FIG. 1

Randomized, double-blind, 2-period crossover study
N = 18

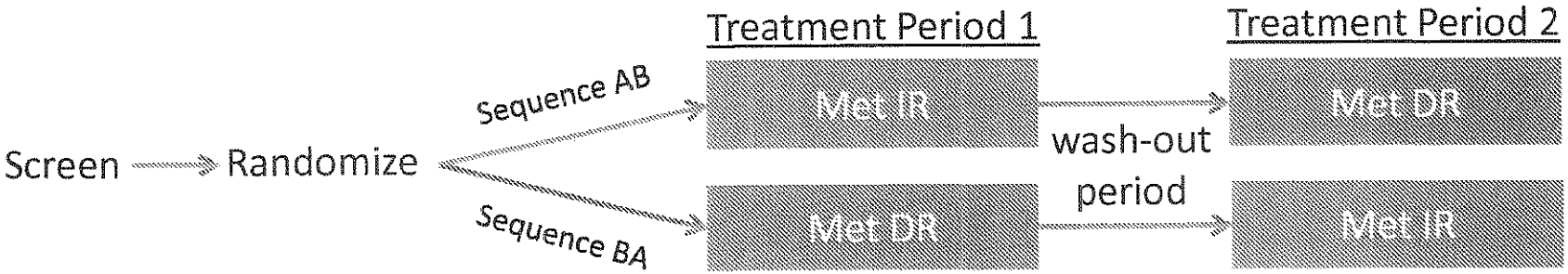


FIG. 2

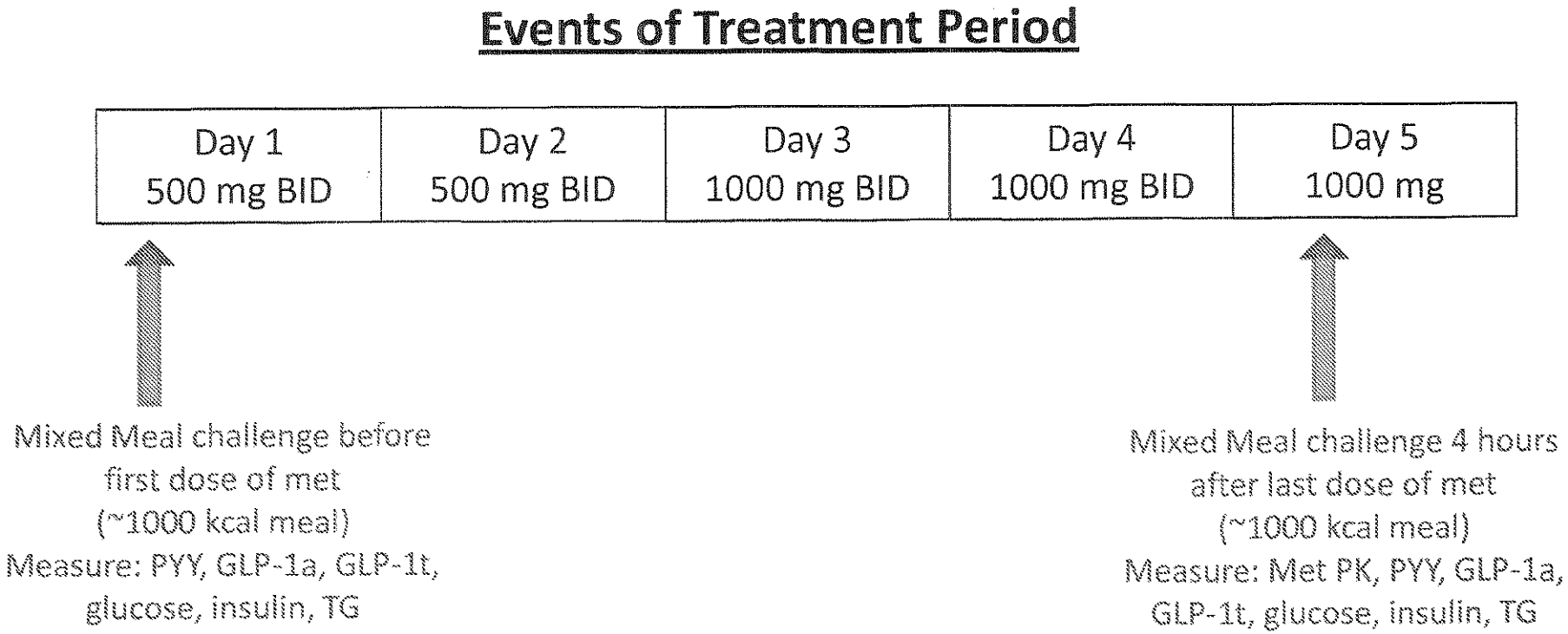

Events of Treatment Period
Day 1
500 mg BID
Day 2
500 mg BID
Day 3
1000 mg BID
Day 4
1000 mg BID
Day 5
1000 mg
Mixed Meal challenge before first dose of met (~1000 kcal meal) Measure: PYY, GLP-1a, GLP-1t, glucose, insulin, TG
Mixed Meal challenge 4 hours after last dose of met (~1000 kcal meal) Measure: Met PK, PYY, GLP-1a, GLP-1t, glucose, insulin, TG

FIG. 3

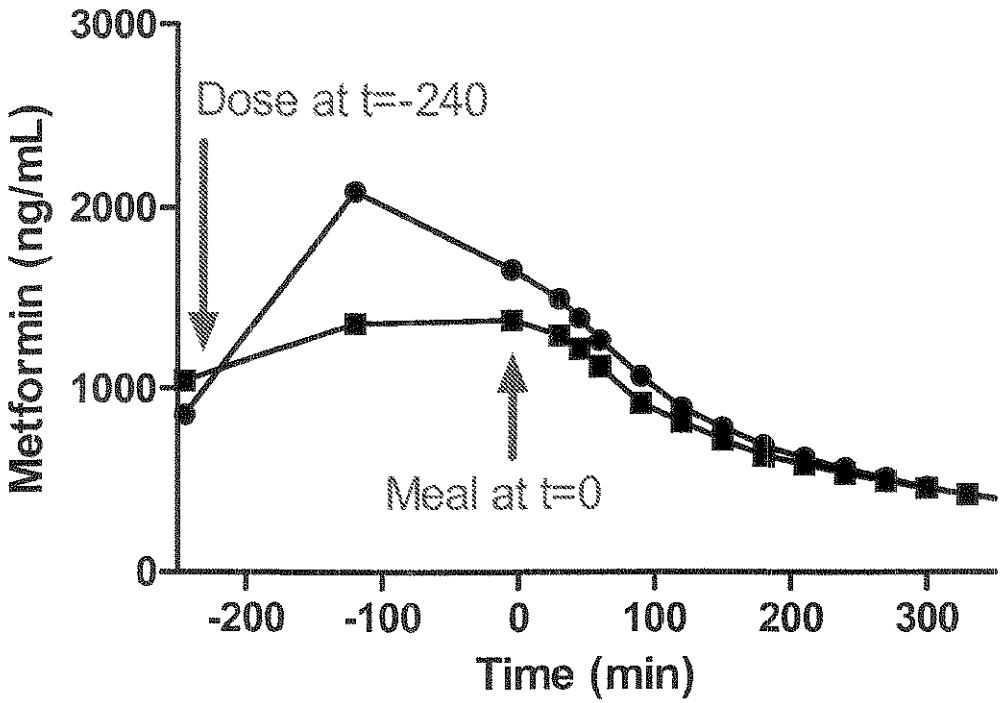
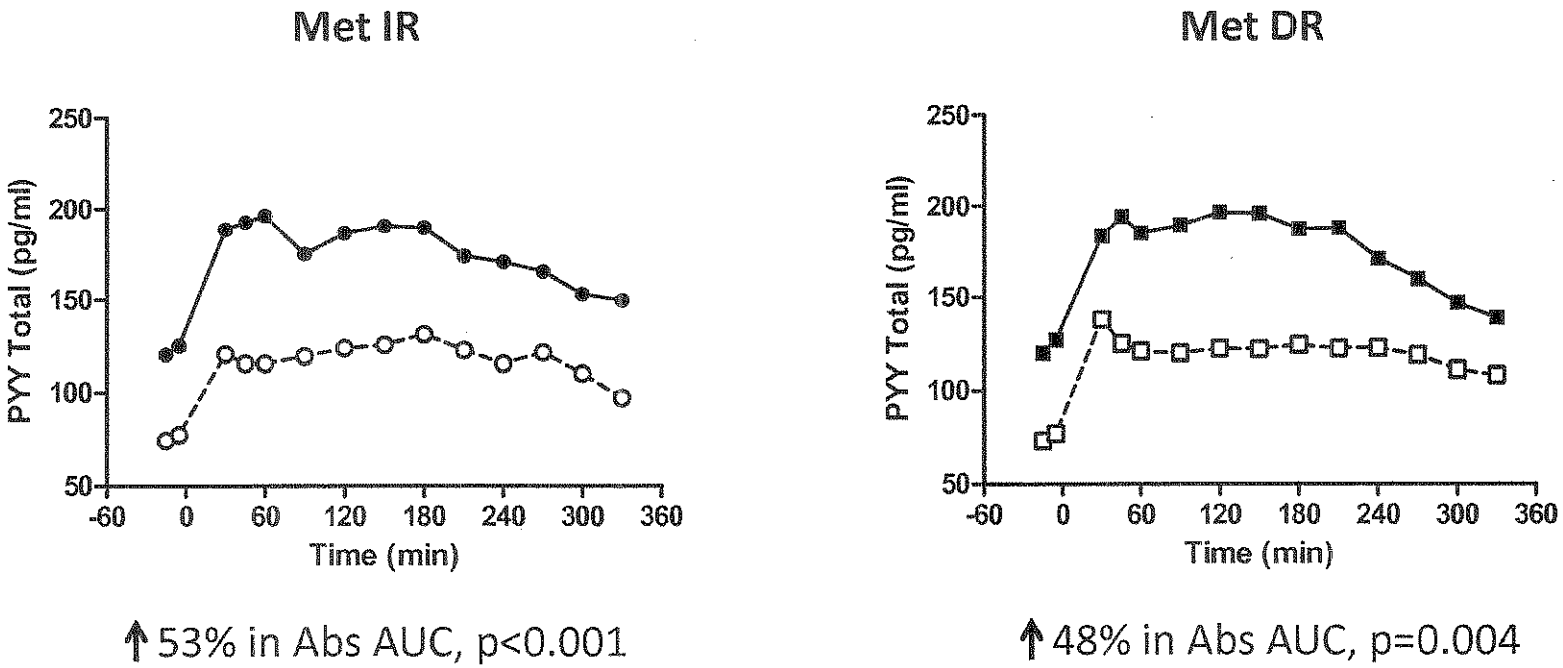

