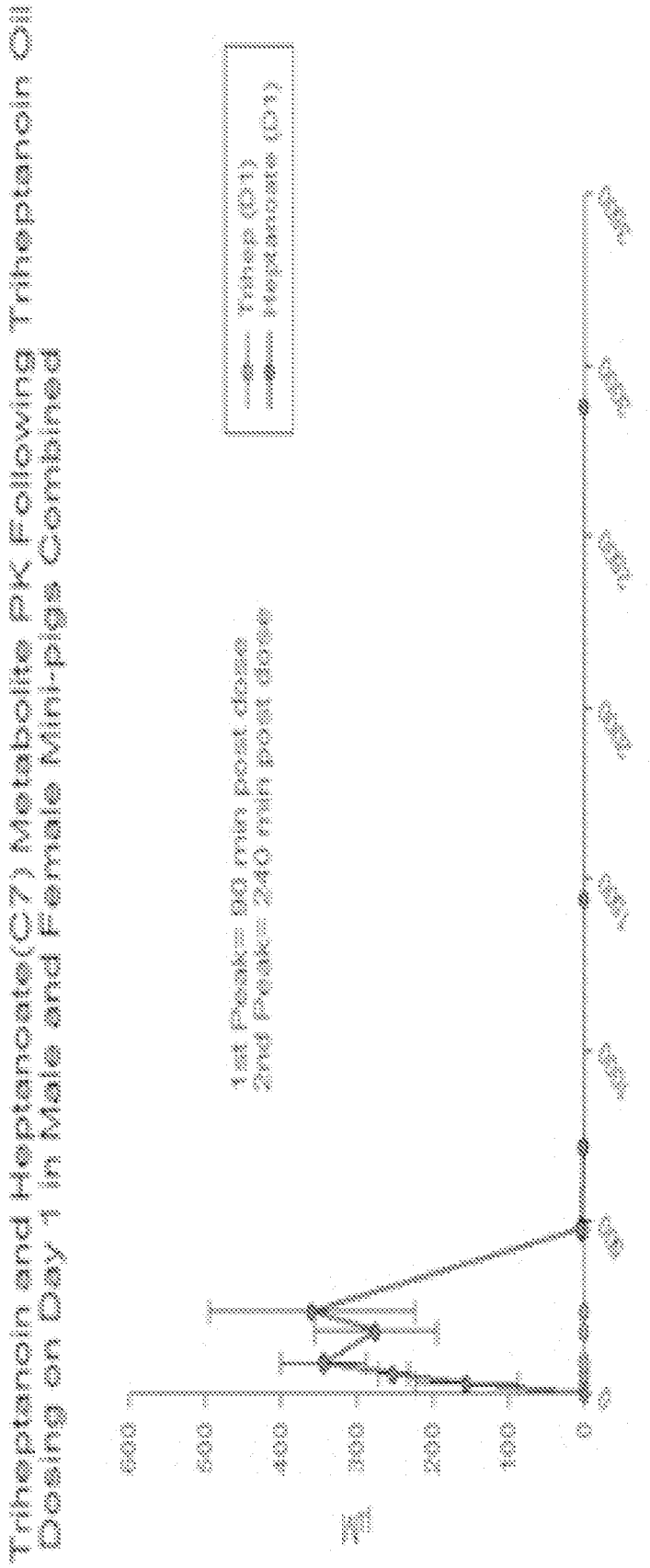

Trihexyphenidyl and Heptanoate(C7) Metabolite PK Following Trihexyphenidyl Oil Dosing on Day 1 in Male and Female Mini-pigs Combined
Time post dosing (minutes)
1st Peak= 90 min post dose
2nd Peak= 240 min post dose
Trihexyphenidyl (ng/mL)
Heptanoate (C7) (ng/mL)

