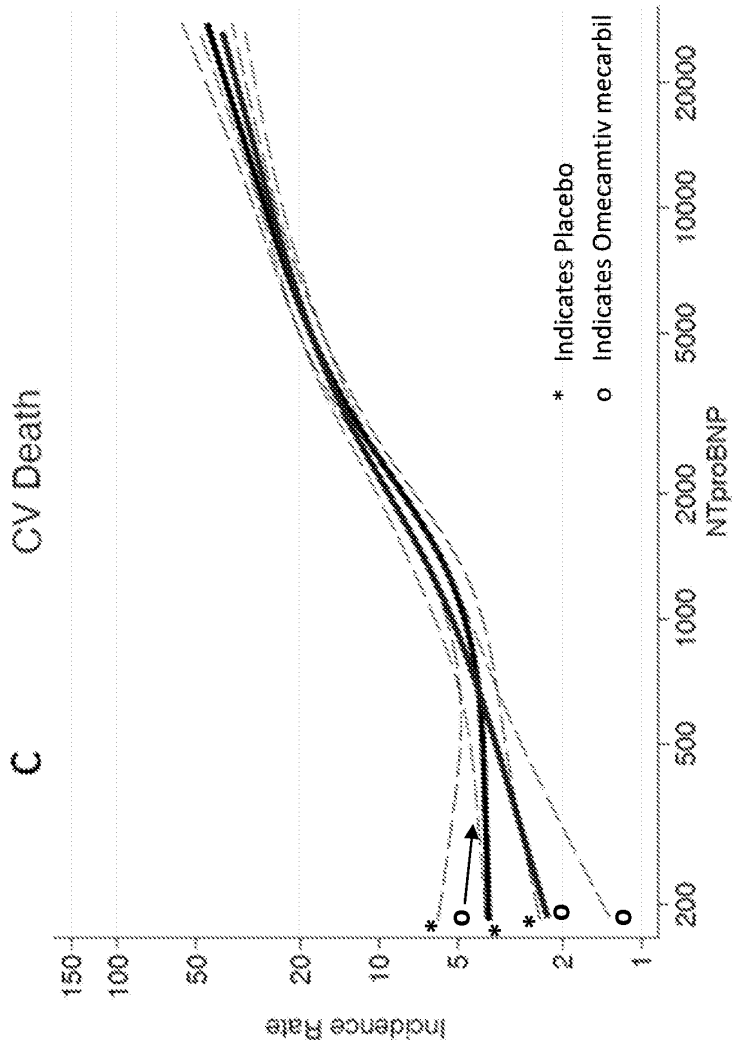

C
CV Death
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 17C

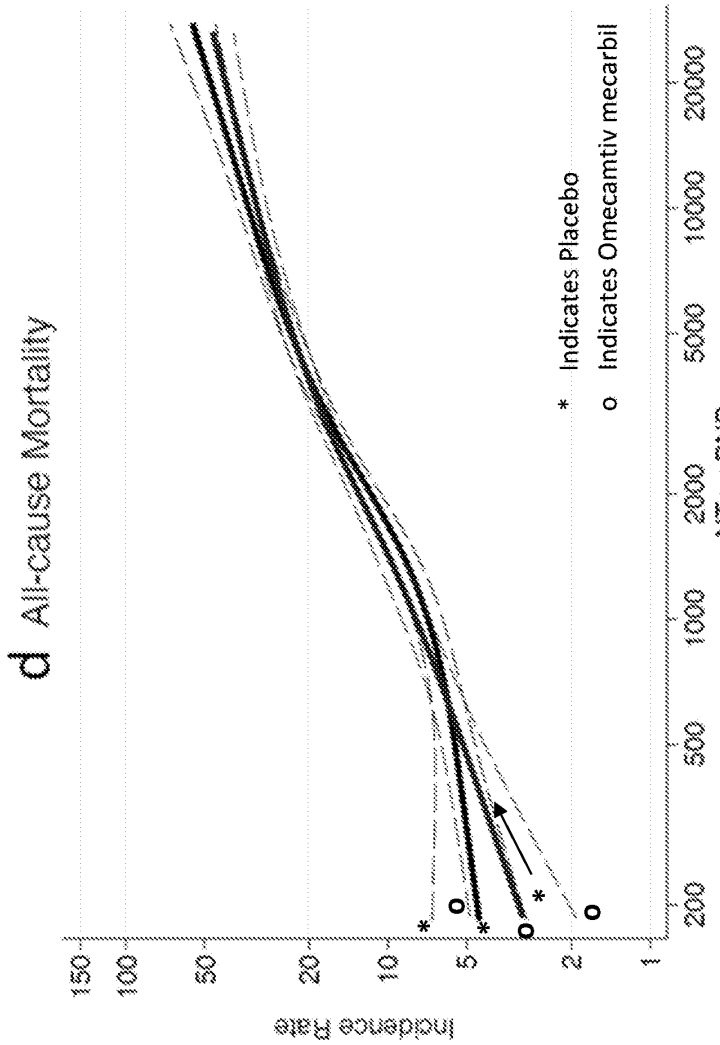

d All-cause Mortality
Incidence Rate
150
100
50
20
10
5
2
1
200
500
1000
2000
5000
10000
20000
NTproBNP
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 17D

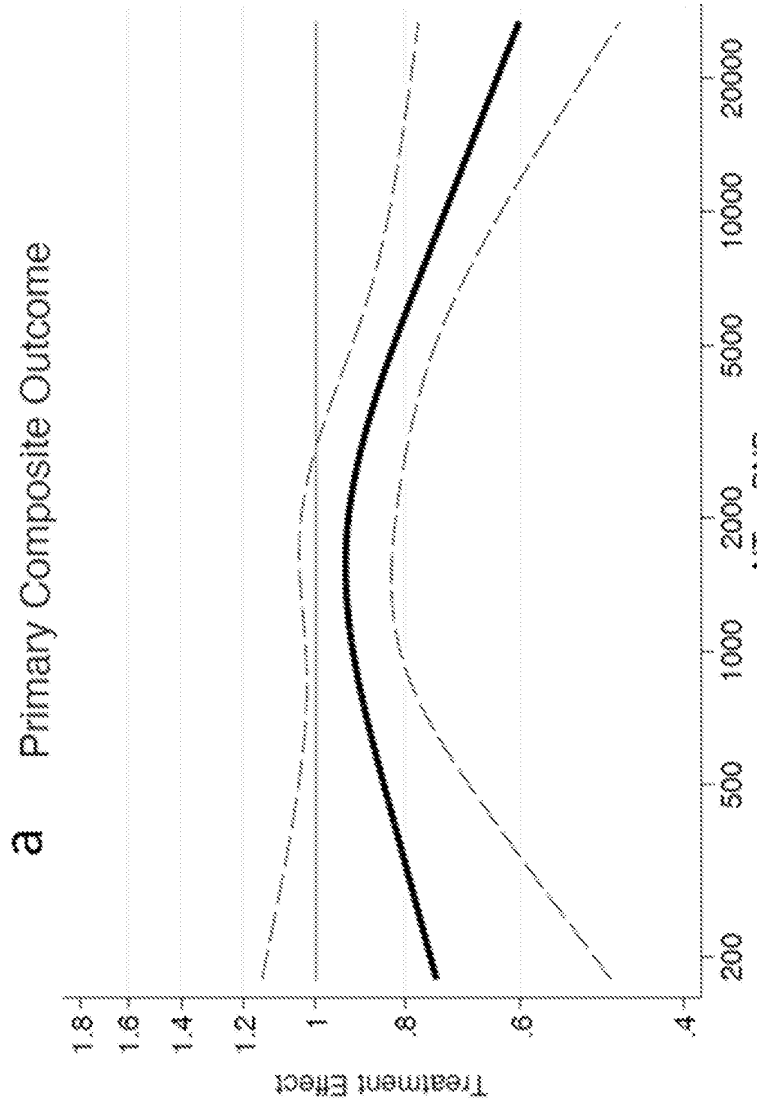

a Primary Composite Outcome
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 18A