3000
2000
1000
0
Metformin (ng/mL)
Dose at t=-240
Meal at t=0
-200
-100
0
100
200
300
Time (min)

FIG. 4A



↑53% in Abs AUC, p<0.001

↑48% in Abs AUC, p=0.004

FIG. 4B

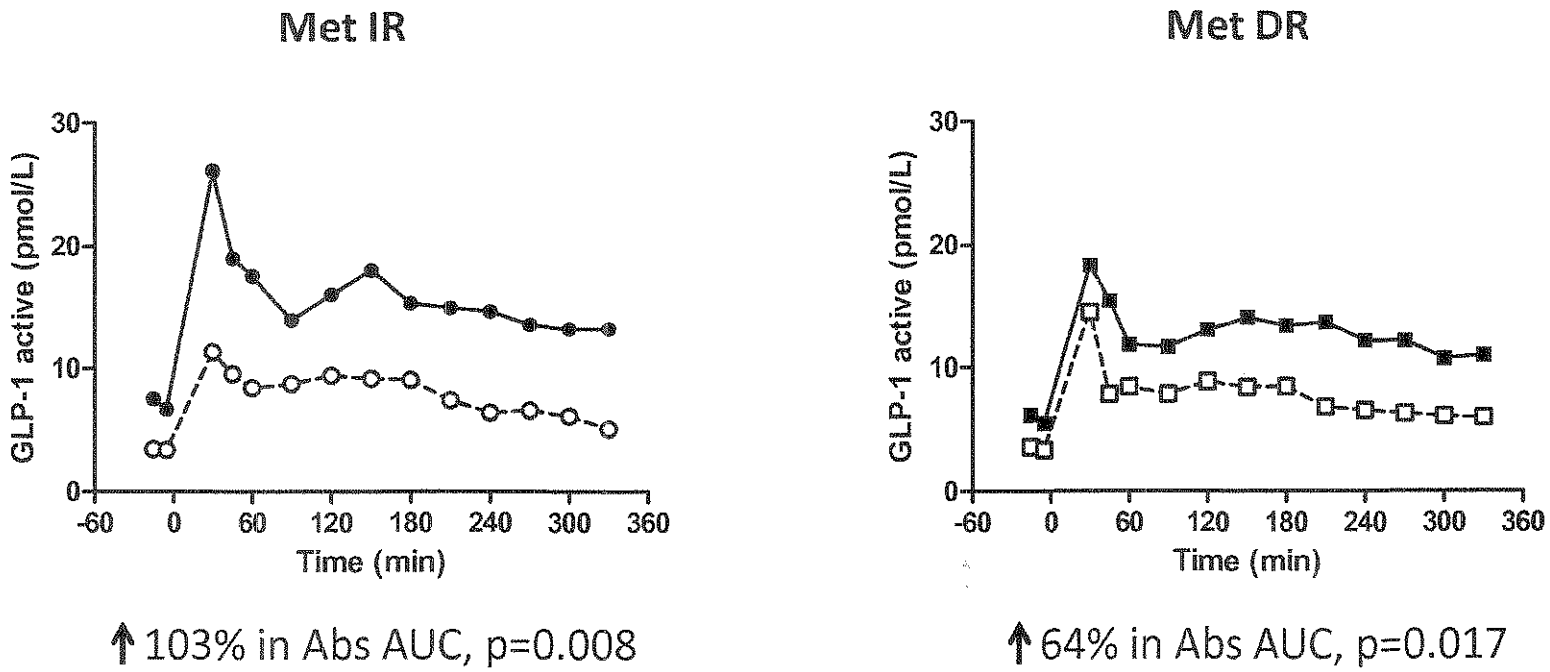
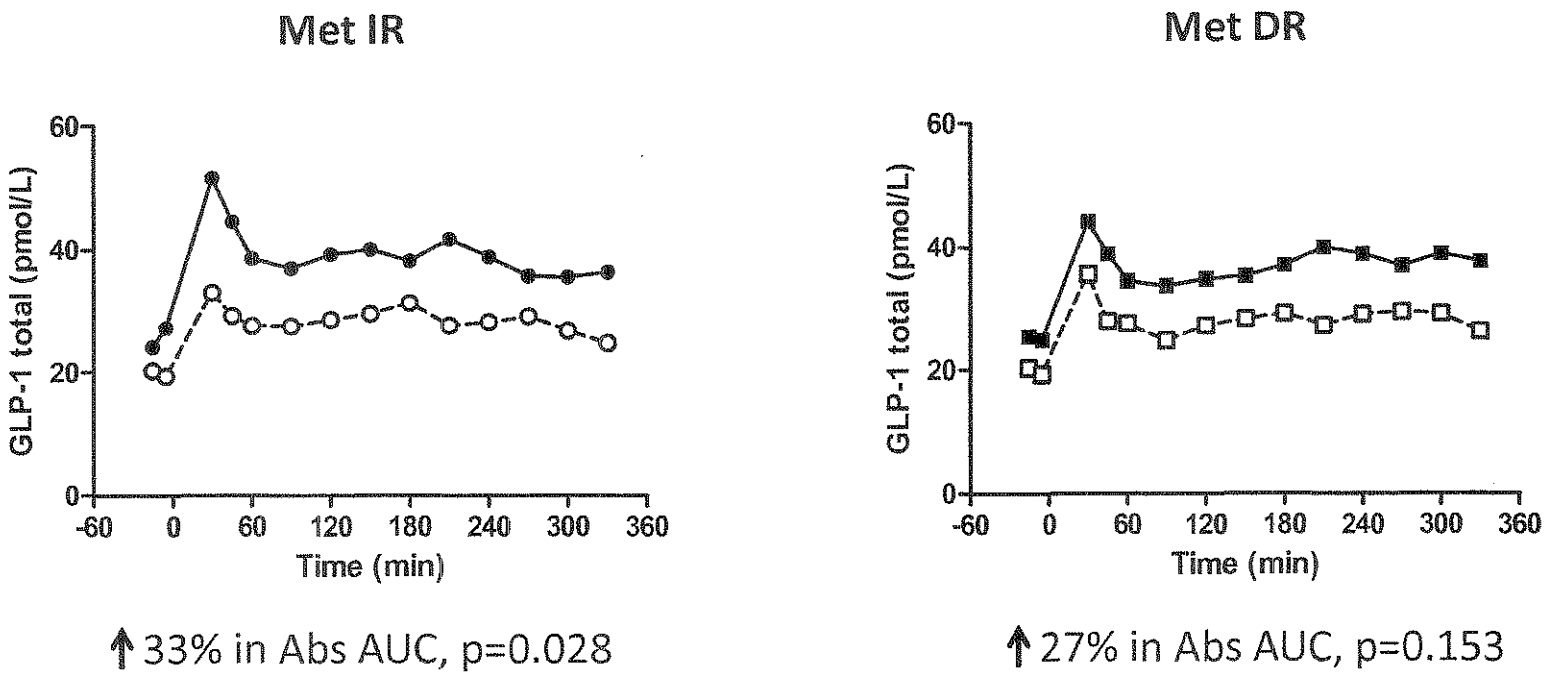

Met IR
GLP-1 active (pmol/L)
30
20
10
0
-60
0
60
120
180
240
300
360
Time (min)
↑103% in Abs AUC, p=0.008
Met DR
GLP-1 active (pmol/L)
30
20
10
0
-60
0
60
120
180
240
300
360
Time (min)
↑64% in Abs AUC, p=0.017