Figure 1

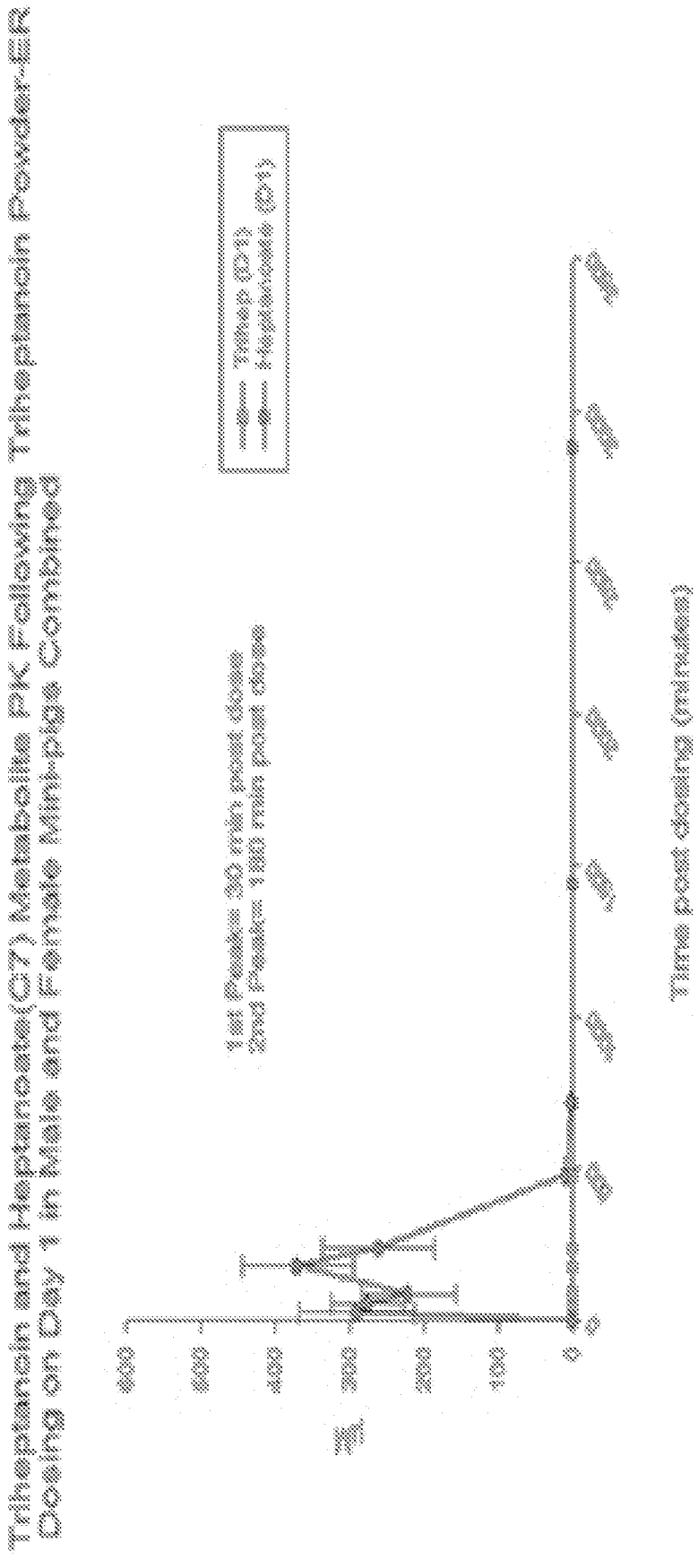

Trihexyphenidyl (CY1)
Metabolite (CY1)
1st Peaks = 30 min post dose
2nd Peaks = 180 min post dose
Time post dosing (minutes)

Figure 2

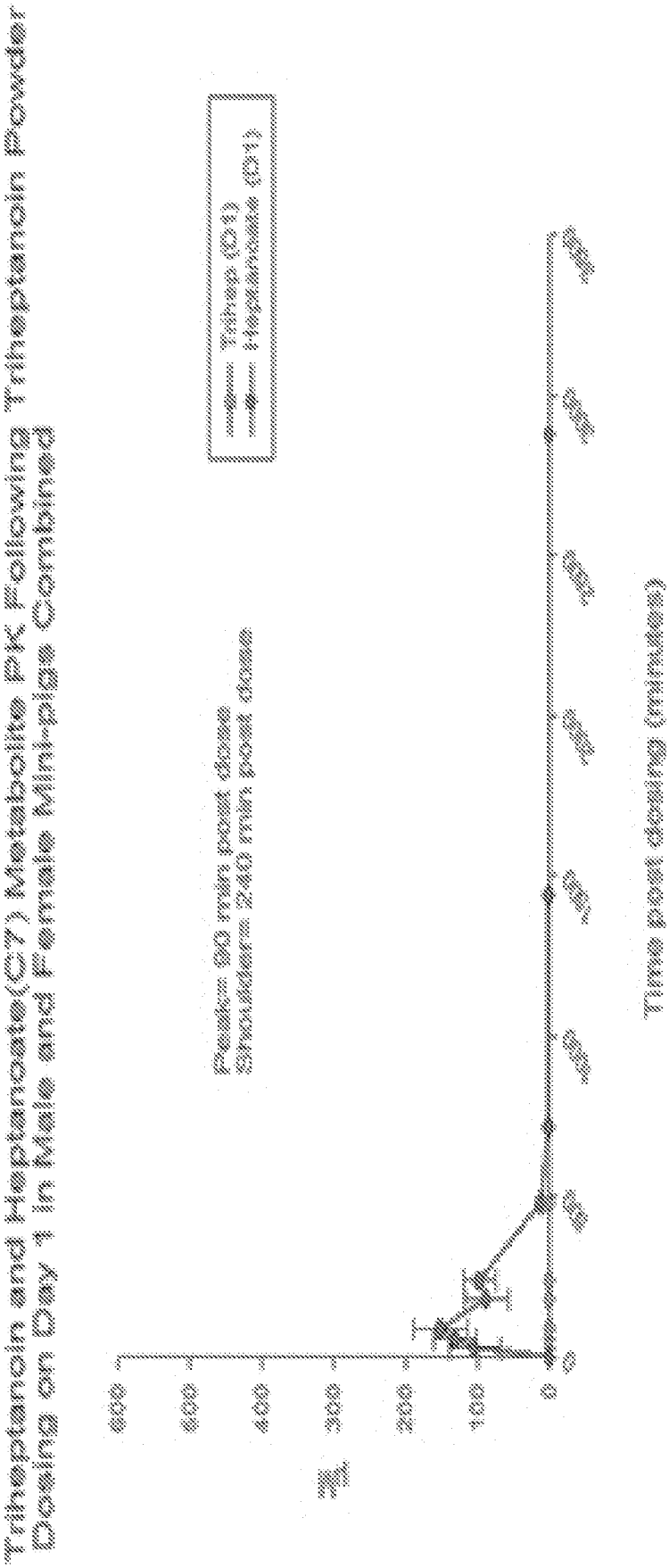

Trihexyphenidyl (C11)
Heptanoate (C17)
Peak at 60 min post dose
Shoulder at 240 min post dose
ng/mL
0
100
200
300
400
600
800
0
60
120
180
240
300
360
420
480
540
600
Time post dosing (minutes)