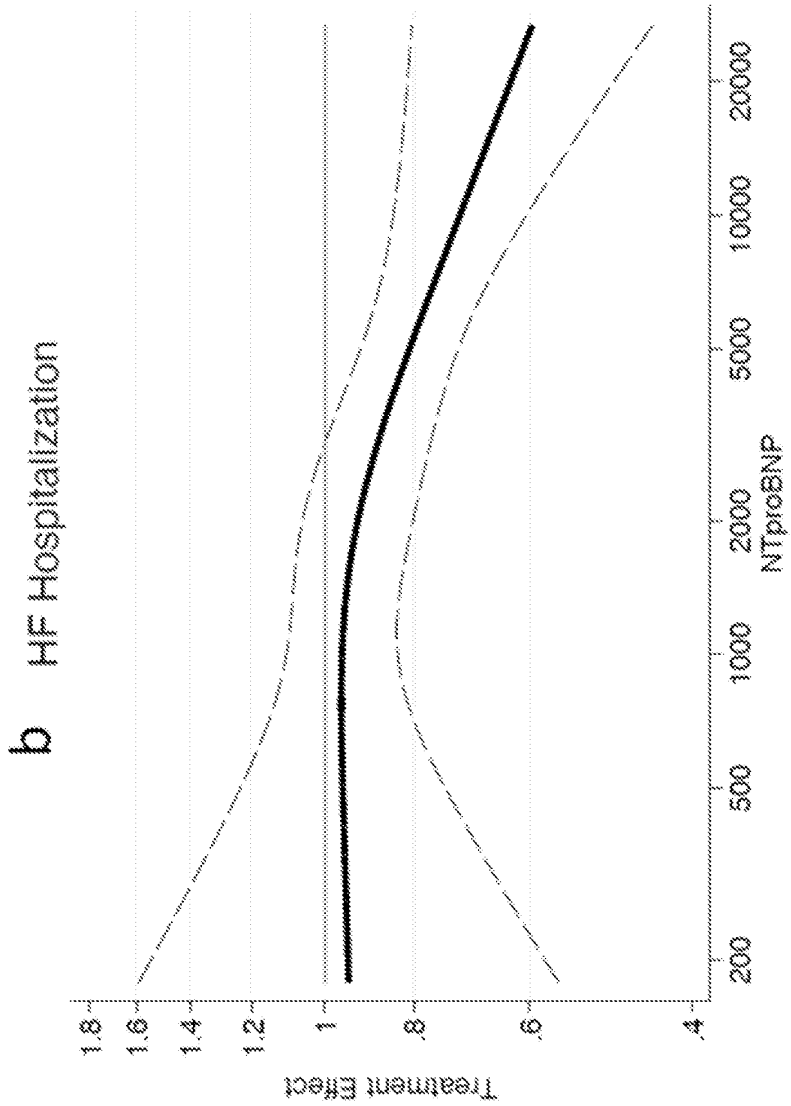

b HF Hospitalization
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 18B

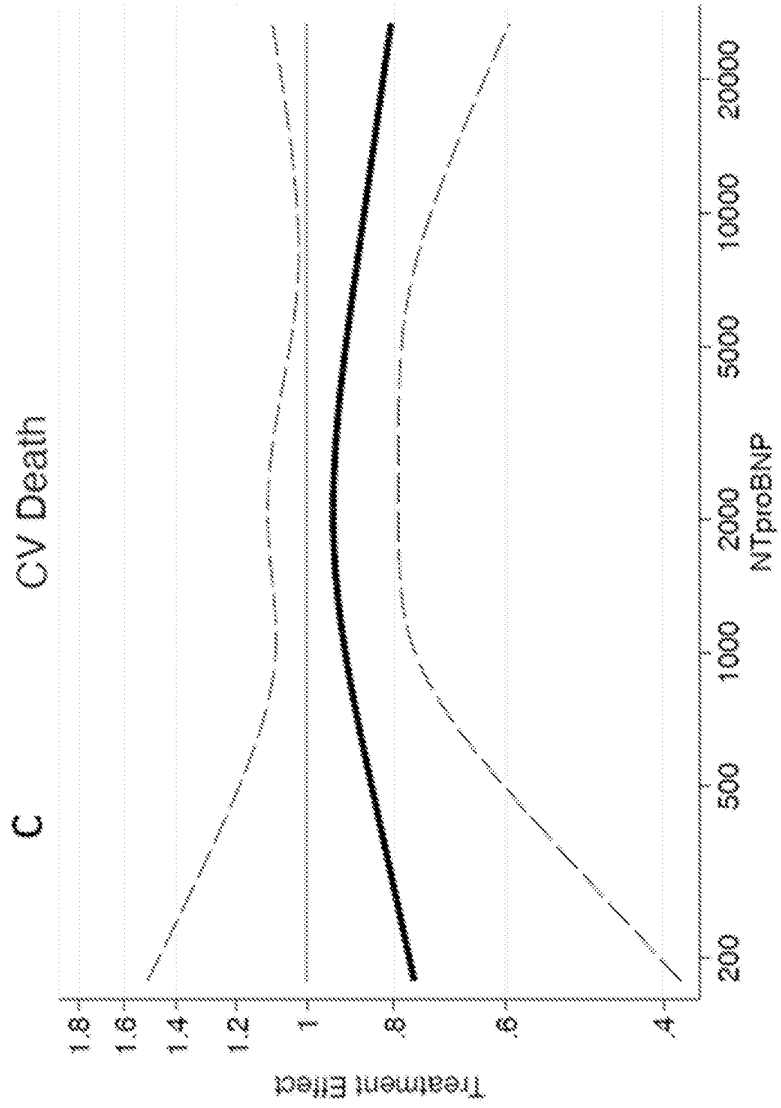

C
CV Death
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 18C

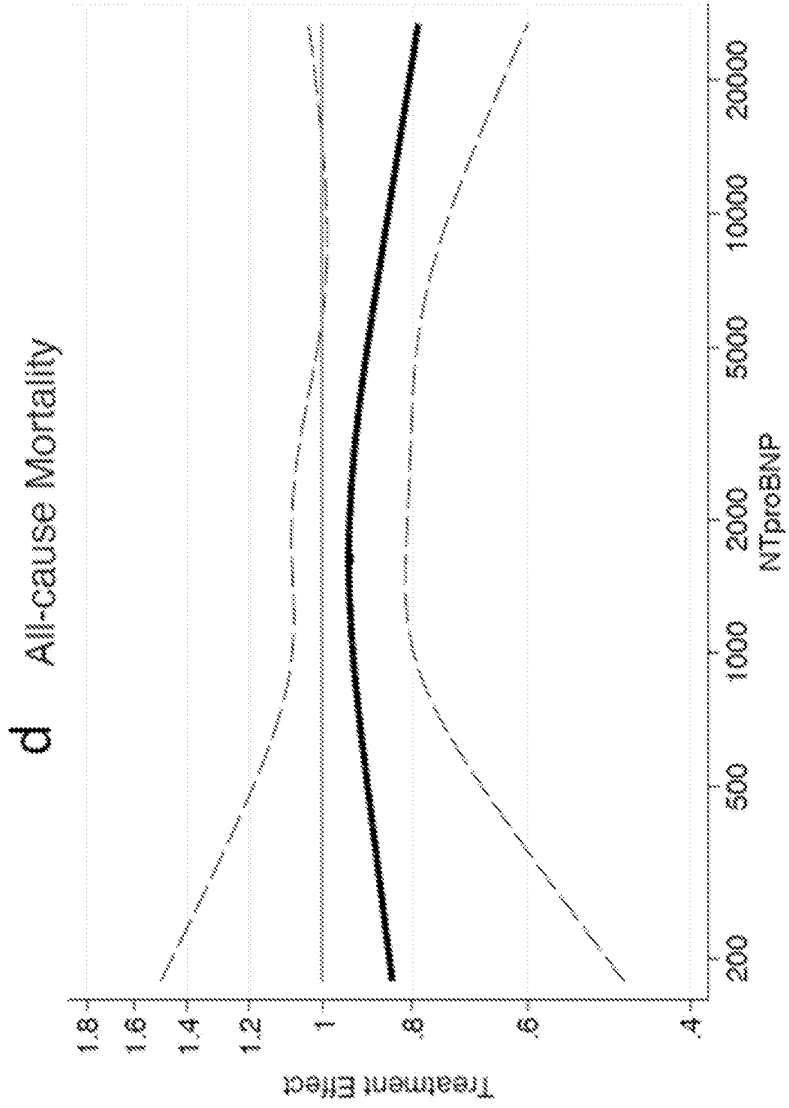

d All-cause Mortality
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 18D

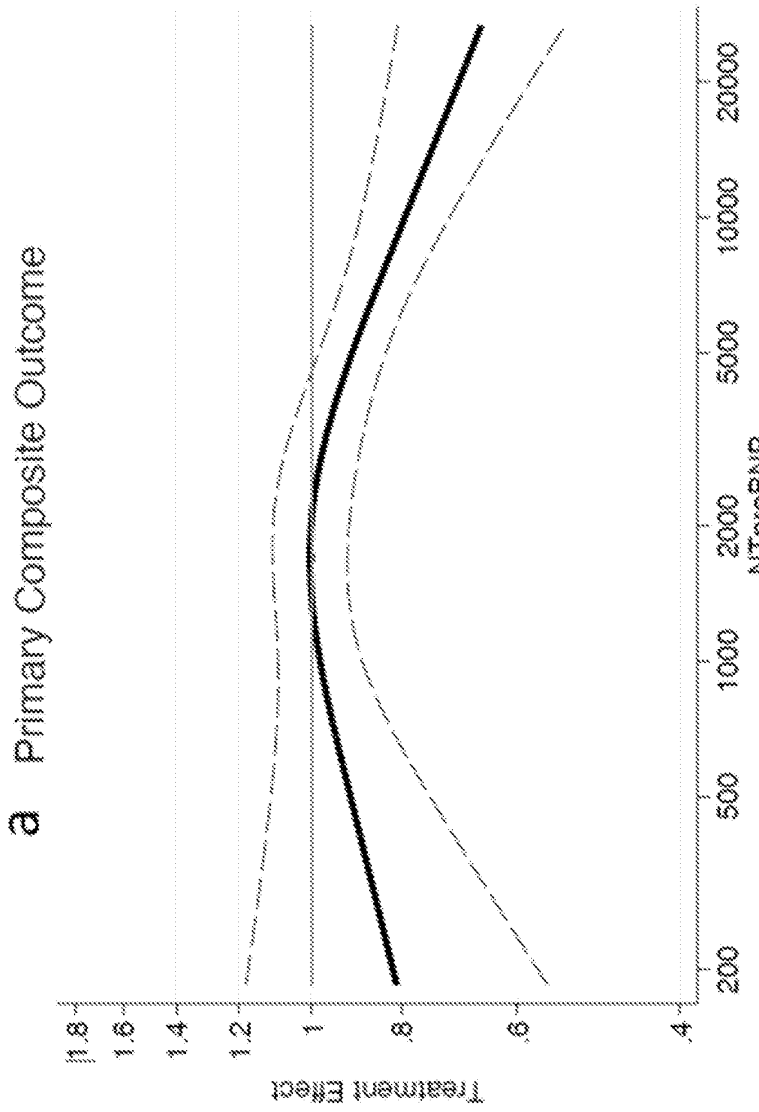

a Primary Composite Outcome
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 19A