FIG. 4C



↑33% in Abs AUC, p=0.028

↑27% in Abs AUC, p=0.153

FIG. 5A

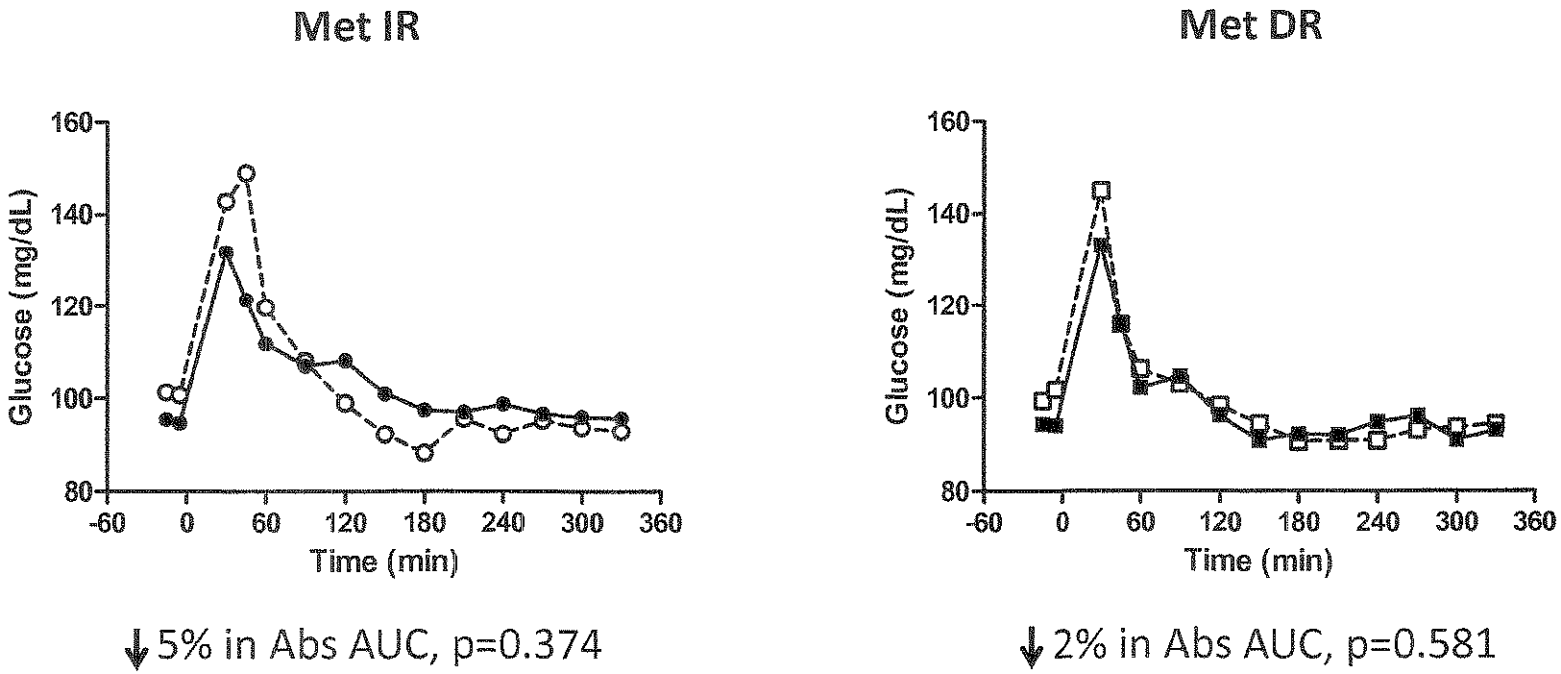

Met IR
Met DR
Glucose (mg/dL)
160
140
120
100
80
-60
0
60
120
180
240
300
360
Time (min)
↓5% in Abs AUC, p=0.374
↓2% in Abs AUC, p=0.581

FIG. 5B

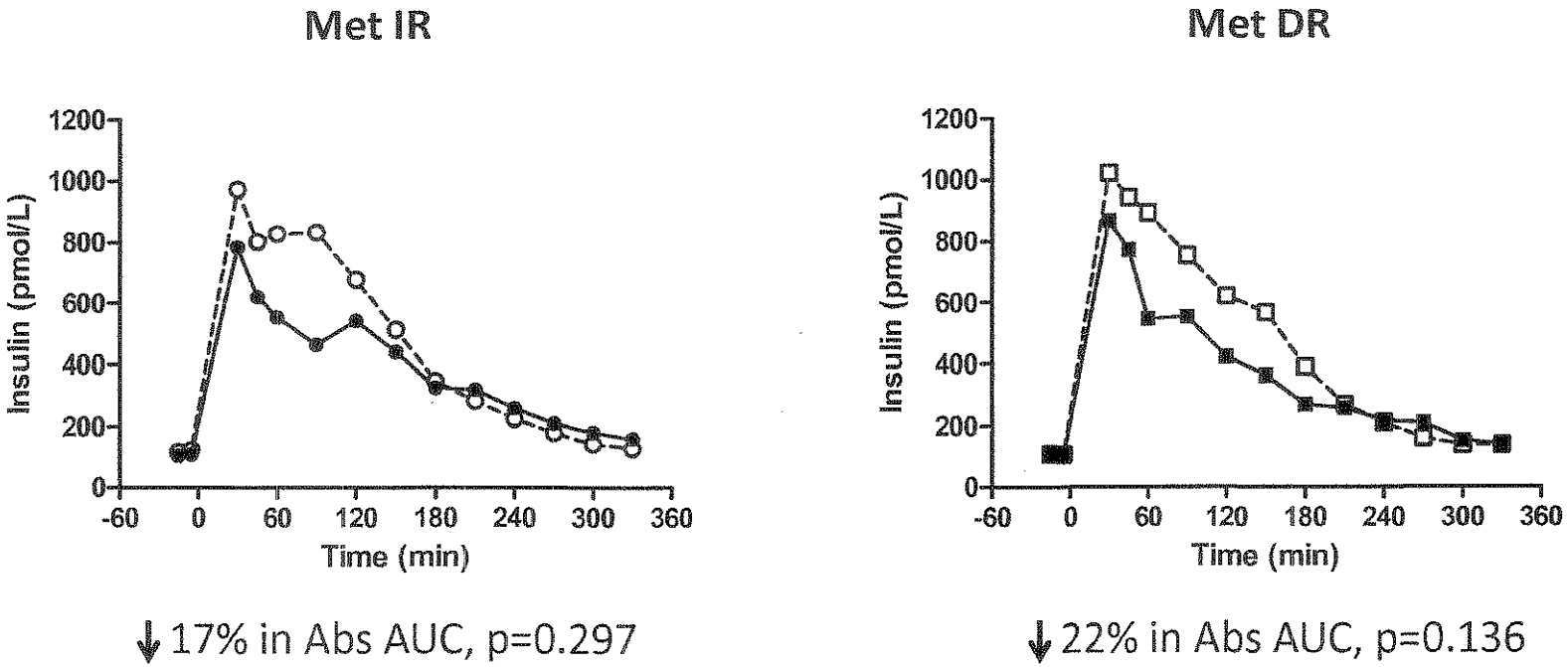

Met IR
Insulin (pmol/L)
1200
1000
800
600
400
200
0
-60
0
60
120
180
240
300
360
Time (min)
↓17% in Abs AUC, p=0.297
Met DR
Insulin (pmol/L)
1200
1000
800
600
400
200
0
-60
0
60
120
180
240
300
360
Time (min)
↓22% in Abs AUC, p=0.136

FIG. 6

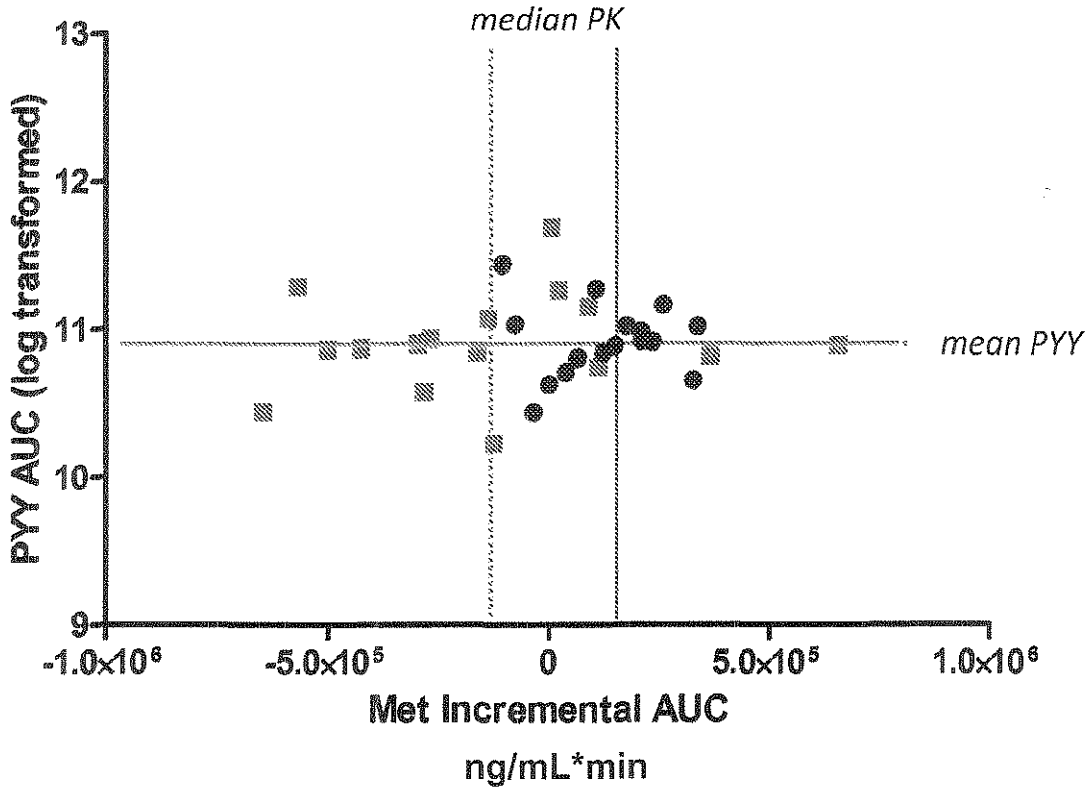

median PK
mean PYY
PYY AUC (log transformed)
13
12
11
10
9
-1.0x10^6
-5.0x10^5
0
5.0x10^5
1.0x10^6
Met Incremental AUC
ng/mL*min

FIG. 7A

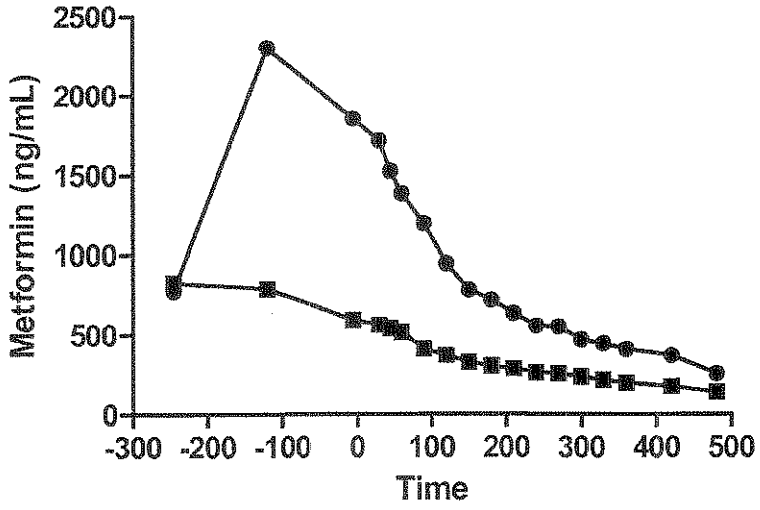
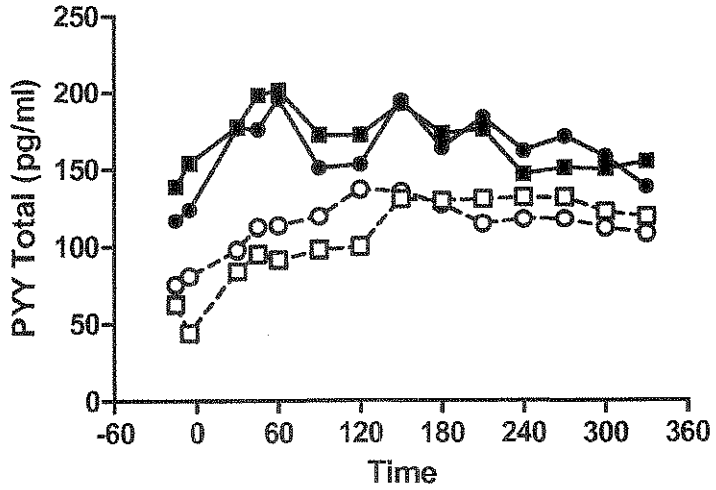