Figure 3

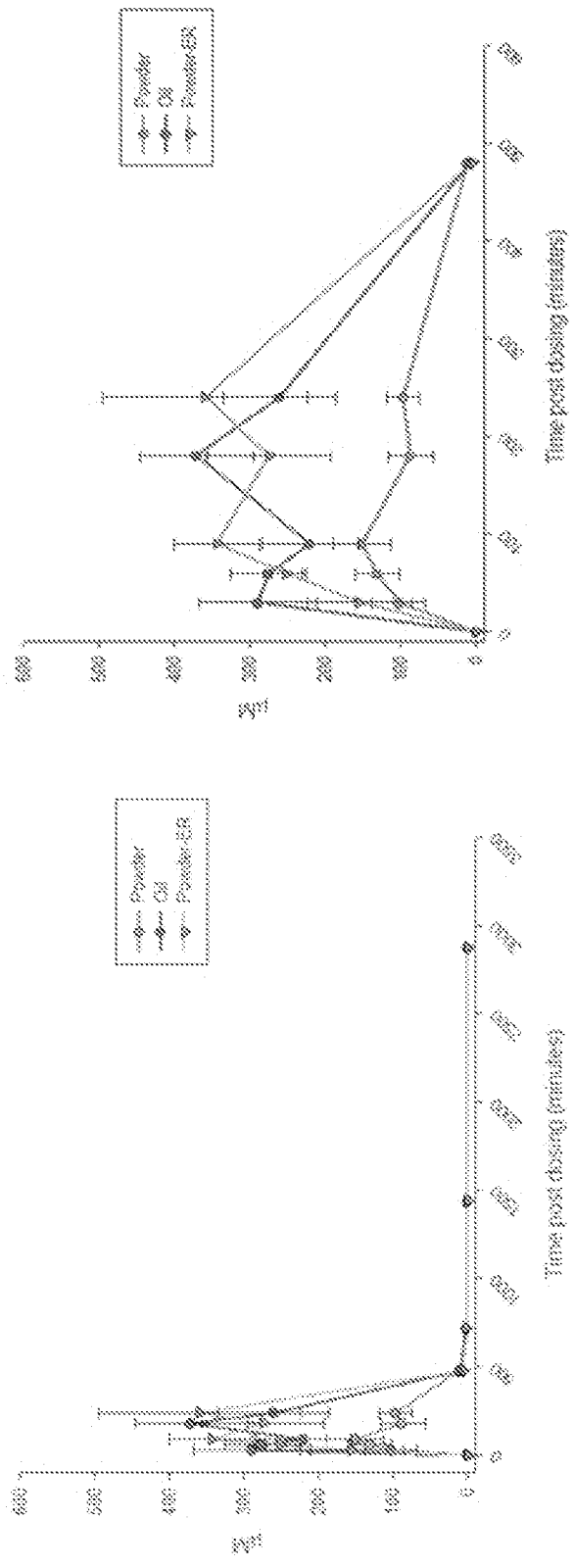

PK upto 48hr timepoint
Heptanoate(C7) Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Powder
Oil
Powder-ER
Time post dosing (minutes)
PK upto 8hr timepoint
Heptanoic acid (C7) Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Powder
Oil
Powder-ER
Time post dosing (minutes)

Figure 4

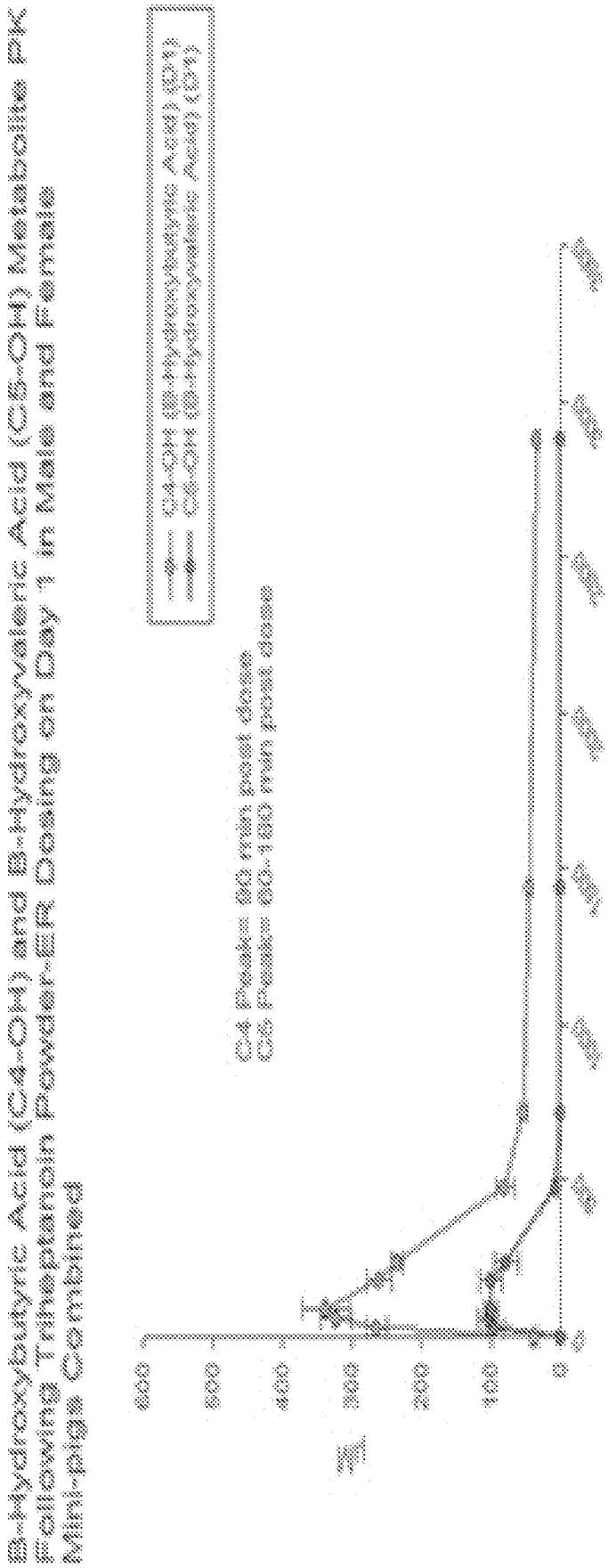

B-Hydroxybutyric Acid (C4-OH) and B-Hydroxyvaleric Acid (C5-OH) Metabolite PK Following Triheptanoin Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
C4-OH (B-Hydroxybutyric Acid) (C4)
C5-OH (B-Hydroxyvaleric Acid) (C5)
C4 Peaks= 60 min post dose
C5 Peaks= 60-180 min post dose
600
500
400
300
200
100
0
Time post dosing (minutes)