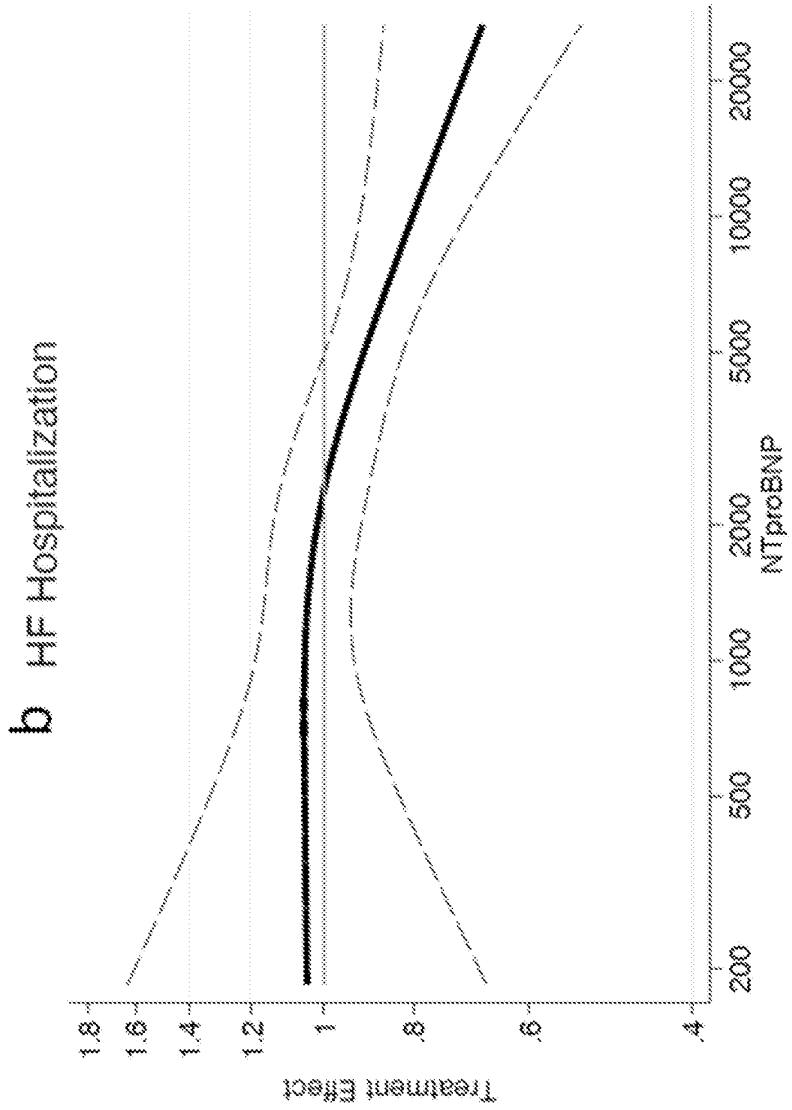

b HF Hospitalization
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 19B

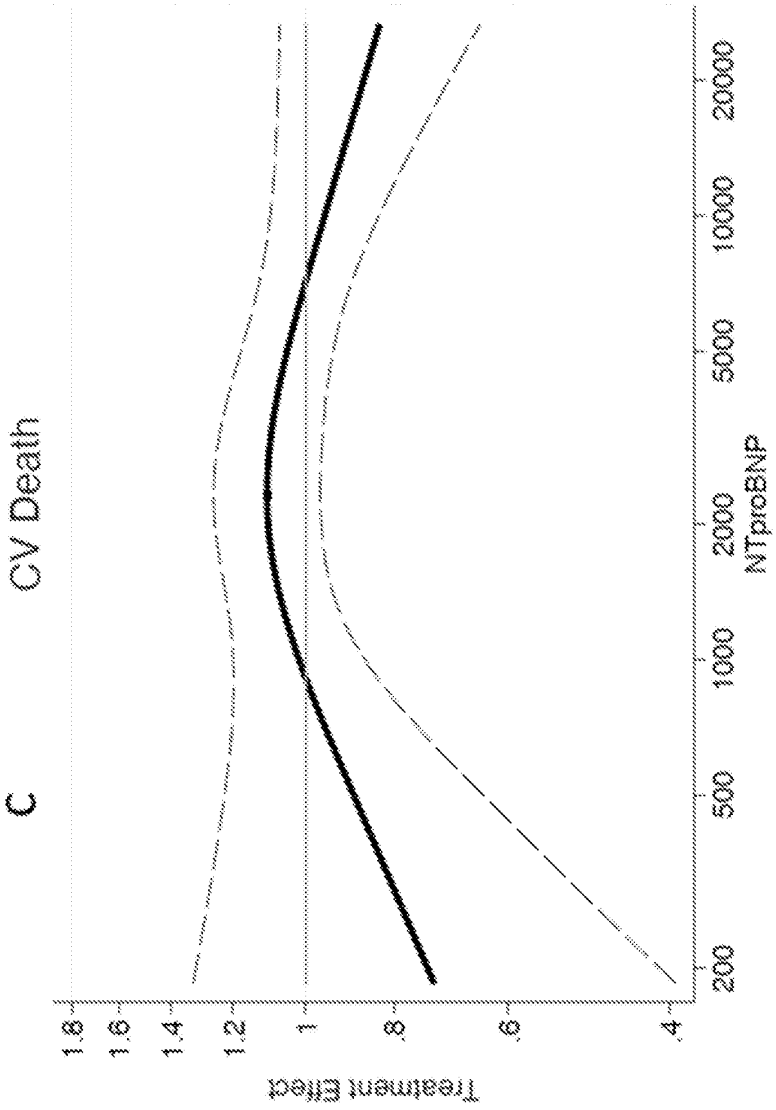

C
CV Death
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 19C

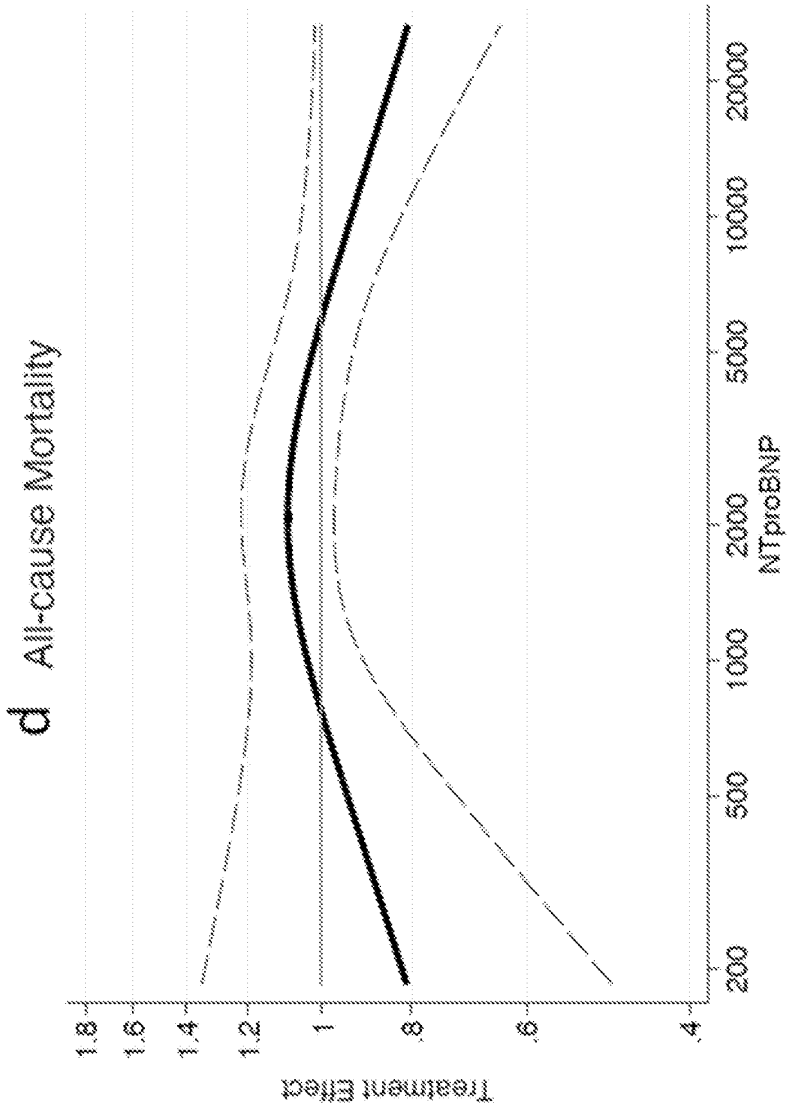

d All-cause Mortality
Treatment Effect
1.8
1.6
1.4
1.2
1
.8
.6
.4
200
500
1000
2000
5000
10000
20000
NTproBNP

FIGURE 19D

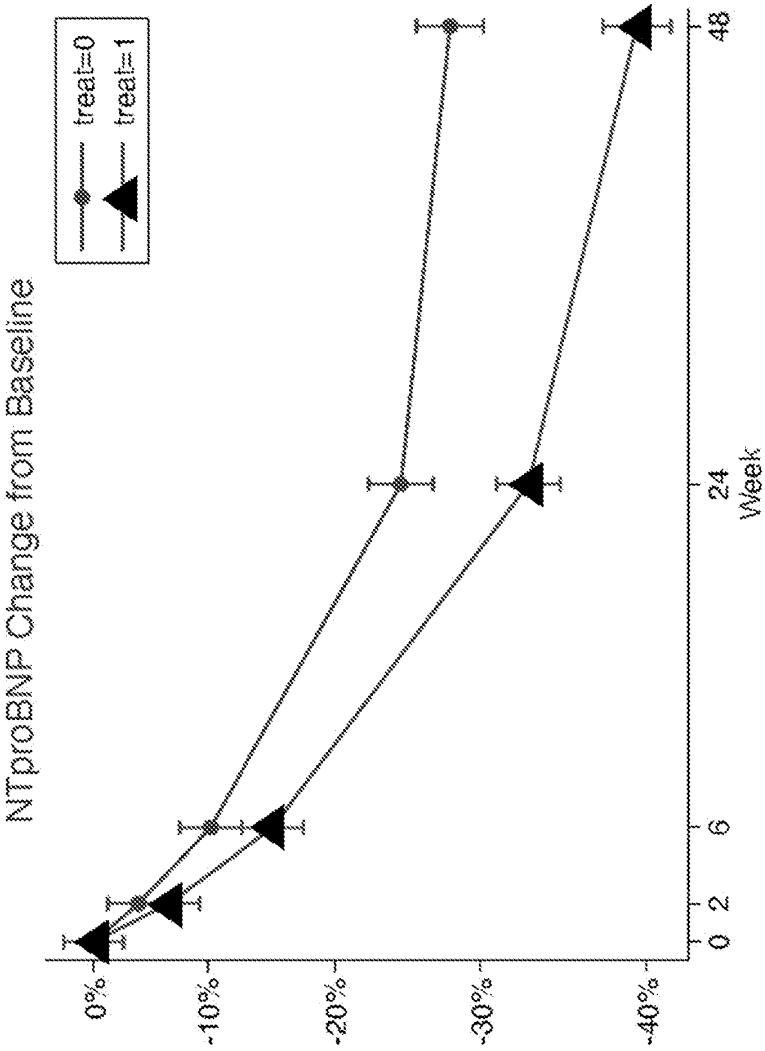

NTproBNP Change from Baseline
treat=0
treat=1
0%
-10%
-20%
-30%
-40%
0
2
6
24
48
Week

FIGURE 20A

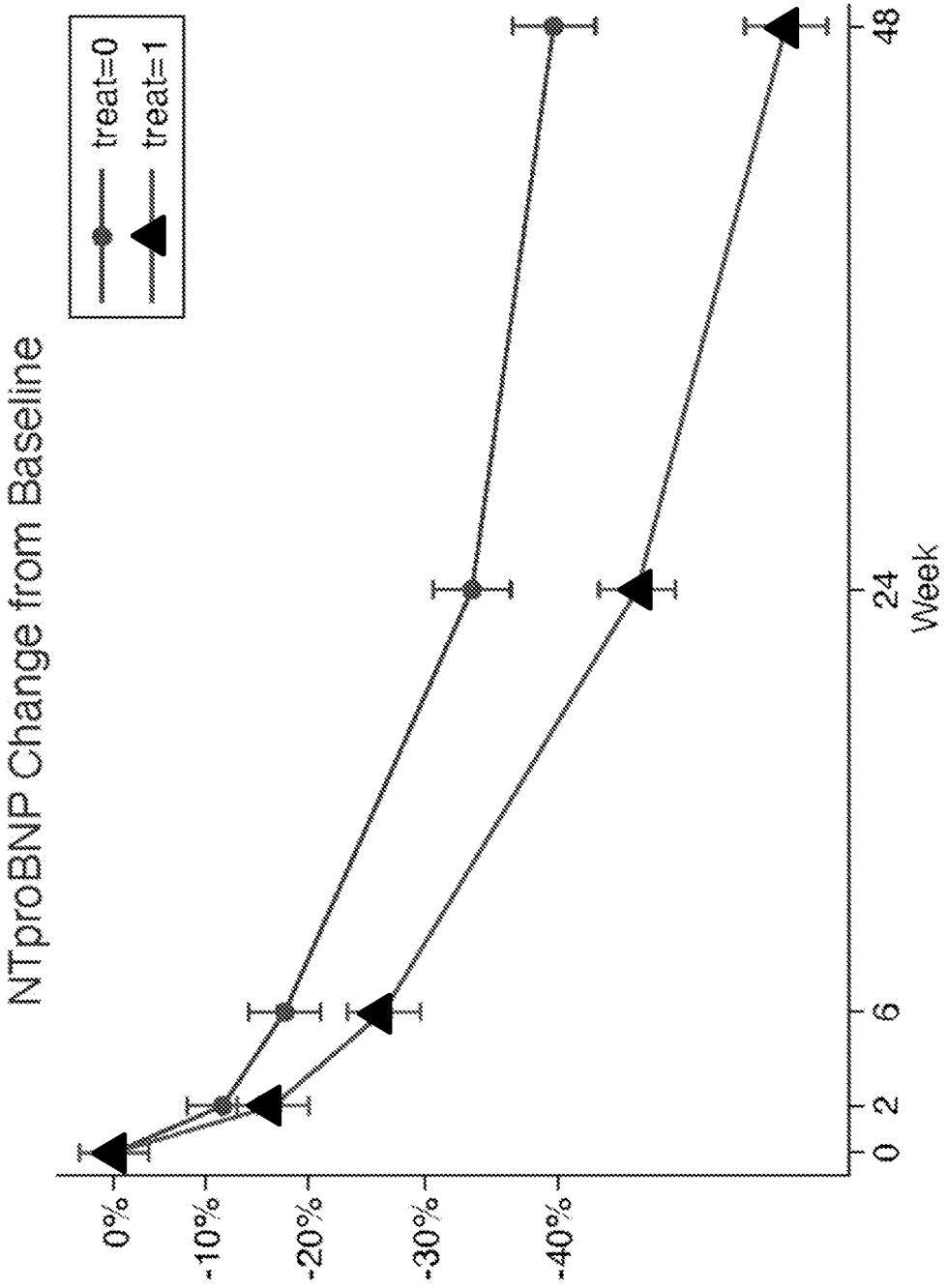

NTproBNP Change from Baseline
treat=0
treat=1
0%
-10%
-20%
-30%
-40%
0
2
6
24
48
Week

FIGURE 20B

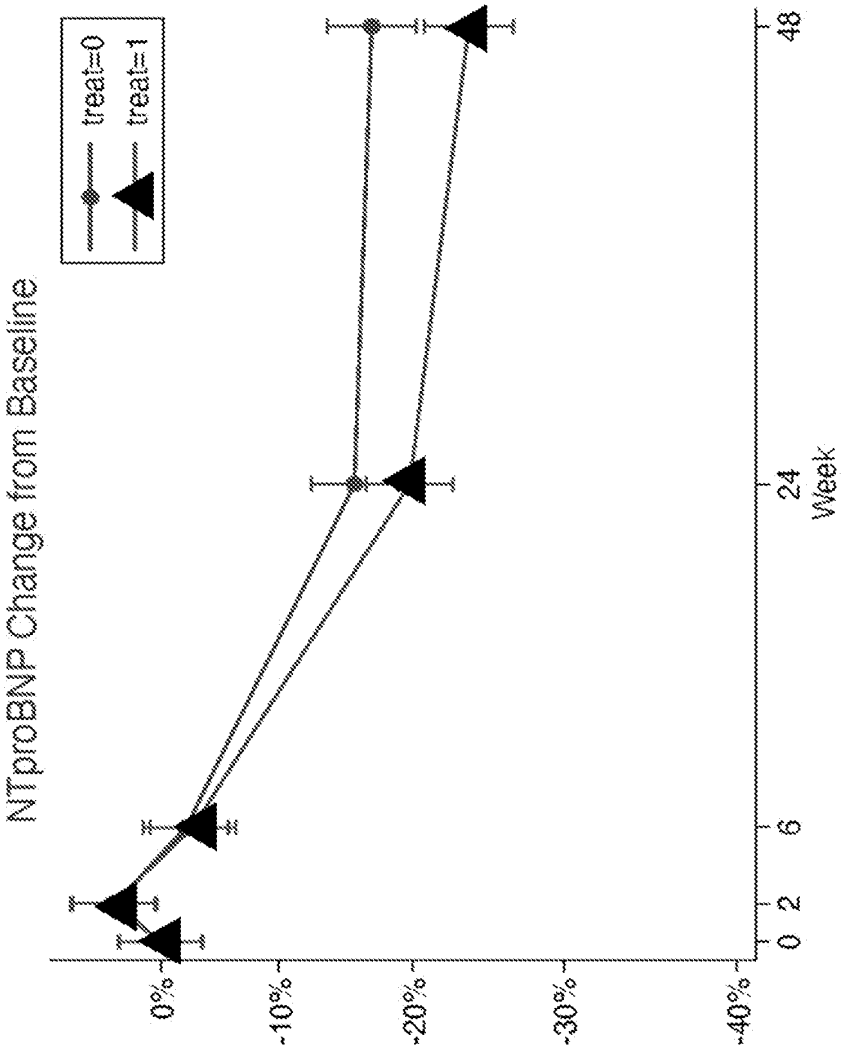

NTproBNP Change from Baseline
treat=0
treat=1
0%
-10%
-20%
-30%
-40%
0
2
6
24
48
Week