Metformin (ng/mL)
2500
2000
1500
1000
500
0
-300 -200 -100 0 100 200 300 400 500
Time

FIG. 7B


PYY Total (pg/ml)
250
200
150
100
50
0
-60 0 60 120 180 240 300 360
Time

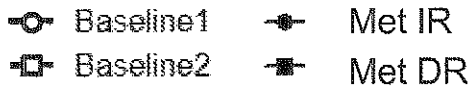

Baseline1
Met IR
Baseline2
Met DR

FIG. 8

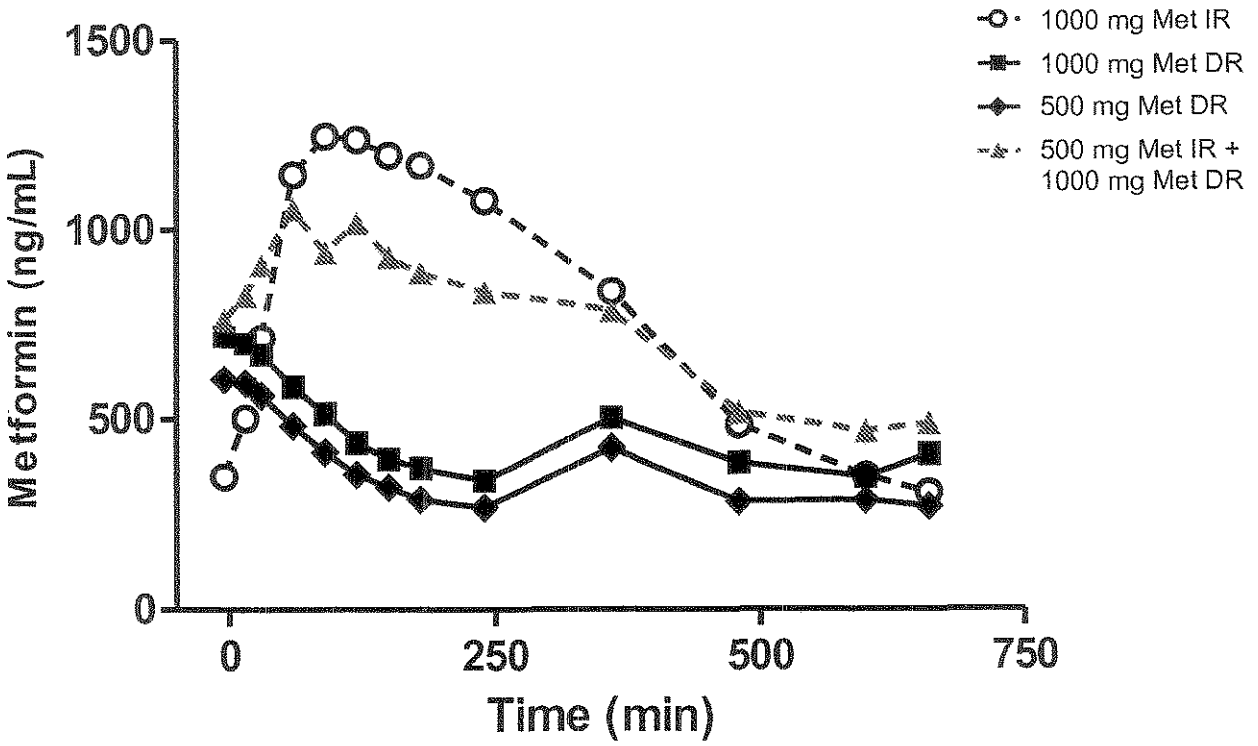

1000 mg Met IR
1000 mg Met DR
500 mg Met DR
500 mg Met IR +
1000 mg Met DR
Metformin (ng/mL)
1500
1000
500
0
0
250
500
750
Time (min)

FIG. 9

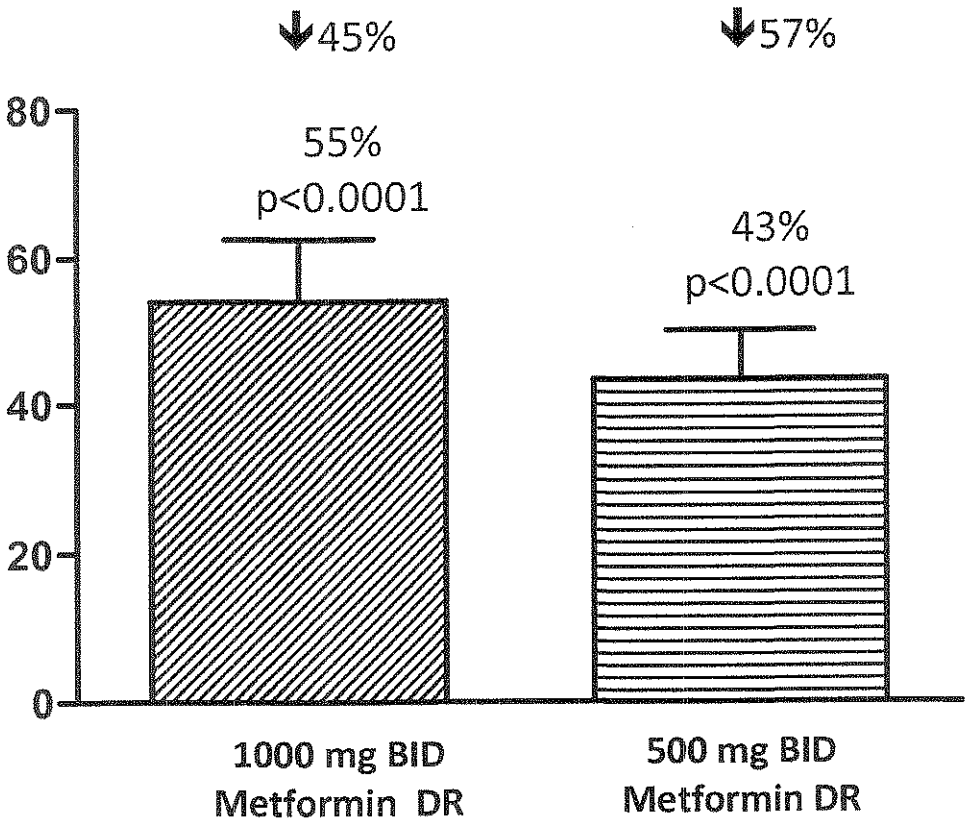

↓45%
↓57%
80
60
40
20
0
55%
p<0.0001
43%
p<0.0001
1000 mg BID
Metformin DR
500 mg BID
Metformin DR