Figure 5

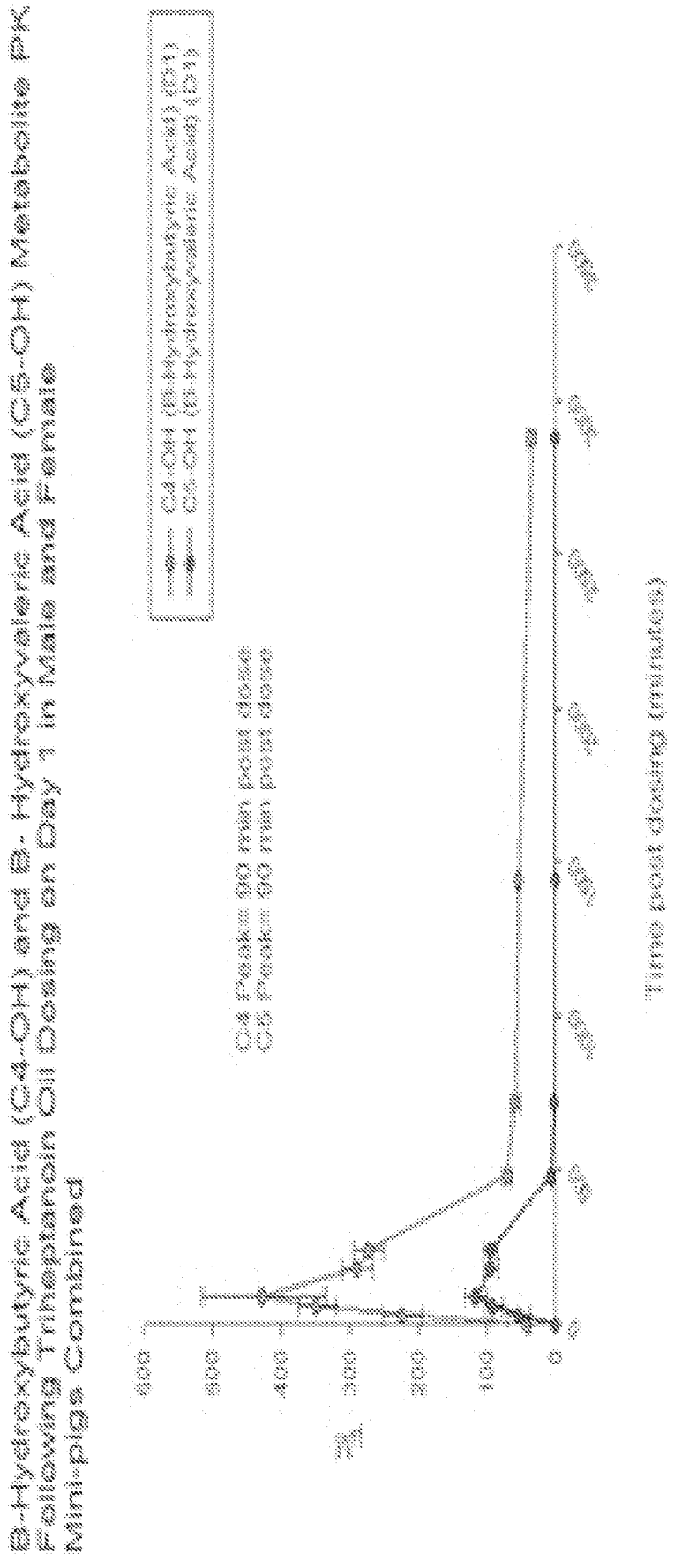

β-Hydroxybutyric Acid (C4-OH) and β- Hydroxyvaleric Acid (C5-OH) Metabolite PK Following Trineptanain Oil Dosing on Day 1 in Male and Female Mini-pigs Combined
C4-OH (β-Hydroxybutyric Acid) (C4)
C5-OH (β-Hydroxyvaleric Acid) (C5)
C4 Dose = 60 mg/kg dose
C5 Dose = 60 mg/kg dose
Time post dosing (minutes)
0
100
200
300
400
600
800
1000