FIGURE 20C

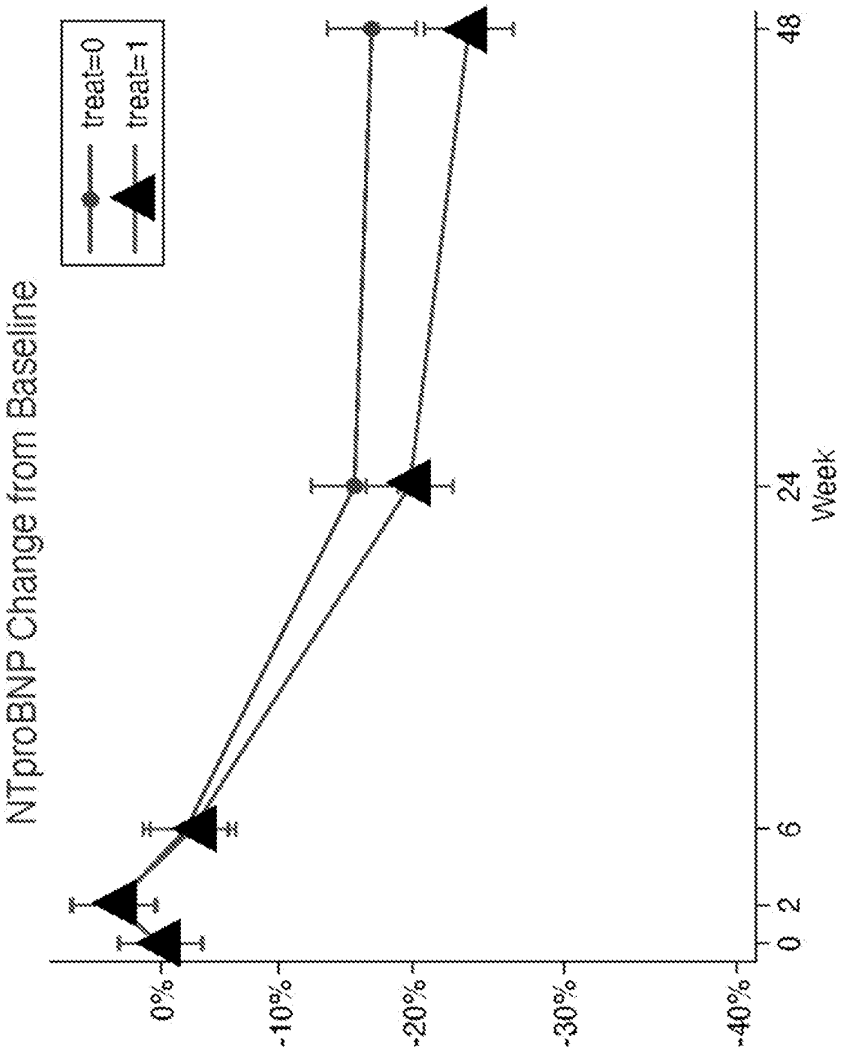

NTproBNP Change from Baseline
treat=0
treat=1
0%
-10%
-20%
-30%
-40%
0
2
6
24
48
Week

FIGURE 20D

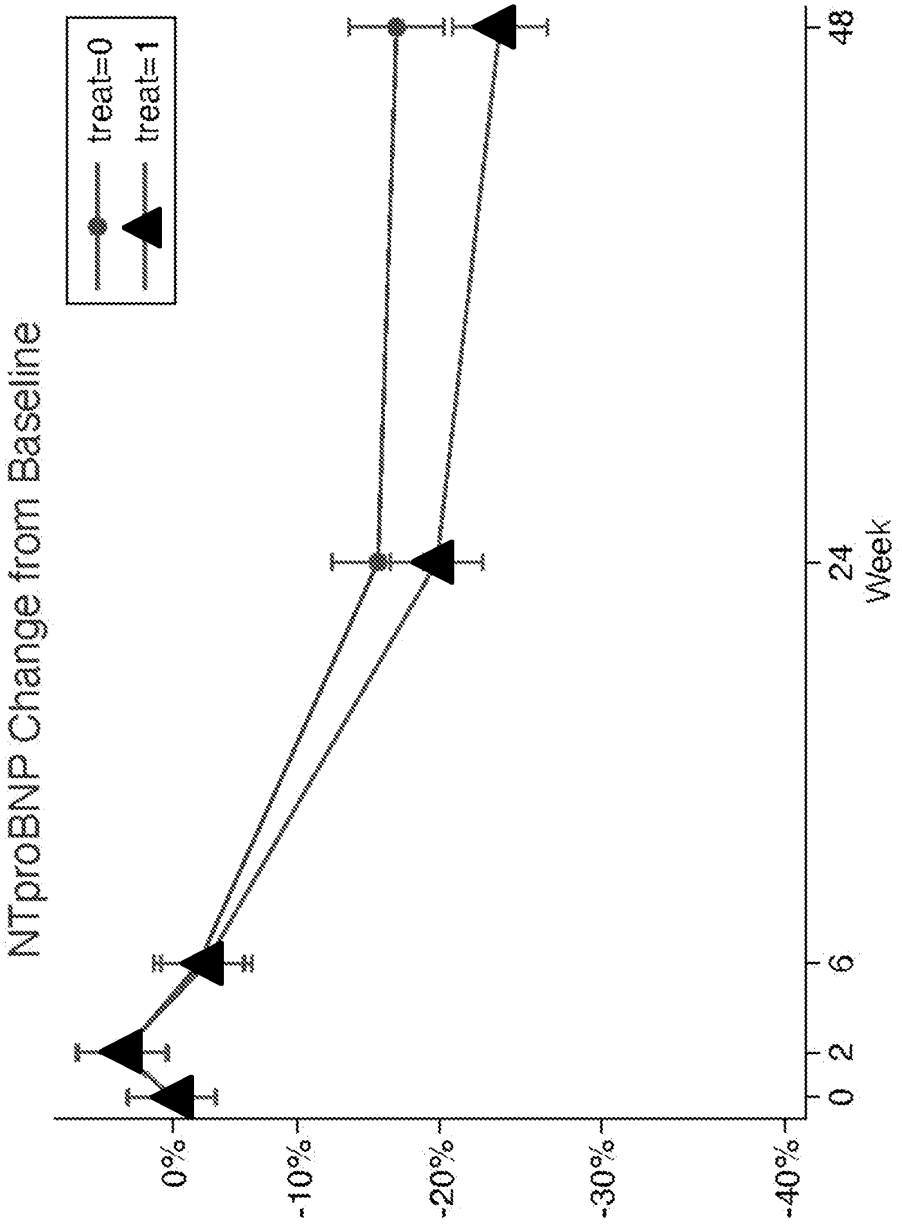

NTproBNP Change from Baseline
treat=0
treat=1
0%
-10%
-20%
-30%
-40%
0
2
6
24
48
Week

FIGURE 20E

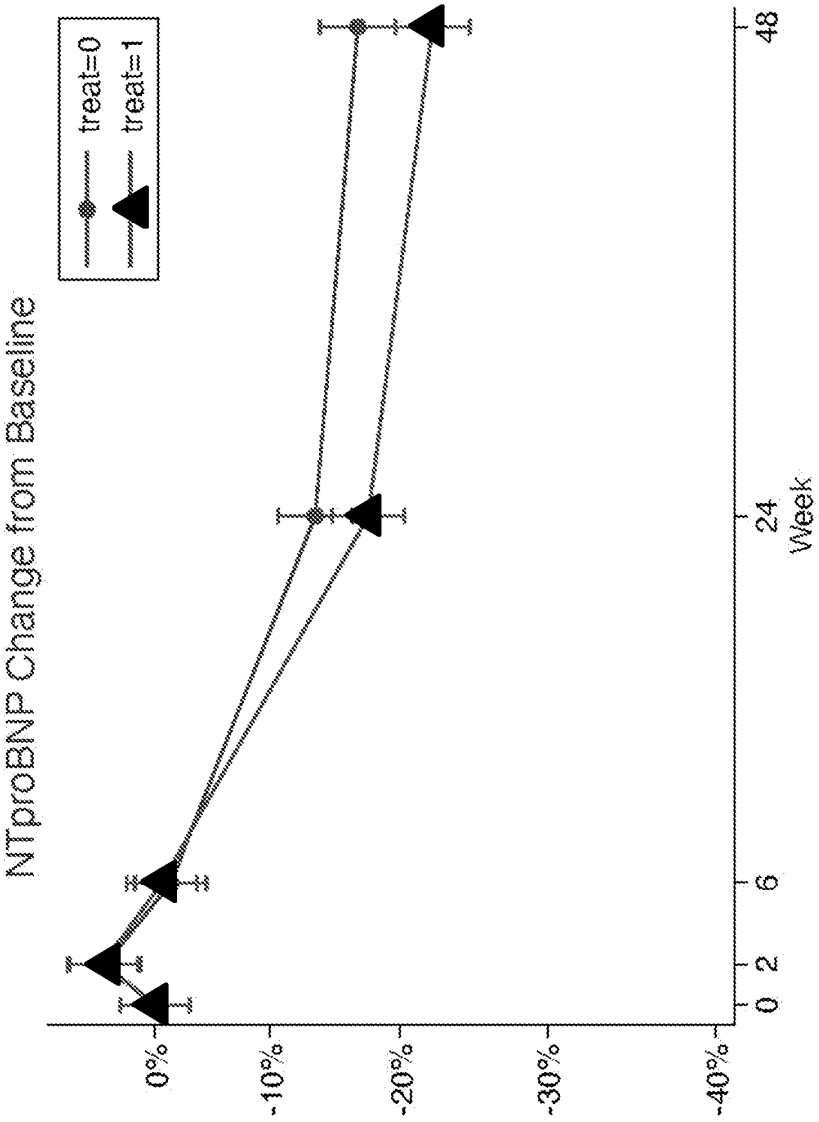

NTproBNP Change from Baseline
treat=0
treat=1
0%
-10%
-20%
-30%
-40%
0
2
6
24
48
Week

FIGURE 20F

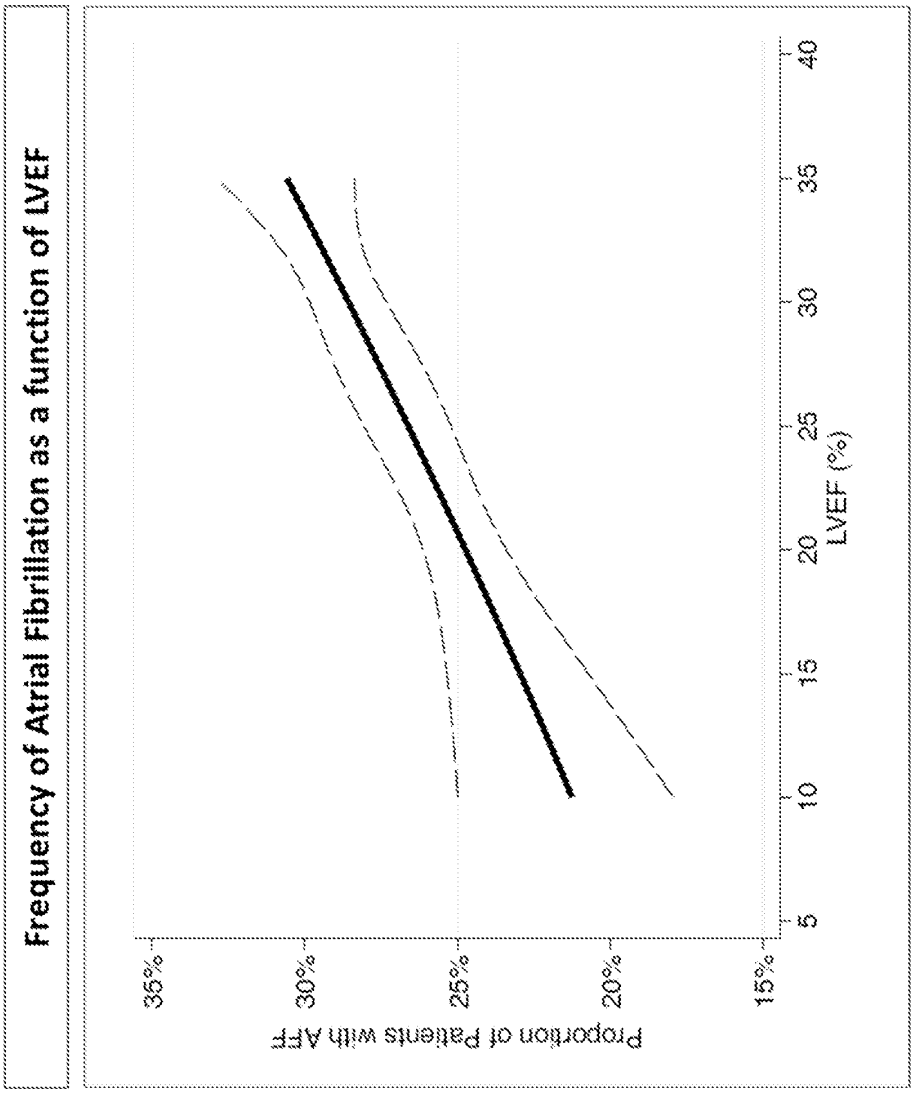

Frequency of Atrial Fibrillation as a function of LVEF
Proportion of Patients with AFF
36%
30%
25%
20%
15%
5
10
15
20
25
30
35
40
LVEF (%)