FIG. 10

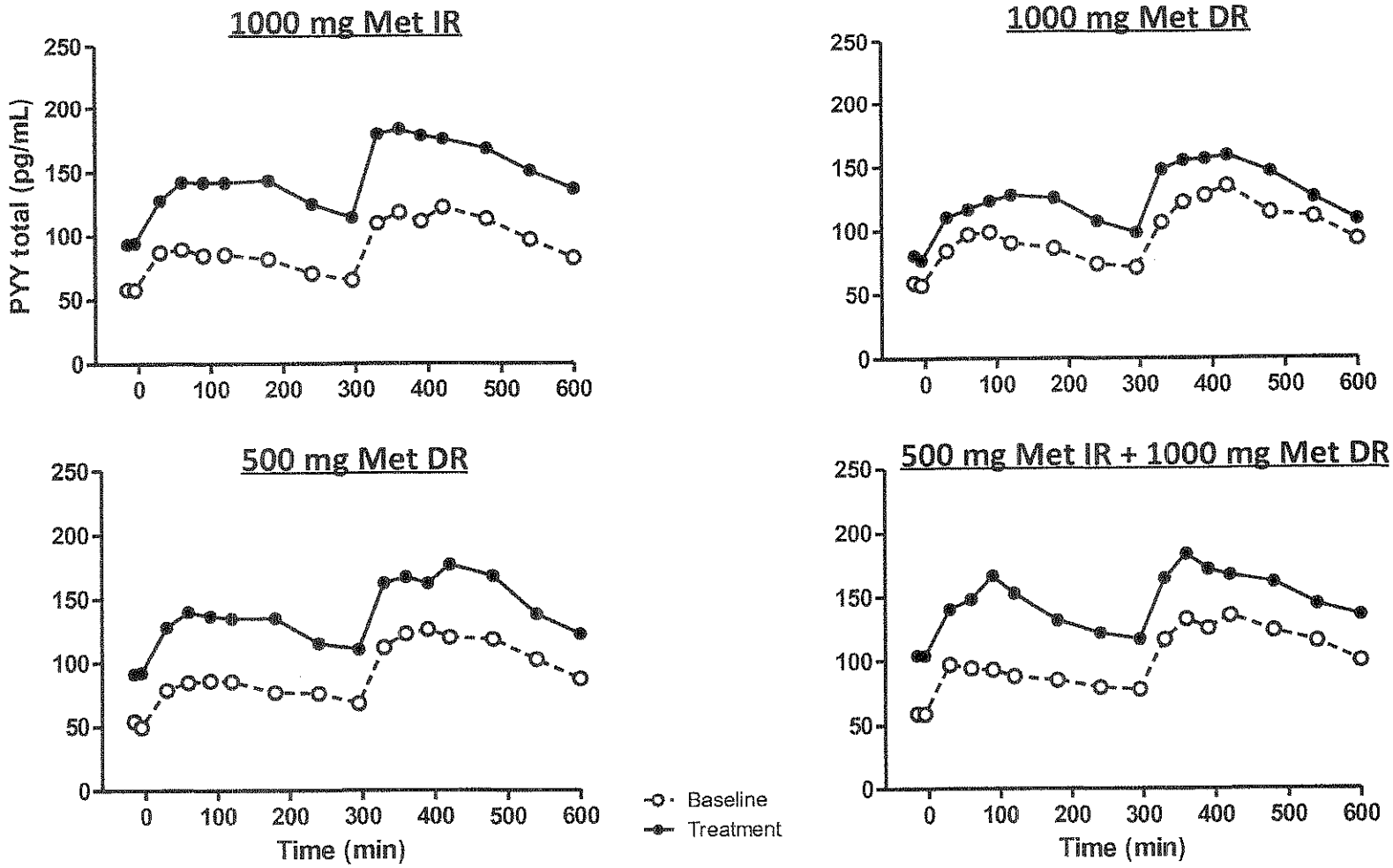

1000 mg Met IR
1000 mg Met DR
500 mg Met DR
500 mg Met IR + 1000 mg Met DR
PYY total (pg/mL)
Time (min)
Baseline
Treatment

FIG. 11

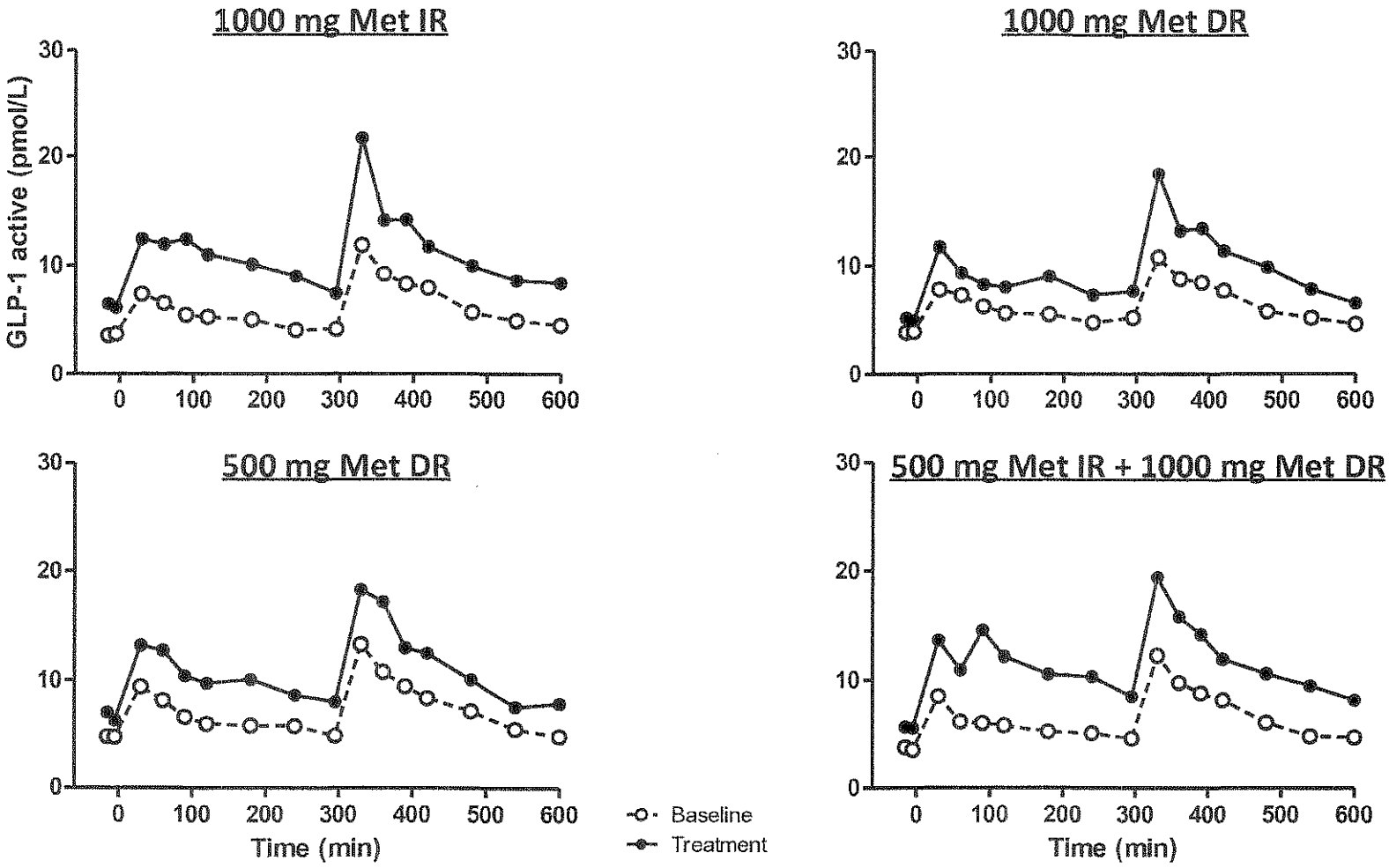

1000 mg Met IR
1000 mg Met DR
500 mg Met DR
500 mg Met IR + 1000 mg Met DR
GLP-1 active (pmol/L)
0
10
20
30
0
100
200
300
400
500
600
Time (min)
Baseline
Treatment

FIG. 12

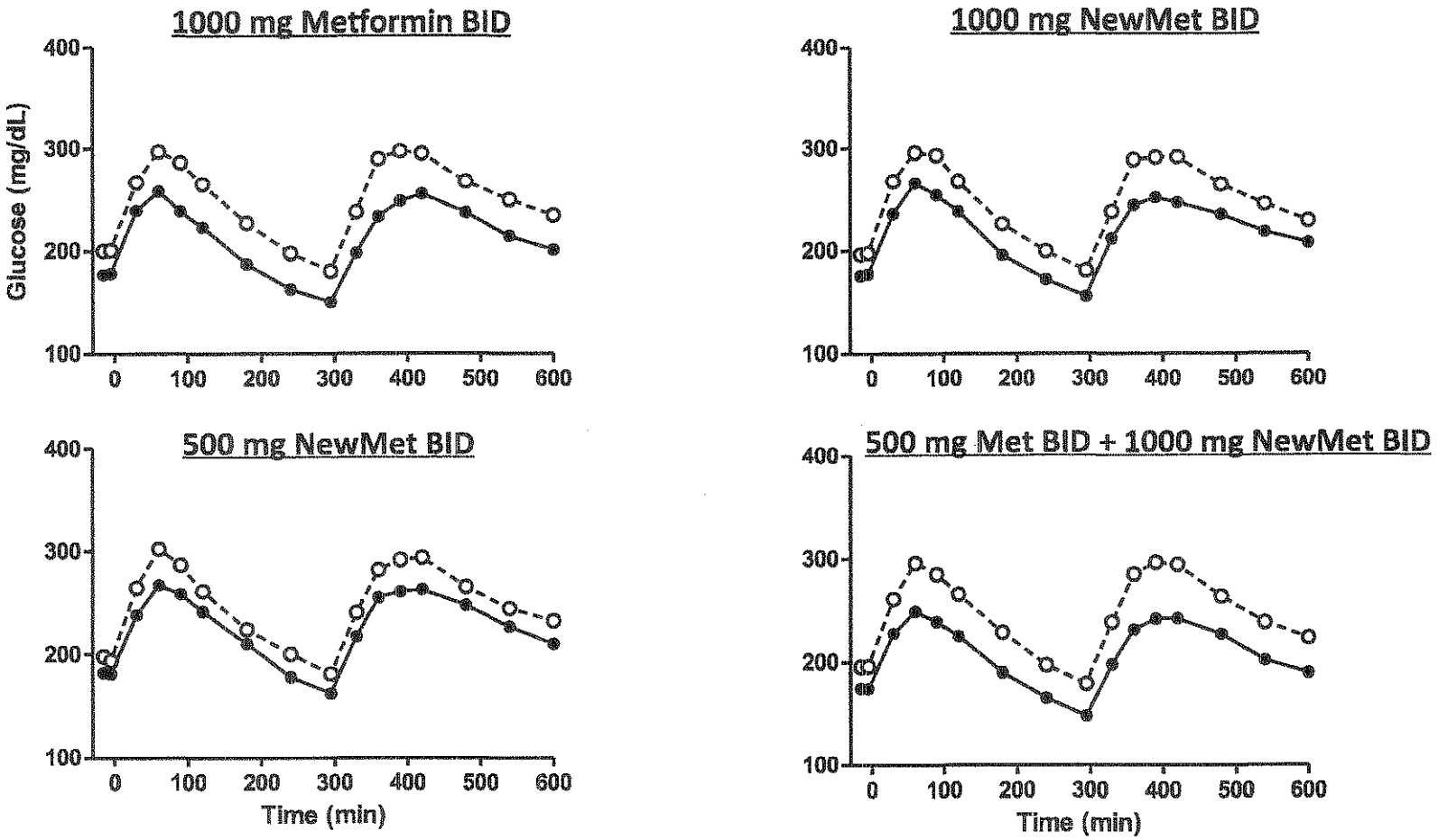

1000 mg Metformin BID
1000 mg NewMet BID
500 mg NewMet BID
500 mg Met BID + 1000 mg NewMet BID
Glucose (mg/dL)
Time (min)
400
300
200
100
0
100
200
300
400
500
600