Figure 6

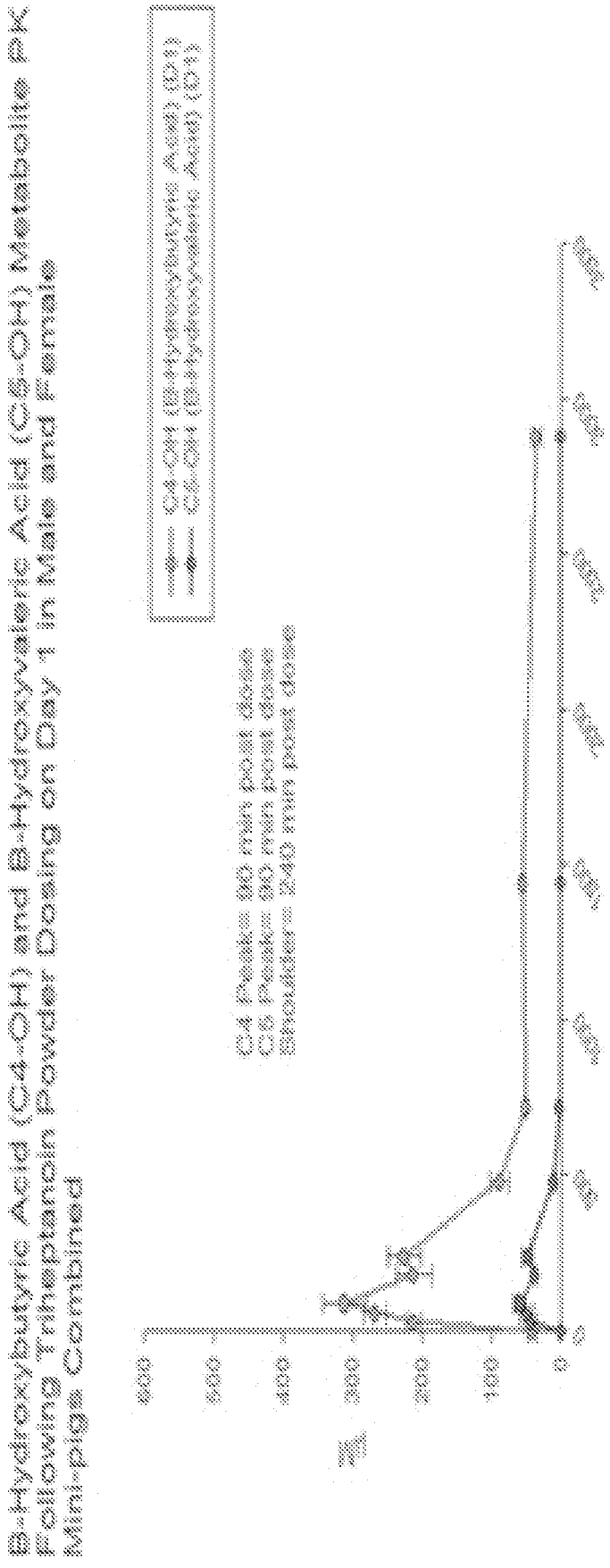

B-Hydroxybutyric Acid (C4-OH) and B-Hydroxyvaleric Acid (C5-OH) Metabolite PK Following Trihexaphen Powder Dosing on Day 1 in Male and Female Mini-pigs Combined
C4-OH (B-Hydroxybutyric Acid) (D1)
C5-OH (B-Hydroxyvaleric Acid) (D1)
C4 Peaks 60 min post dose
C5 Peaks 60 min post dose
Shoulder = 240 min post dose
Time post dosing (minutes)
6000
5000
4000
3000
2000
1000
0

Figure 7

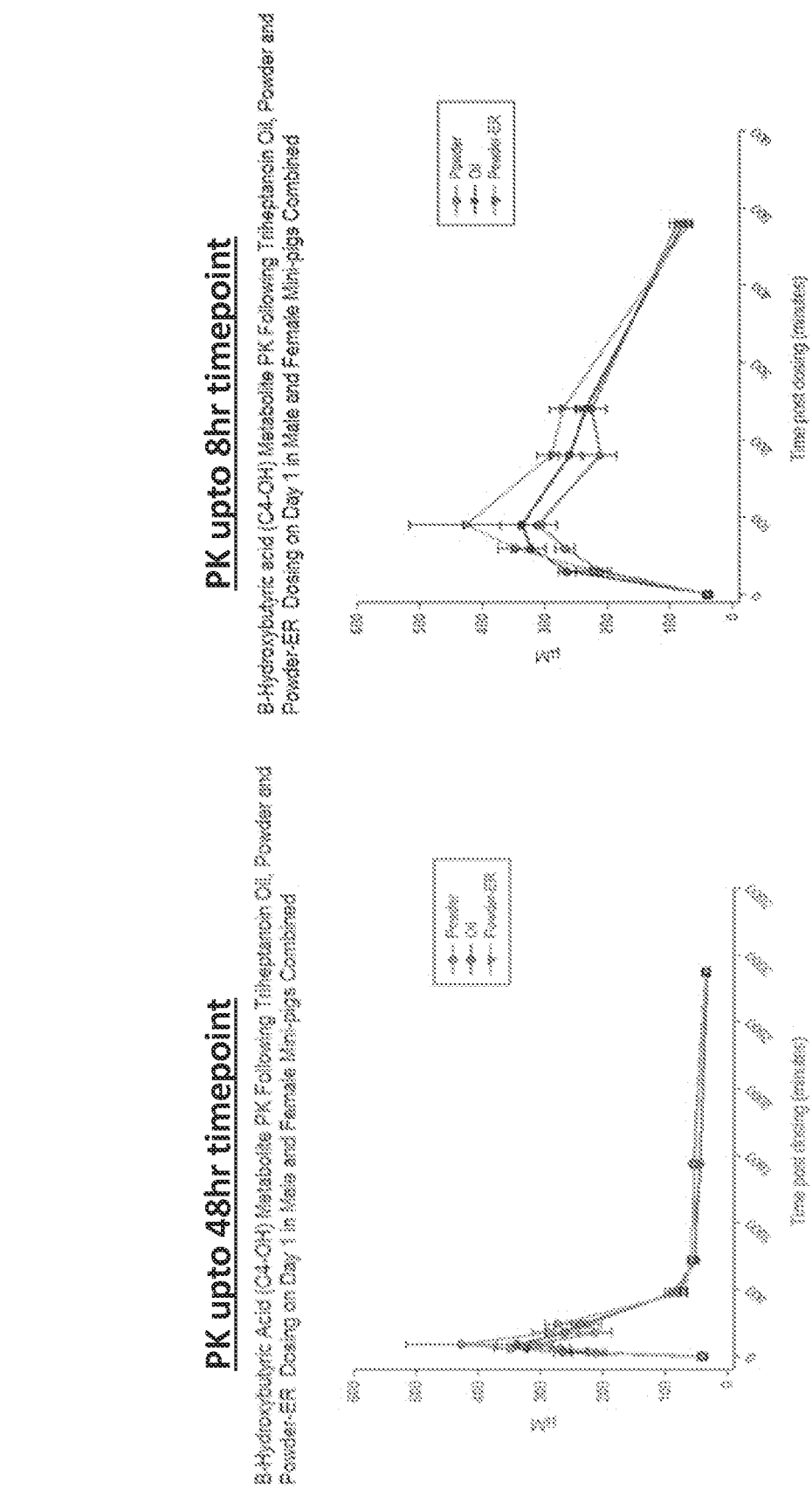

PK upto 48hr timepoint
8-Hydroxybutyric Acid (C4-OH) Metabolite PK Following Tiotropium Oil, Powder and Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Powder
Oil
Powder-ER
Time post dosing (minutes)
PK upto 8hr timepoint
8-Hydroxybutyric acid (C4-OH) Metabolite PK Following Tiotropium Oil, Powder and Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Powder
Oil
Powder-ER
Time post dosing (minutes)