FIGURE 21A

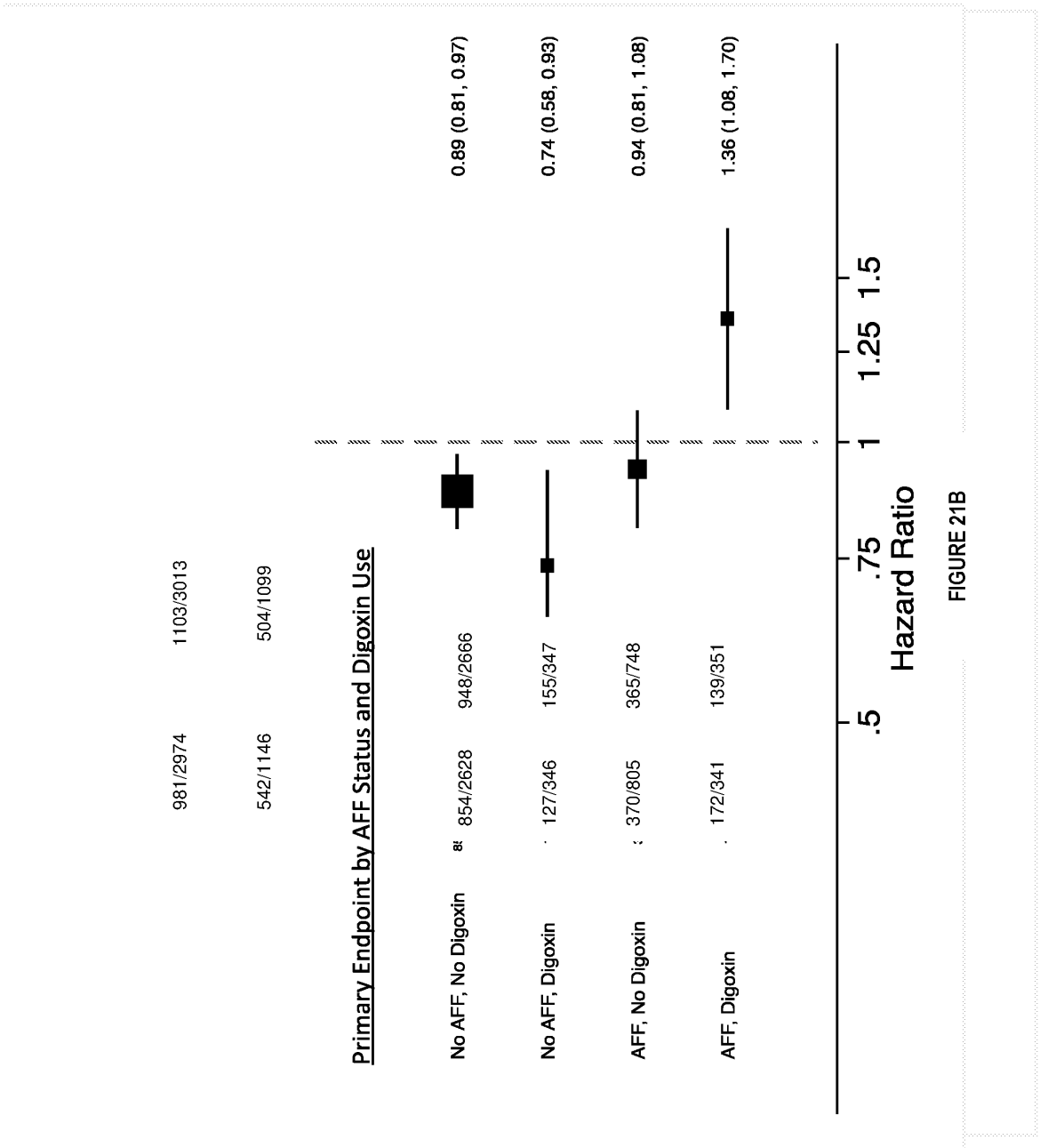

Primary Endpoint by AFF Status and Digoxin Use
No AFF, No Digoxin
854/2628
948/2666
0.89 (0.81, 0.97)
No AFF, Digoxin
127/346
155/347
0.74 (0.58, 0.93)
AFF, No Digoxin
370/805
365/748
0.94 (0.81, 1.08)
AFF, Digoxin
172/341
139/351
1.36 (1.08, 1.70)
981/2974
1103/3013
542/1146
504/1099
.5
.75
1
1.25
1.5
Hazard Ratio

FIGURE 21B

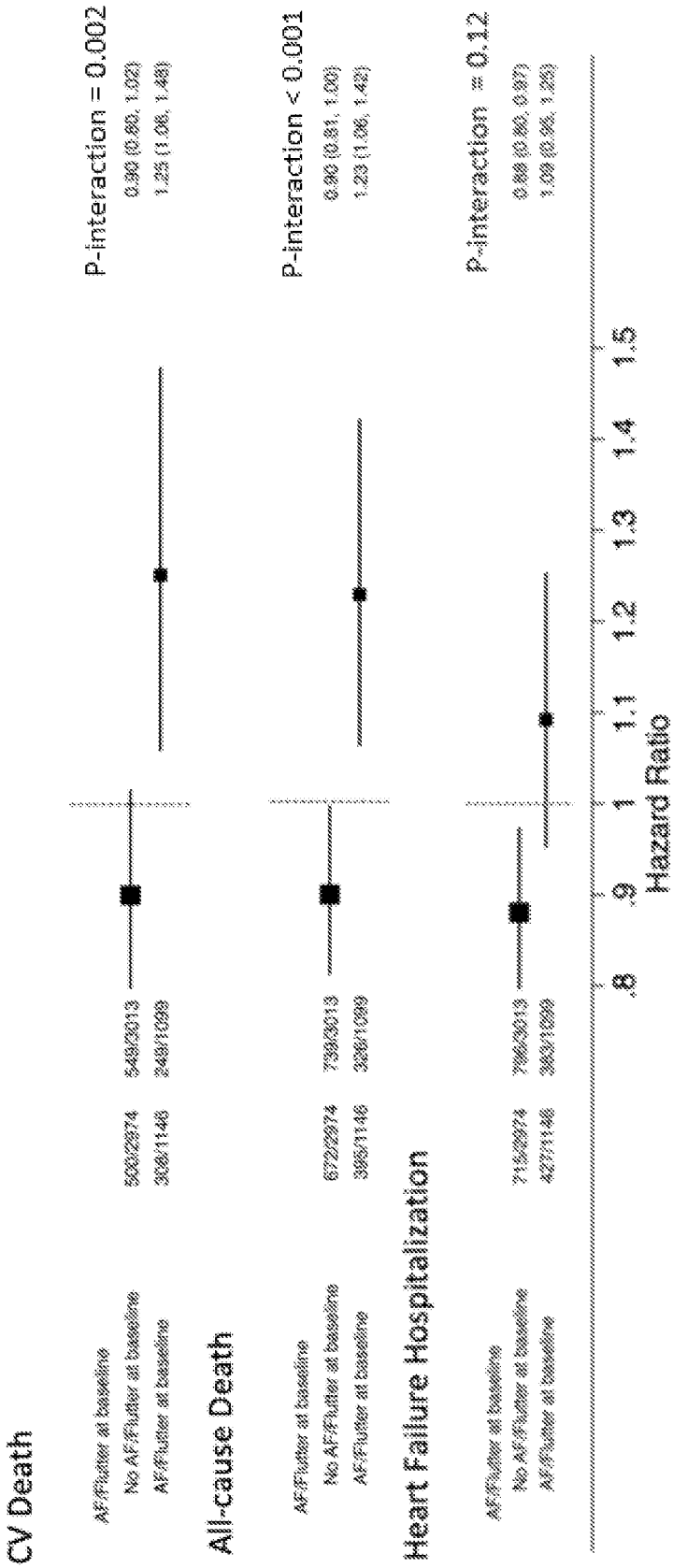

CV Death
AF/Flutter at baseline
No AF/Flutter at baseline
AF/Flutter at baseline
520/2874
308/1148
549/3013
249/1099
P-interaction = 0.002
0.90 (0.80, 1.02)
1.23 (1.06, 1.45)
All-cause Death
AF/Flutter at baseline
No AF/Flutter at baseline
AF/Flutter at baseline
672/2874
382/1148
739/3013
326/1099
P-interaction < 0.001
0.90 (0.81, 1.00)
1.23 (1.06, 1.42)
Heart Failure Hospitalization
AF/Flutter at baseline
No AF/Flutter at baseline
AF/Flutter at baseline
715/2874
427/1148
796/3013
363/1099
P-interaction = 0.12
0.89 (0.80, 0.97)
1.09 (0.96, 1.23)
.8
.9
1
1.1
1.2
1.3
1.4
1.5
Hazard Ratio

FIGURE 21C

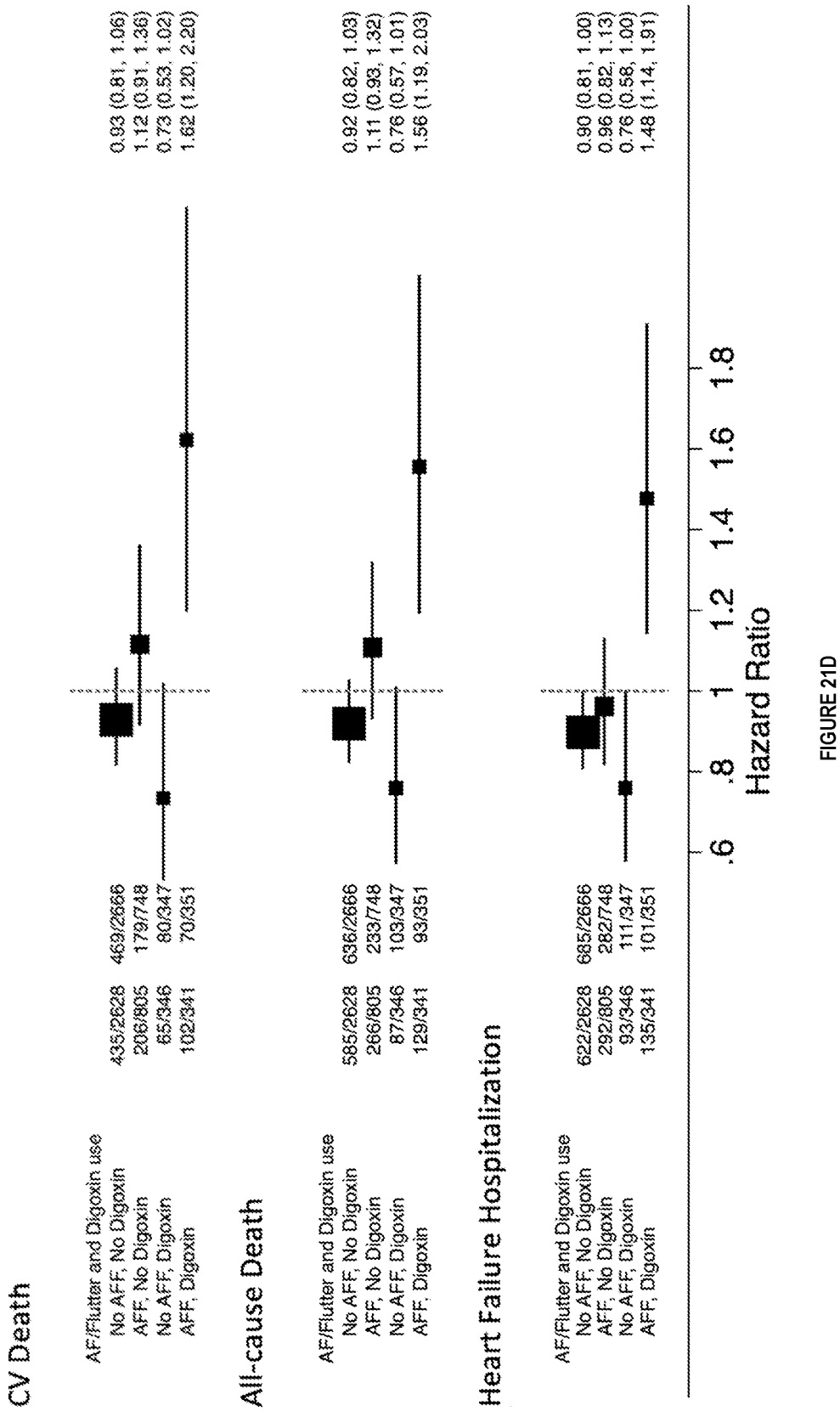

CV Death
AF/Flutter and Digoxin use
No AFF, No Digoxin 435/2628 469/2666 0.93 (0.81, 1.06)
AFF, No Digoxin 206/805 179/748 1.12 (0.91, 1.36)
No AFF, Digoxin 65/346 80/347 0.73 (0.53, 1.02)
AFF, Digoxin 102/341 70/351 1.62 (1.20, 2.20)
All-cause Death
AF/Flutter and Digoxin use
No AFF, No Digoxin 585/2628 636/2666 0.92 (0.82, 1.03)
AFF, No Digoxin 266/805 233/748 1.11 (0.93, 1.32)
No AFF, Digoxin 87/346 103/347 0.76 (0.57, 1.01)
AFF, Digoxin 129/341 93/351 1.56 (1.19, 2.03)
Heart Failure Hospitalization
AF/Flutter and Digoxin use
No AFF, No Digoxin 622/2628 685/2666 0.90 (0.81, 1.00)
AFF, No Digoxin 292/805 282/748 0.96 (0.82, 1.13)
No AFF, Digoxin 93/346 111/347 0.76 (0.58, 1.00)
AFF, Digoxin 135/341 101/351 1.48 (1.14, 1.91)
.6
.8
1
1.2
1.4
1.6
1.8
Hazard Ratio