FIG. 13

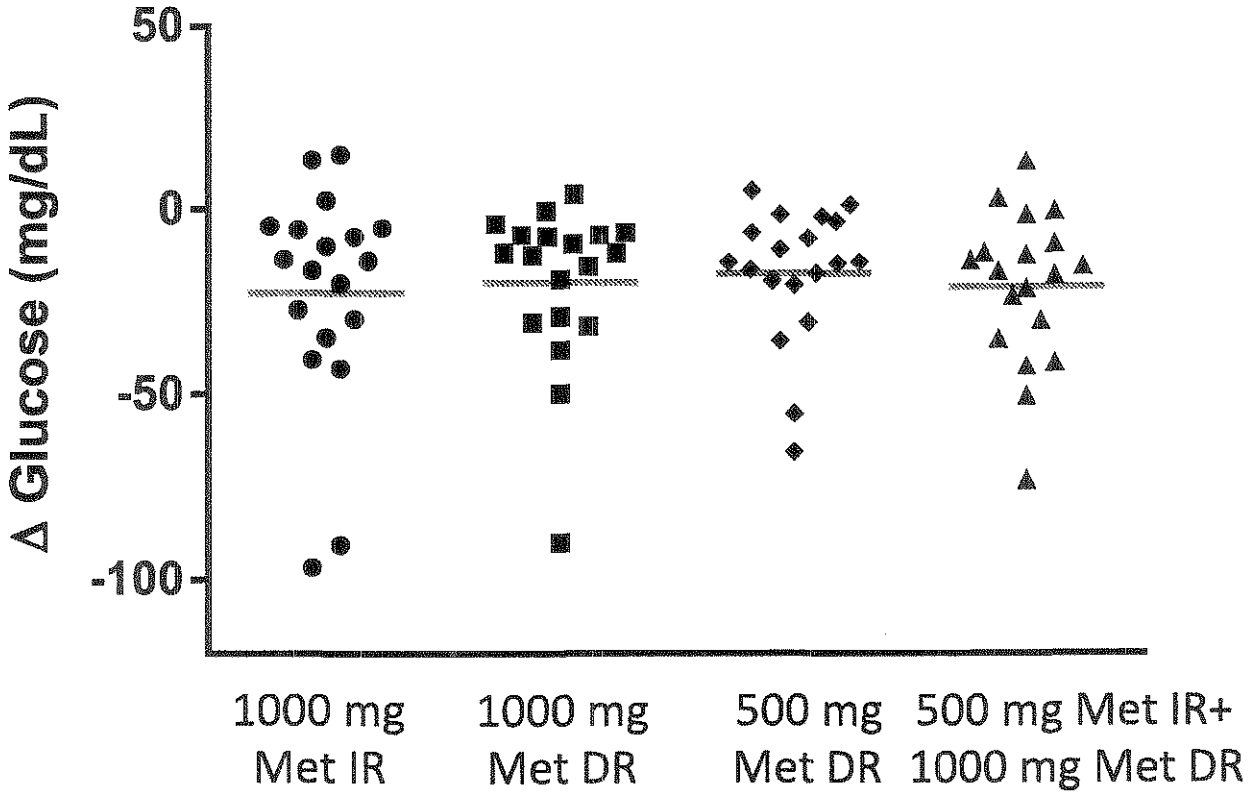

50
0
-50
-100
Δ Glucose (mg/dL)
1000 mg Met IR
1000 mg Met DR
500 mg Met DR
500 mg Met IR+ 1000 mg Met DR

FIG. 14

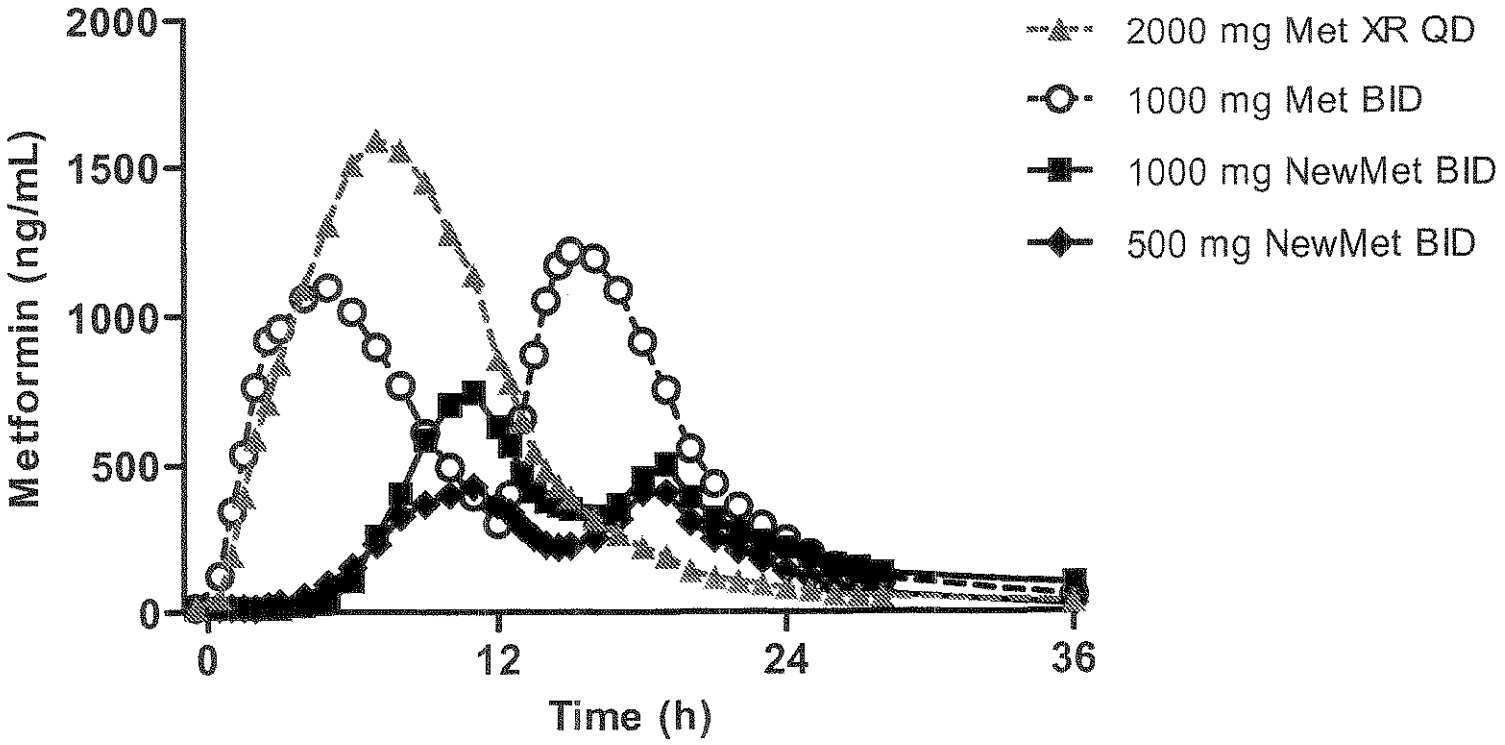

2000
1500
1000
500
0
Metformin (ng/mL)
0
12
24
36
Time (h)
2000 mg Met XR QD
1000 mg Met BID
1000 mg NewMet BID
500 mg NewMet BID

FIG. 15

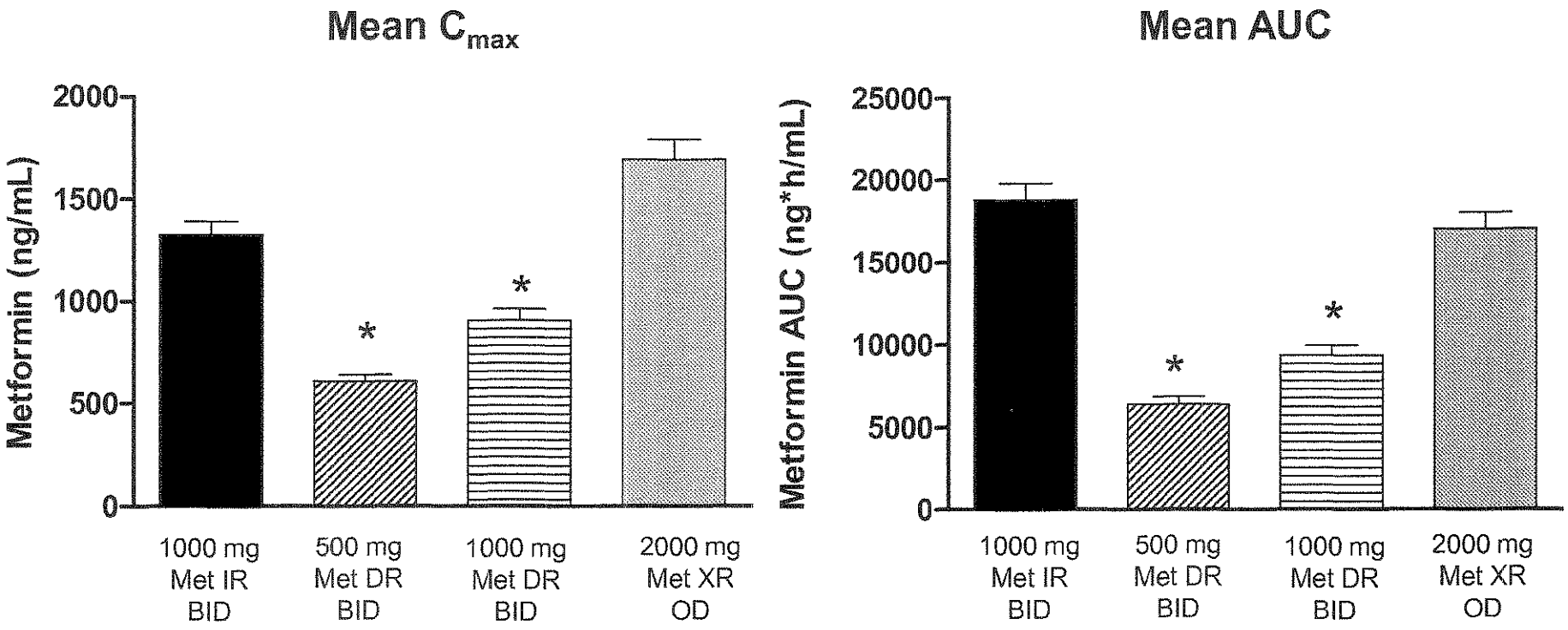

Mean C_{max}
Metformin (ng/mL)
2000
1500
1000
500
0
*
*
1000 mg Met IR BID
500 mg Met DR BID
1000 mg Met DR BID
2000 mg Met XR OD
Mean AUC
Metformin AUC (ng*h/mL)
25000
20000
15000
10000
5000
0
*
*
1000 mg Met IR BID
500 mg Met DR BID
1000 mg Met DR BID
2000 mg Met XR OD