Figure 8

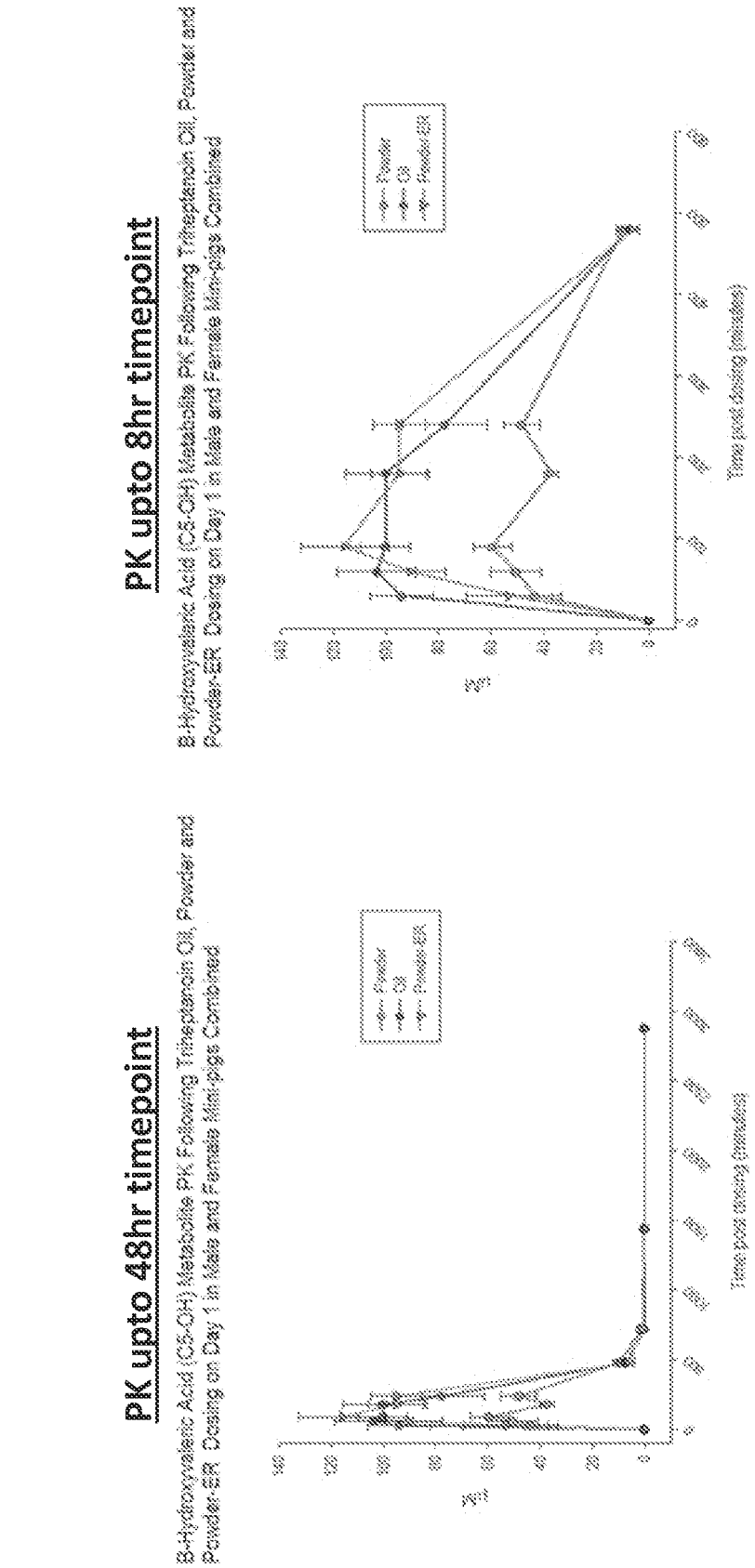

PK upto 48hr timepoint
B-Hydroxyvaleric Acid (C5-OH) Metabolite PK Following Tineptamoin Oil, Powder and Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
PK upto 8hr timepoint
B-Hydroxyvaleric Acid (C5-OH) Metabolite PK Following Tineptamoin Oil, Powder and Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Powder
Oil
Powder-ER
Time post dosing (minutes)