FIGURE 21D

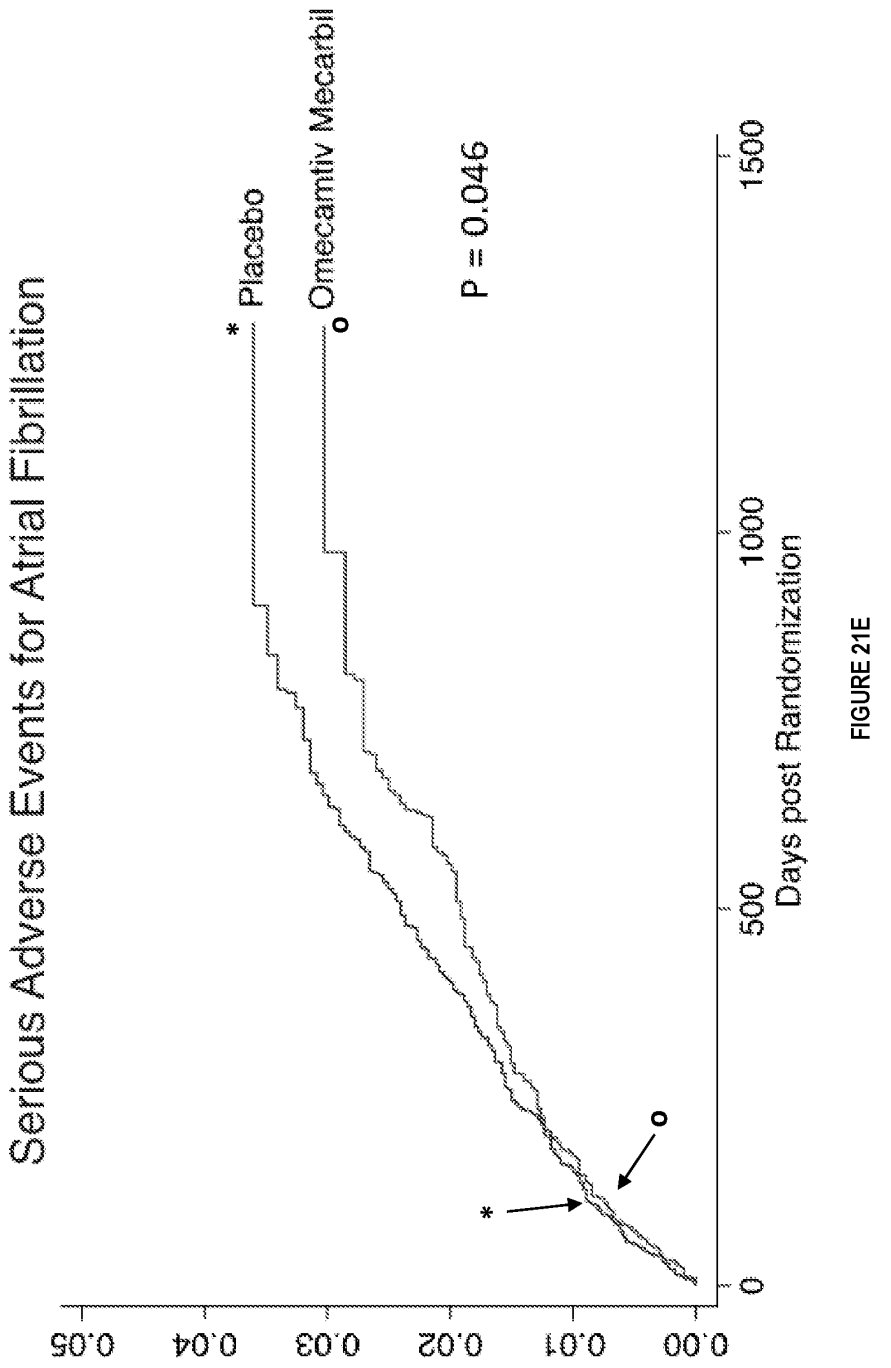

Serious Adverse Events for Atrial Fibrillation
* Placebo
o Omecamtiv Mecarbil
P = 0.046
0.00
0.01
0.02
0.03
0.04
0.05
0
500
1000
1500
Days post Randomization
*
o

FIGURE 21E

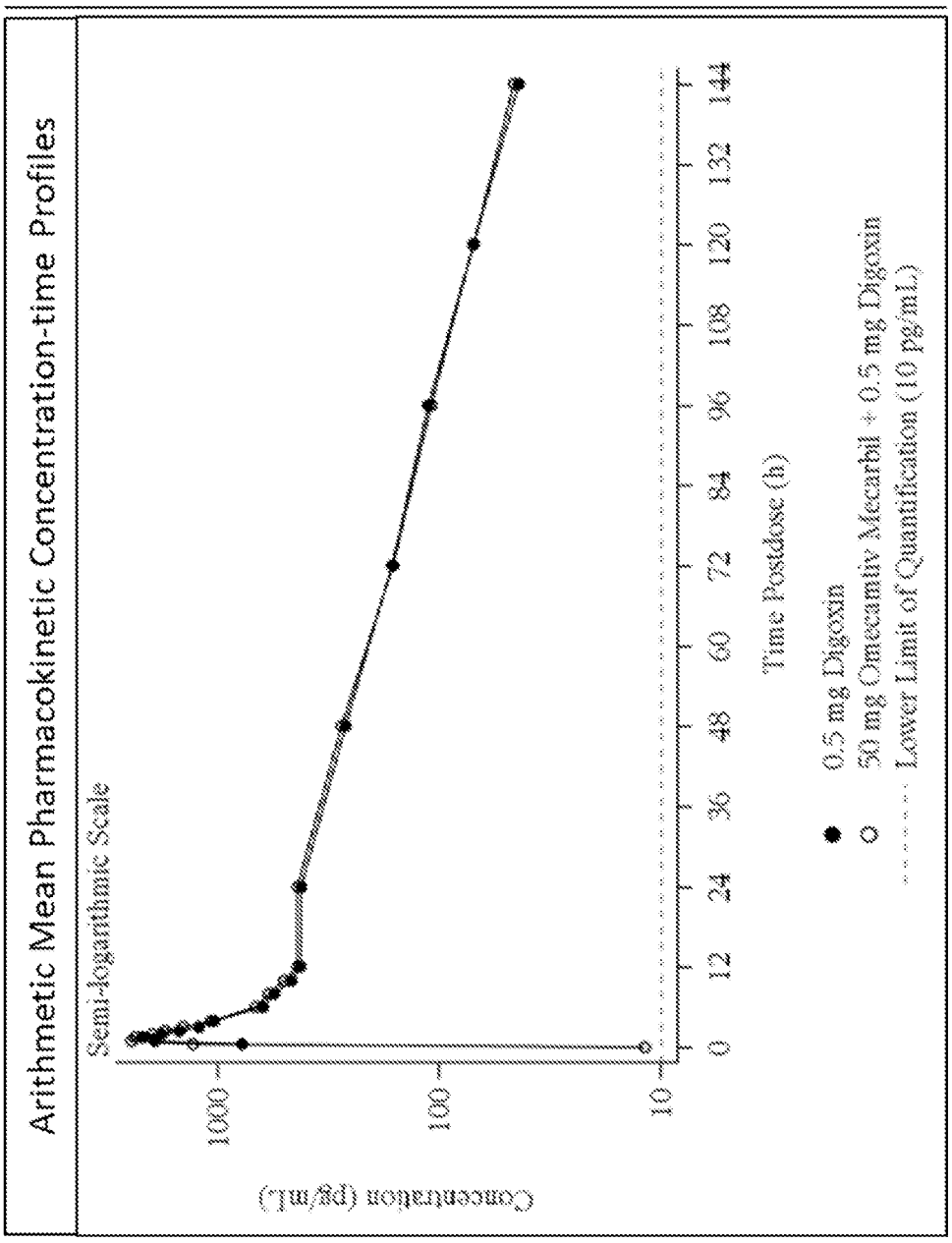

Arithmetic Mean Pharmacokinetic Concentration-time Profiles
Semi-logarithmic Scale
Concentration (pg/mL)
1000
100
10
0
12
24
36
48
60
72
84
96
108
120
132
144
Time Postdose (h)
0.5 mg Digoxin
50 mg Omecamtiv Mecarbil + 0.5 mg Digoxin
Lower Limit of Quantification (10 pg/mL)

FIGURE 21F

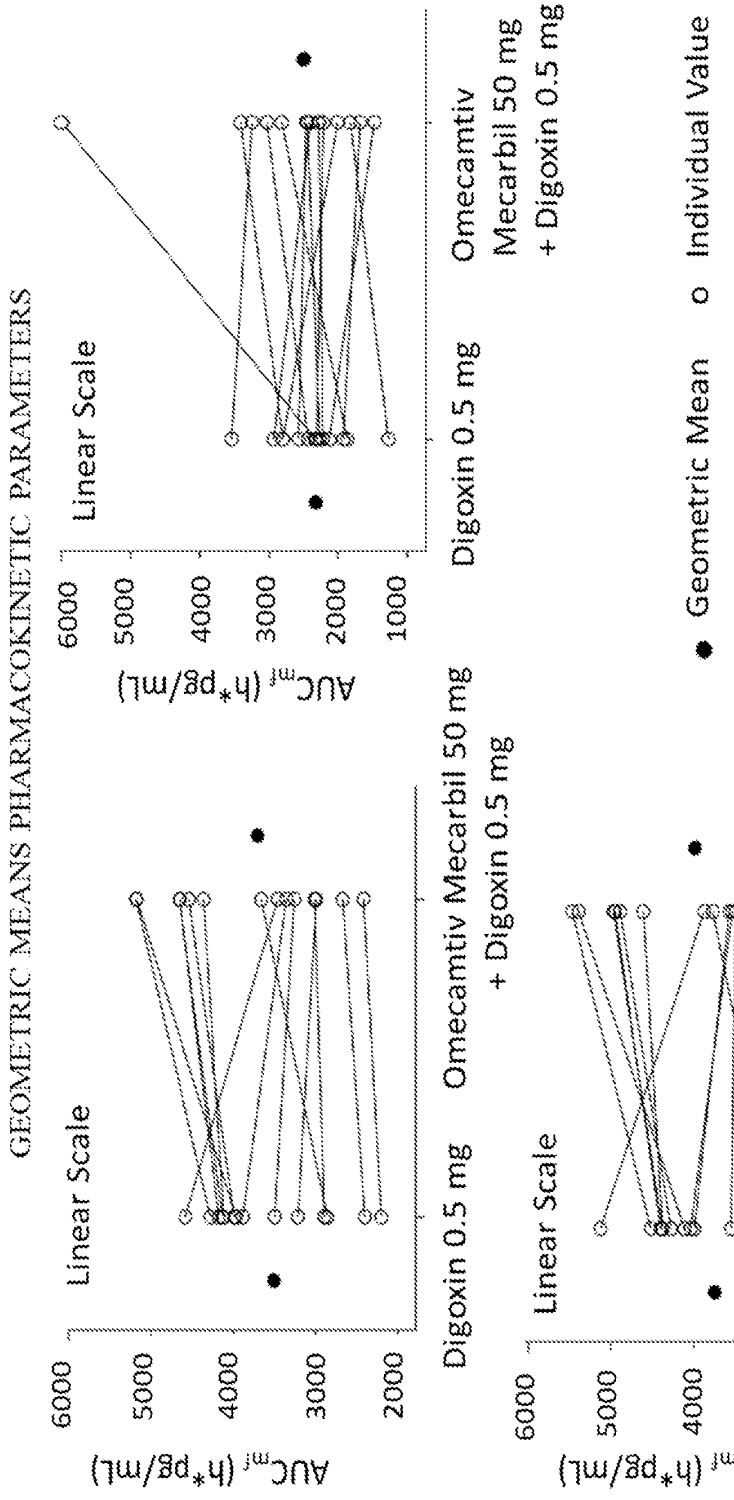

GEOMETRIC MEANS PHARMACOKINETIC PARAMETERS
Linear Scale
AUC_{inf} (h*pg/mL)
6000
5000
4000
3000
2000
1000
Digoxin 0.5 mg
Omecamtiv Mecarbil 50 mg + Digoxin 0.5 mg
Geometric Mean
Individual Value