FIG. 16

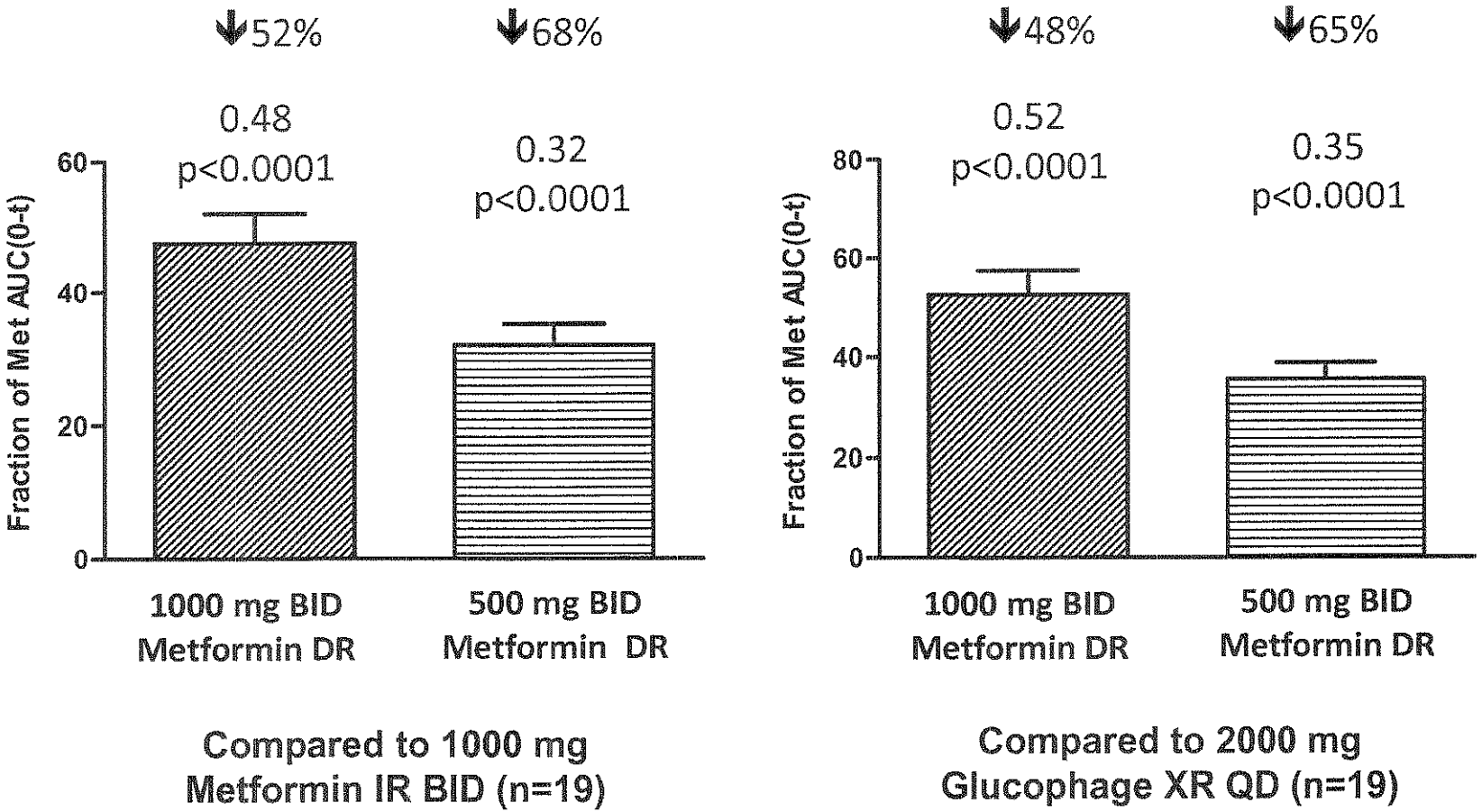

↓52%
↓68%
0.48
p<0.0001
0.32
p<0.0001
Fraction of Met AUC(0-t)
60
40
20
0
1000 mg BID Metformin DR
500 mg BID Metformin DR
Compared to 1000 mg Metformin IR BID (n=19)
↓48%
↓65%
0.52
p<0.0001
0.35
p<0.0001
Fraction of Met AUC(0-t)
80
60
40
20
0
1000 mg BID Metformin DR
500 mg BID Metformin DR
Compared to 2000 mg Glucophage XR QD (n=19)

FIG. 17

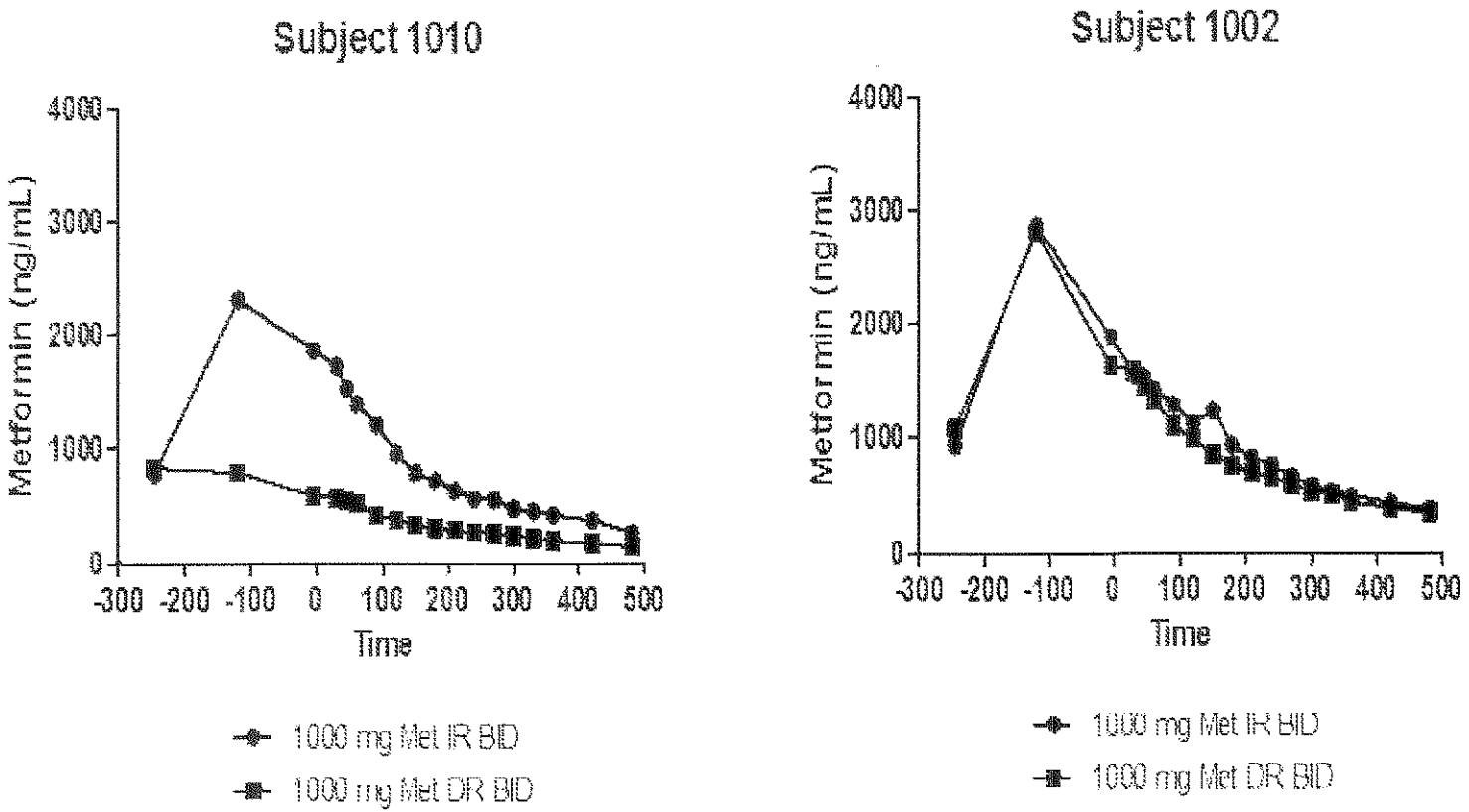

Subject 1010
Metformin (ng/mL)
4000
3000
2000
1000
0
-300 -200 -100 0 100 200 300 400 500
Time
1000 mg Met IR BID
1000 mg Met DR BID
Subject 1002
Metformin (ng/mL)
4000
3000
2000
1000
0
-300 -200 -100 0 100 200 300 400 500
Time
1000 mg Met IR BID
1000 mg Met DR BID