Figure 9

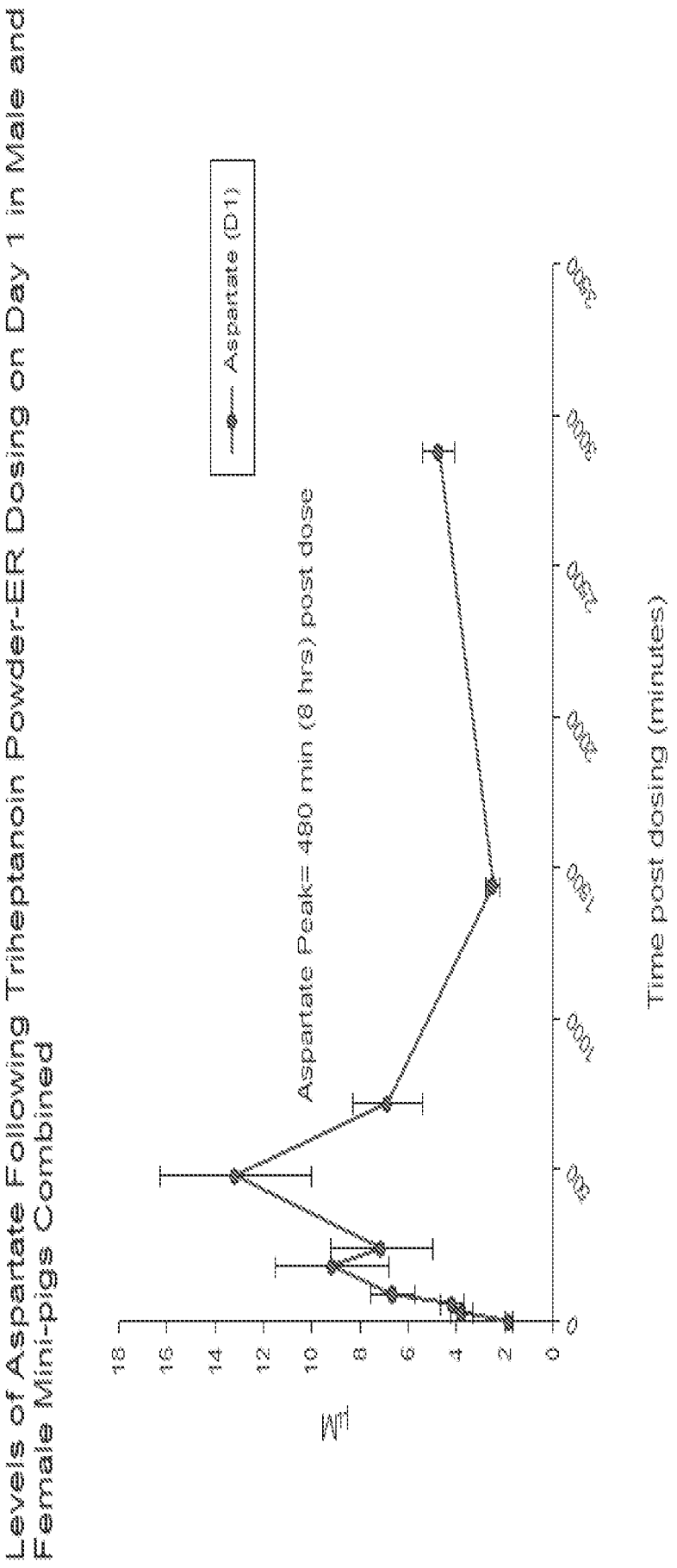

Levels of Aspartate Following Triheptamoin Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Aspartate (D1)
Aspartate Peak= 480 min (8 hrs) post dose
µM
Time post dosing (minutes)
0
2
4
6
8
10
12
14
16
18
0
60
120
180
240
300
360
420

Figure 10

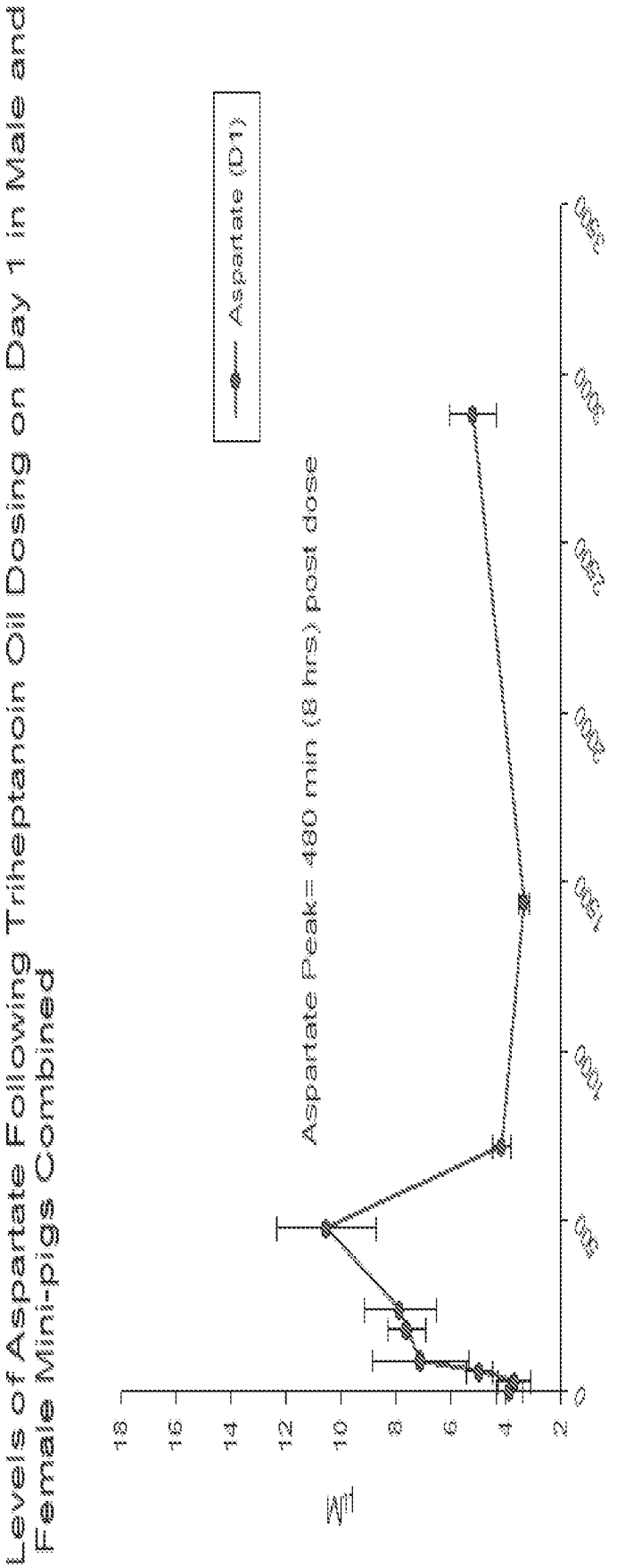

Levels of Aspartate Following Triheptanoin Oil Dosing on Day 1 in Male and Female Mini-pigs Combined
Aspartate (D1)
Aspartate Peak= 480 min (8 hrs) post dose
µM
Time post dosing (minutes)
0
2
4
6
8
10
12
14
16
18