FIGURE 21G

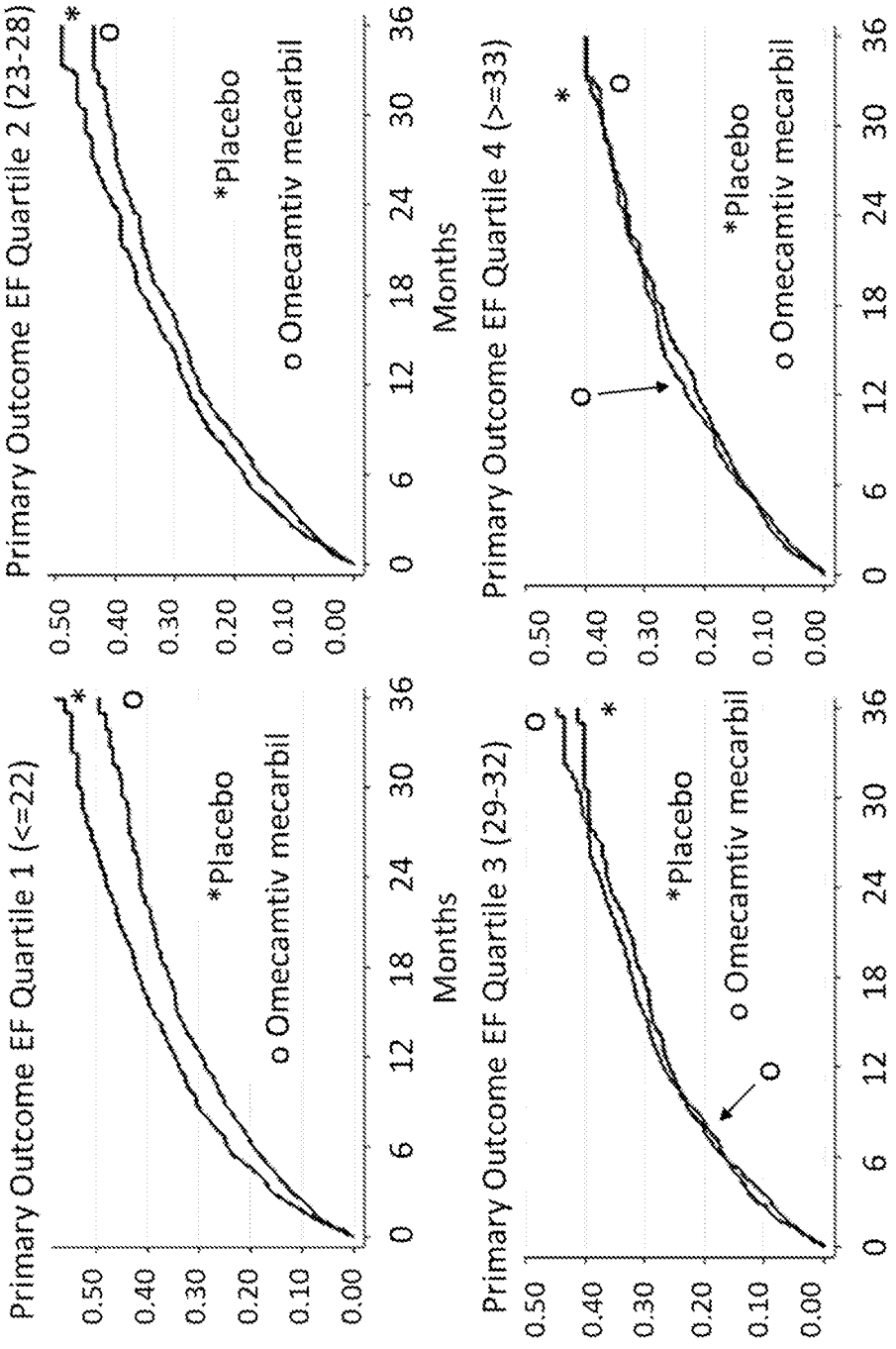

Primary Outcome EF Quartile 1 (<=22)
Primary Outcome EF Quartile 2 (23-28)
Primary Outcome EF Quartile 3 (29-32)
Primary Outcome EF Quartile 4 (>=33)
0.50
0.40
0.30
0.20
0.10
0.00
0 6 12 18 24 30 36
Months
*Placebo
o Omecamtiv mecarbil
*
O

FIGURE 22

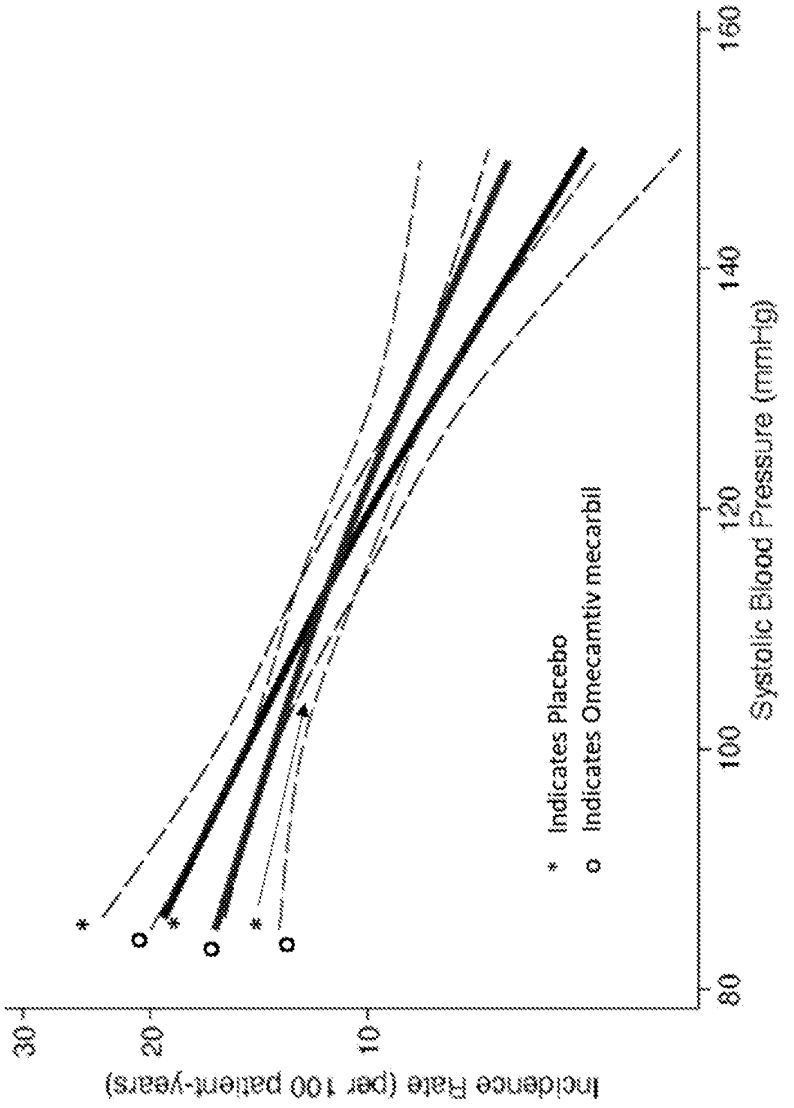

Incidence Rate (per 100 patient-years)
30
20
10
80
100
120
140
160
Systolic Blood Pressure (mmHg)
* Indicates Placebo
o Indicates Omecamtiv mecarbil

FIGURE 23A

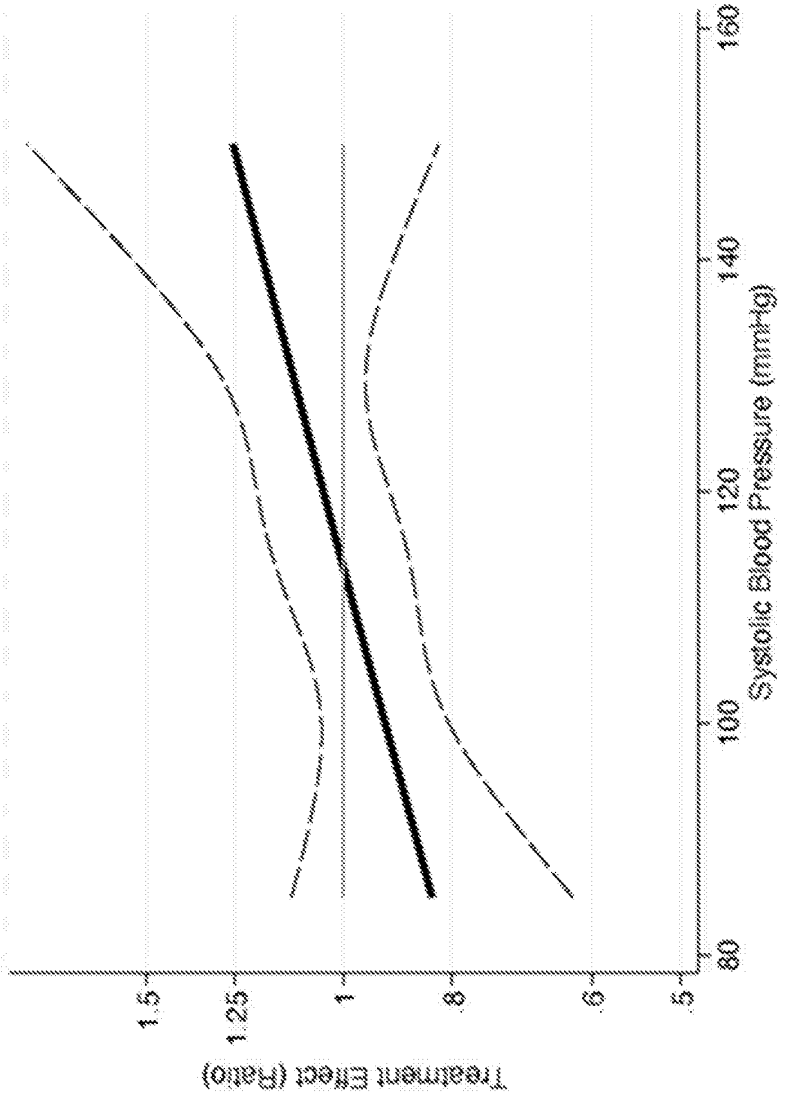

Treatment Effect (Ratio)
1.5
1.25
1
.8
.6
.5
80
100
120
140
160
Systolic Blood Pressure (mmHg)

FIGURE 23B

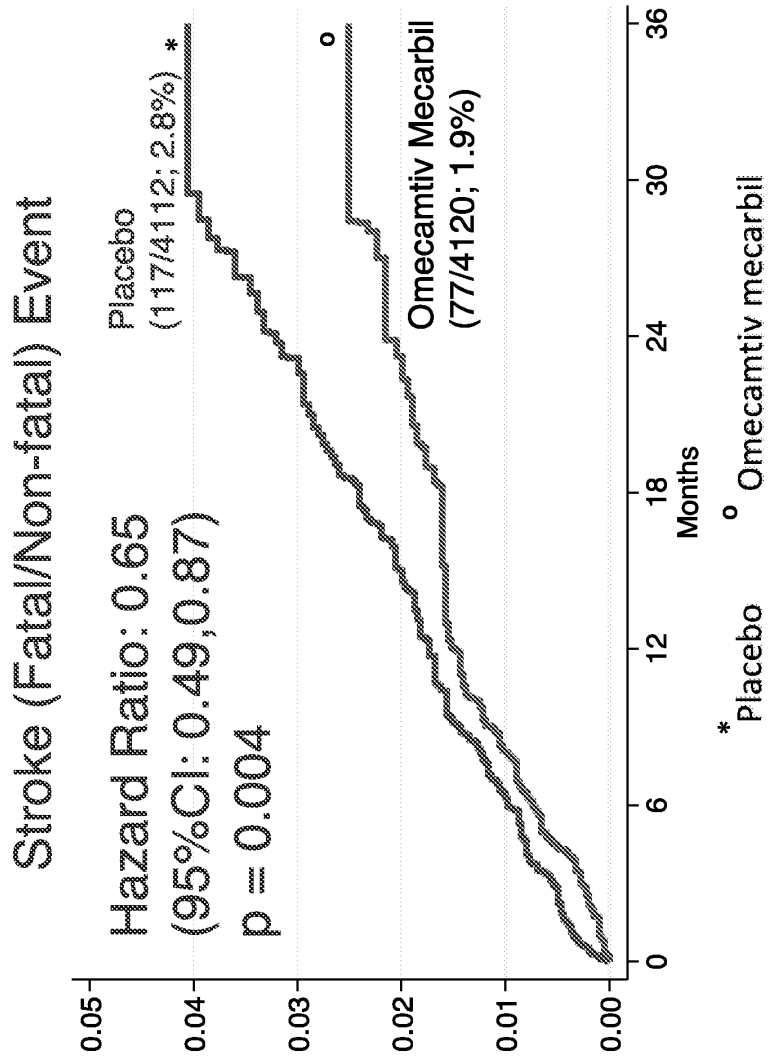

Stroke (Fatal/Non-fatal) Event
Hazard Ratio: 0.65
(95%CI: 0.49,0.87)
p = 0.004
Placebo
(117/4112; 2.8%) *
Omecamtiv Mecarbil
(77/4120; 1.9%)
o
0.05
0.04
0.03
0.02
0.01
0.00
0
6
12
18
24
30
36
Months
*Placebo
oOmecamtiv mecarbil