FIG. 18

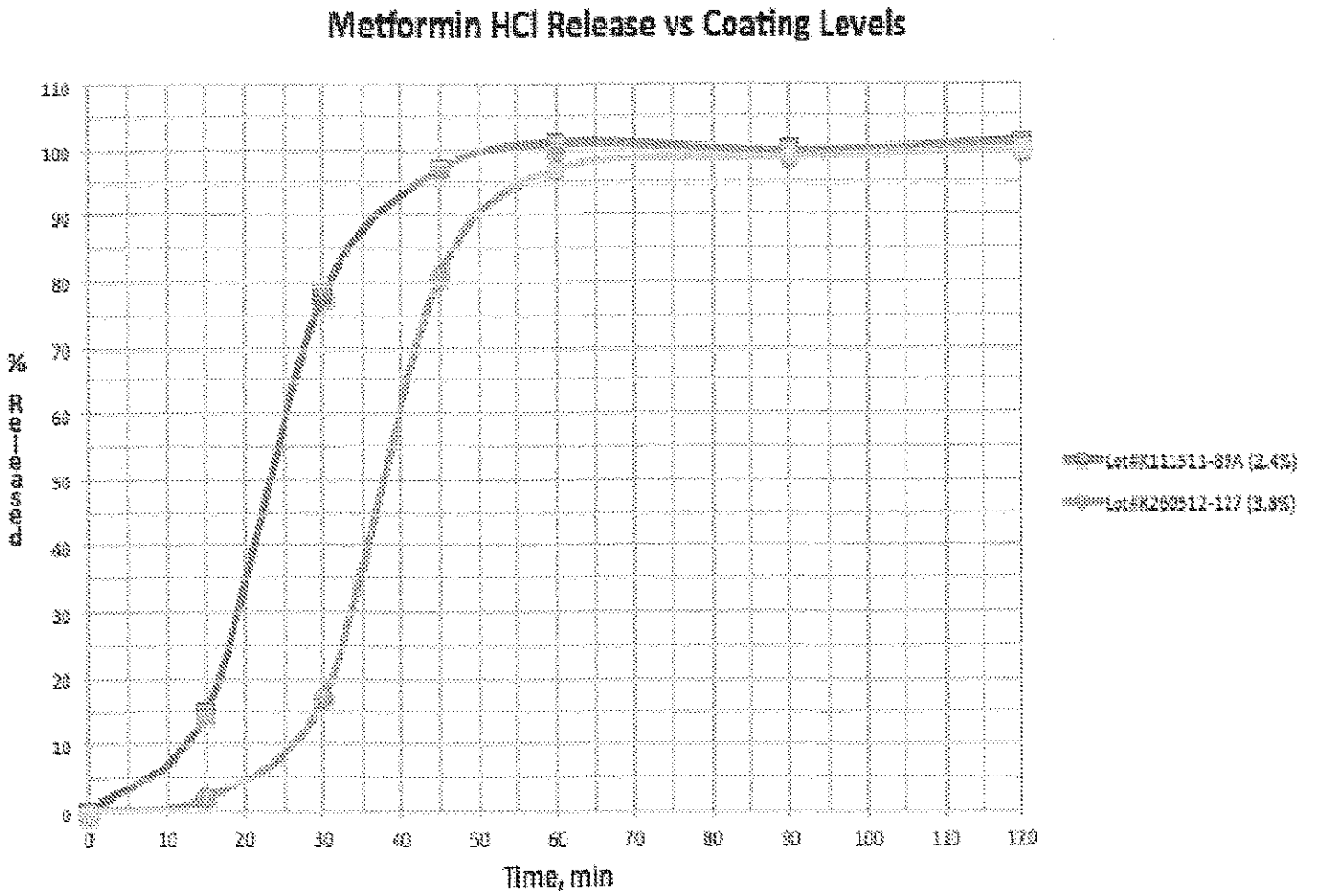

Metformin HCl Release vs Coating Levels
%
Time, min
0
10
20
30
40
50
60
70
80
90
100
110
120

Figure 19

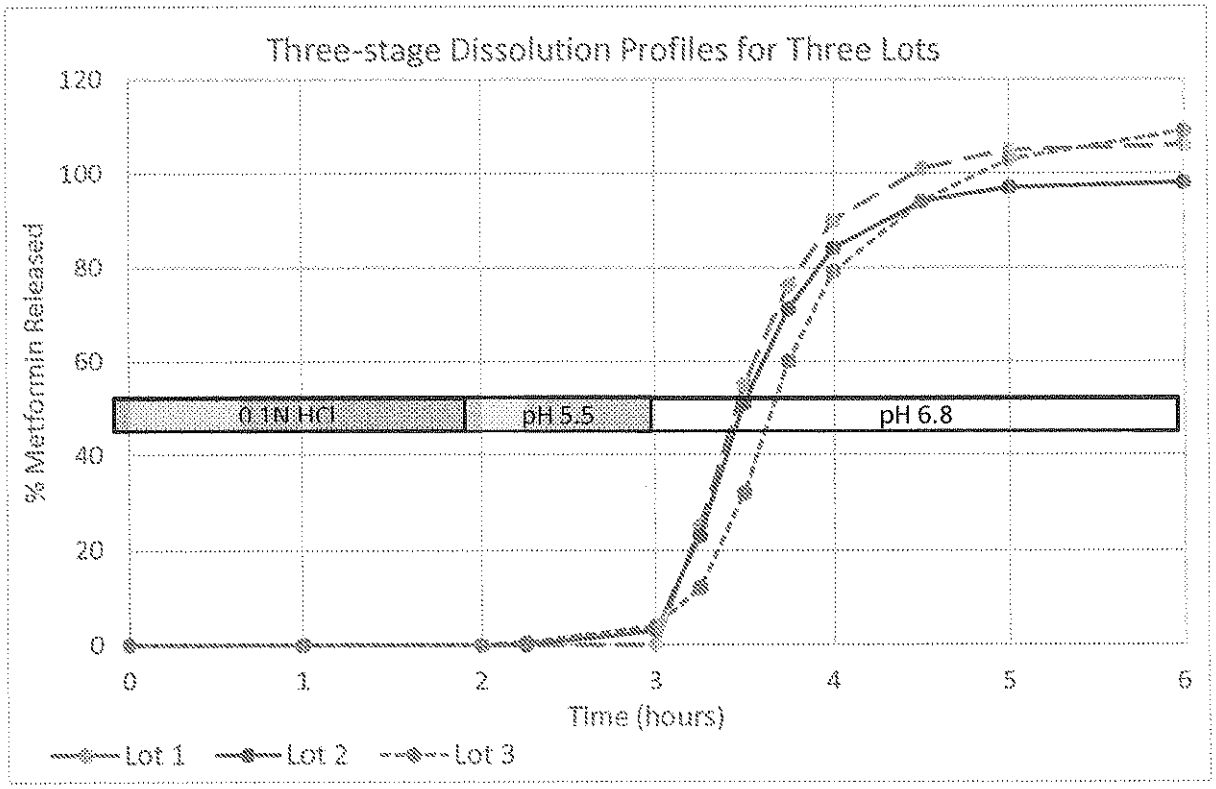
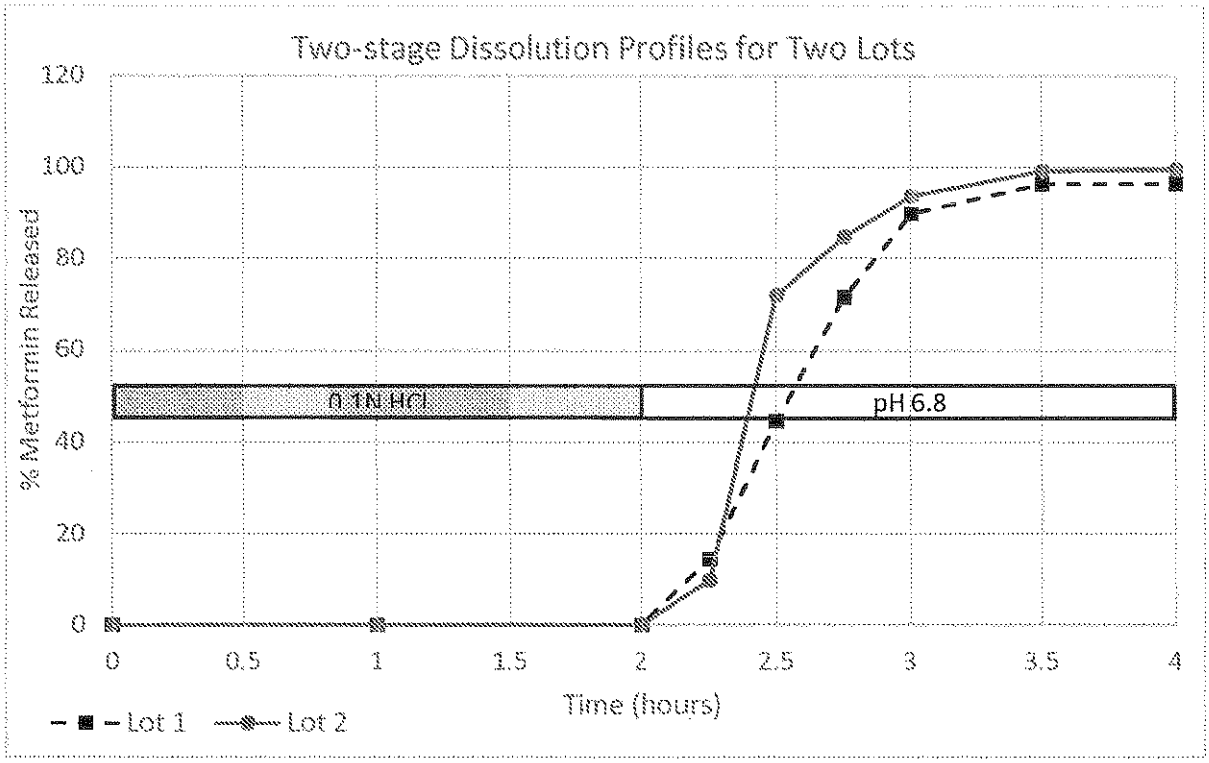

Three-stage Dissolution Profiles for Three Lots
% Metformin Released
120
100
80
60
40
20
0
0.1N HCl
pH 5.5
pH 6.8
0
1
2
3
4
5
6
Time (hours)
Lot 1
Lot 2
Lot 3

Figure 20


Two-stage Dissolution Profiles for Two Lots
% Metformin Released
120
100
80
60
40
20
0
0.1N HCl
pH 6.8
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hours)
Lot 1
Lot 2