FIGURE 24

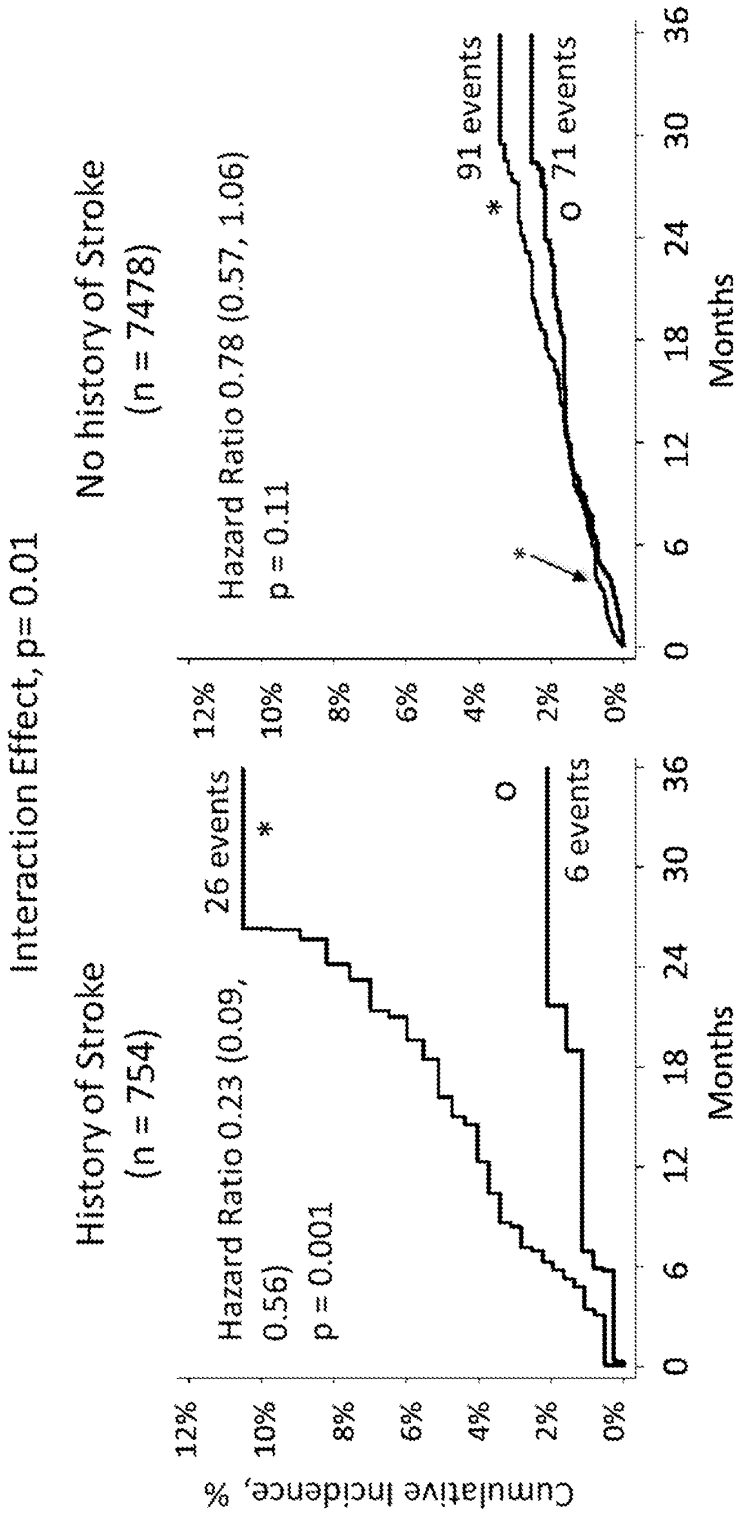

Interaction Effect, p= 0.01
History of Stroke
(n = 754)
Hazard Ratio 0.23 (0.09, 0.56)
p = 0.001
26 events
6 events
No history of Stroke
(n = 7478)
Hazard Ratio 0.78 (0.57, 1.06)
p = 0.11
91 events
71 events
Cumulative Incidence, %
12%
10%
8%
6%
4%
2%
0%
0
6
12
18
24
30
36
Months
Placebo
Omecamtiv mecarbil

FIGURE 25

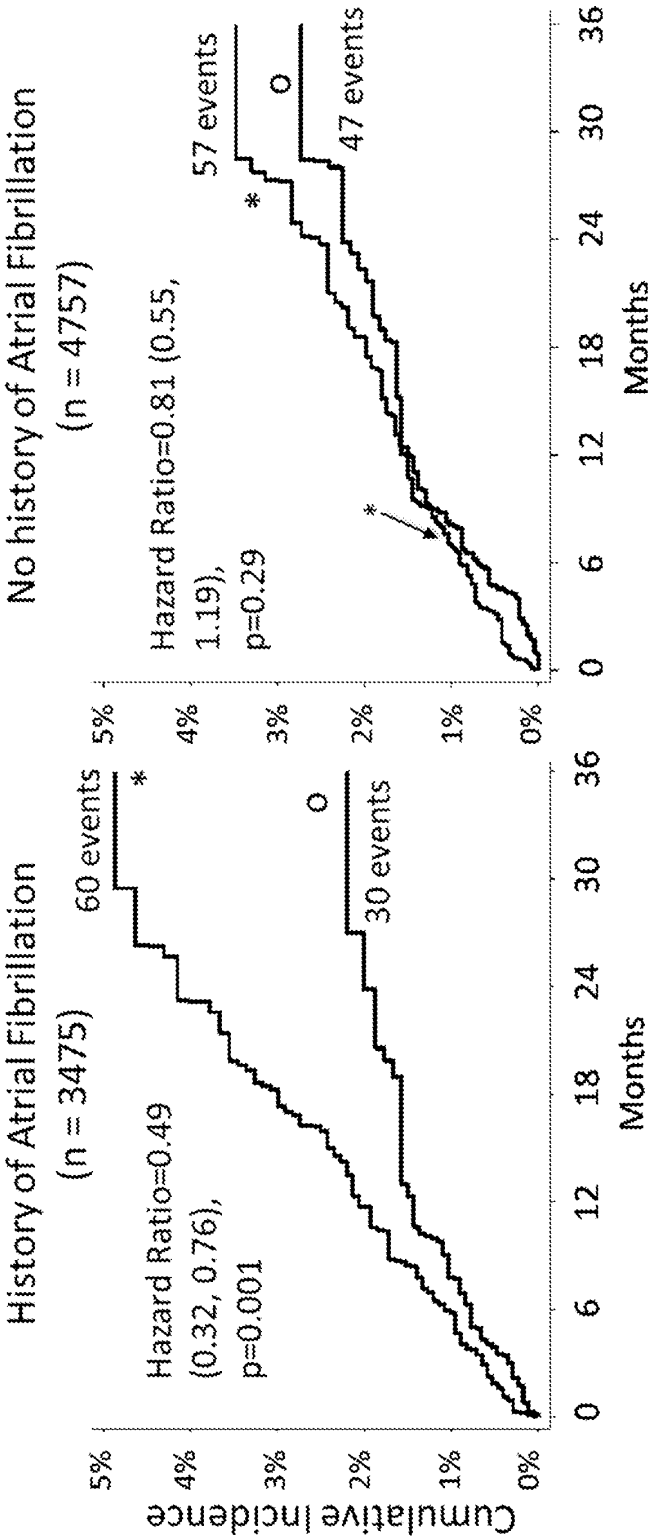

History of Atrial Fibrillation
(n = 3475)
Hazard Ratio=0.49
(0.32, 0.76),
p=0.001
60 events
30 events
No history of Atrial Fibrillation
(n = 4757)
Hazard Ratio=0.81 (0.55,
1.19),
p=0.29
57 events
47 events
Cumulative Incidence
0%
1%
2%
3%
4%
5%
0
6
12
18
24
30
36
Months
* Placebo
o Omecamtiv mecarbil

FIGURE 26

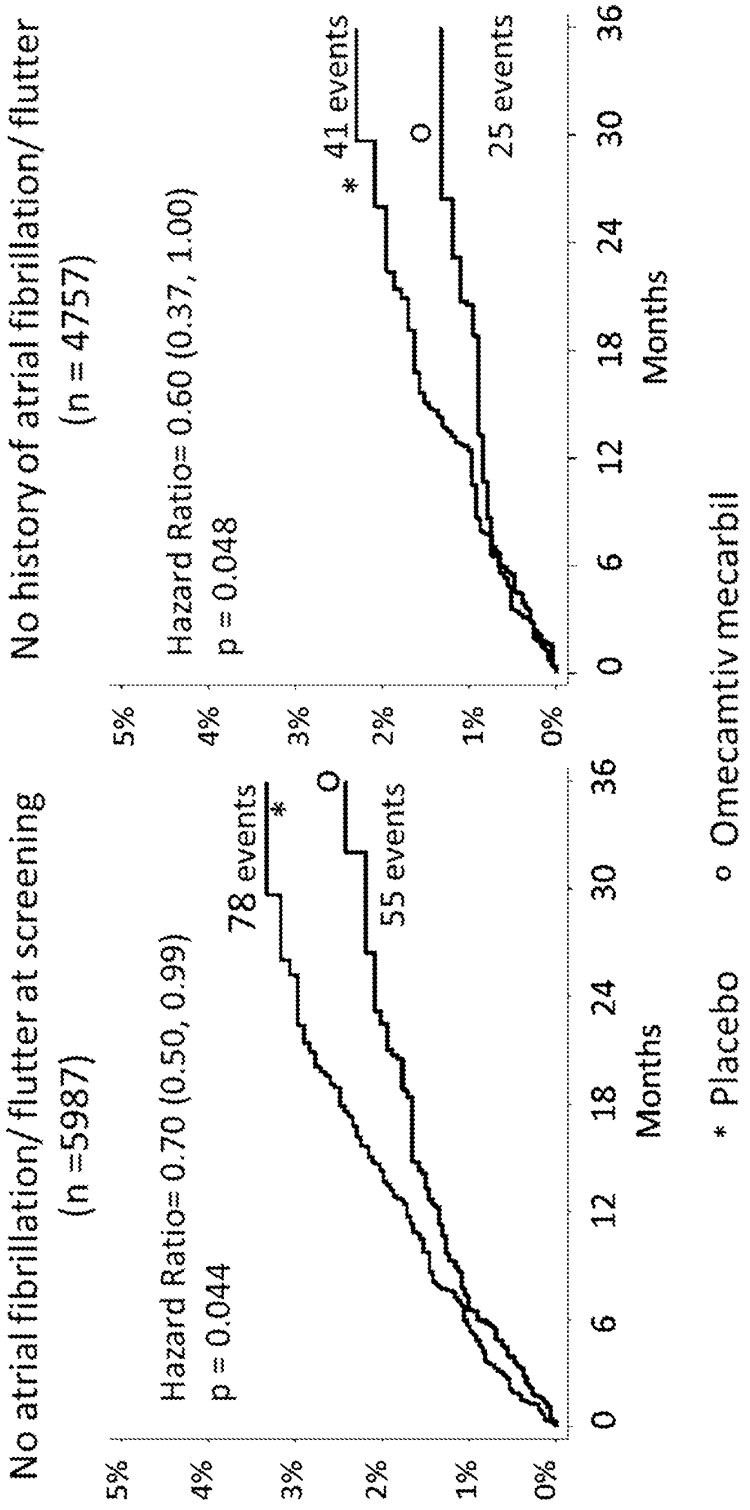

No atrial fibrillation/ flutter at screening
(n =5987)
Hazard Ratio= 0.70 (0.50, 0.99)
p = 0.044
78 events
55 events
No history of atrial fibrillation/ flutter
(n = 4757)
Hazard Ratio= 0.60 (0.37, 1.00)
p = 0.048
41 events
25 events
5%
4%
3%
2%
1%
0%
0
6
12
18
24
30
36
Months
* Placebo
o Omecamtiv mecarbil

FIGURE 27