Figure 11

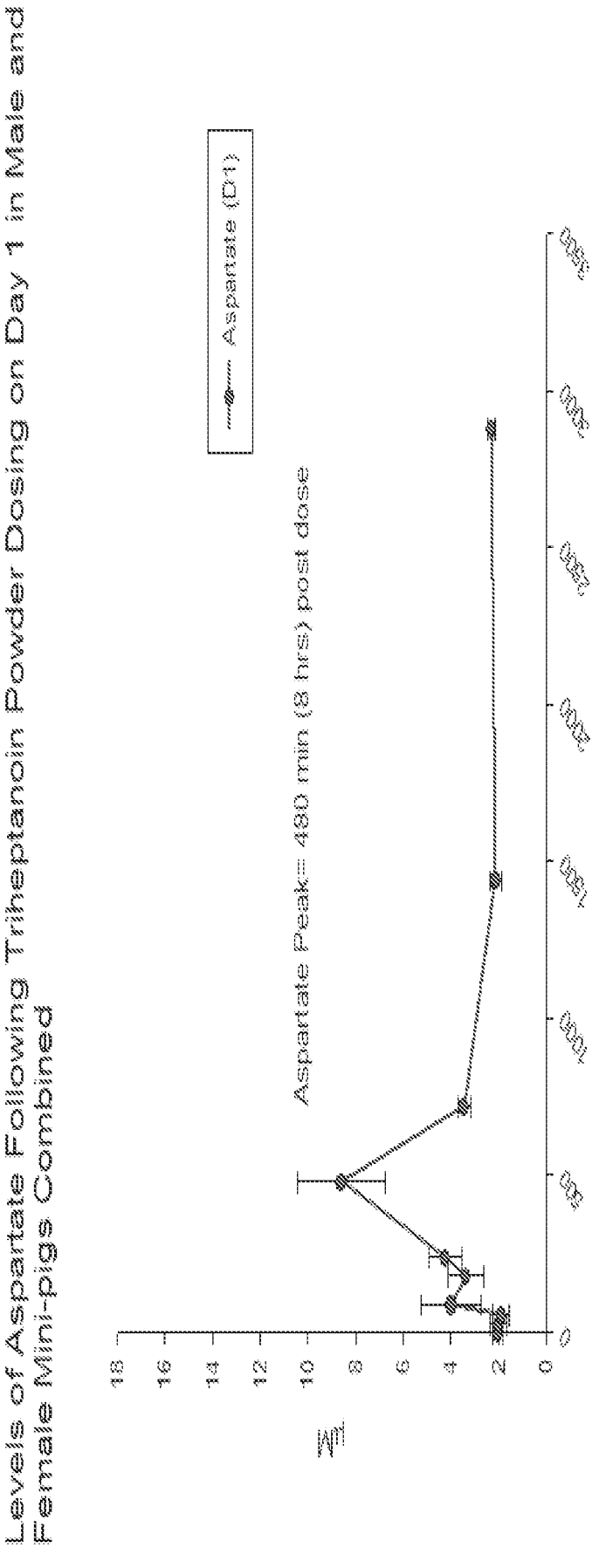

Levels of Aspartate Following Triheptanoin Powder Dosing on Day 1 in Male and Female Mini-pigs Combined
Aspartate (D1)
Aspartate Peak= 480 min (8 hrs) post dose
18
16
14
12
10
8
6
4
2
0
Time post dosing (minutes)

Figure 12

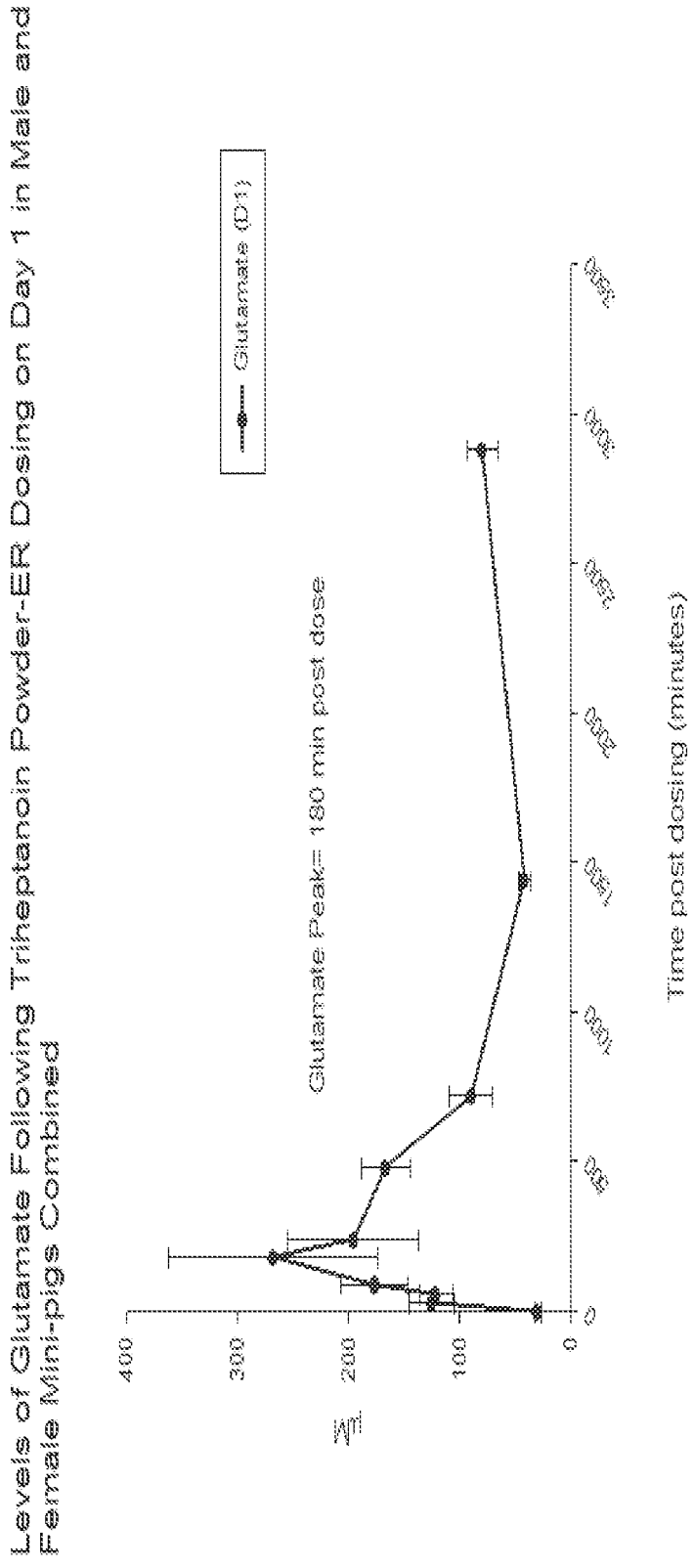

Levels of Glutamate Following Triheptanoin Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Glutamate (D1)
Glutamate Peak= 180 min post dose
400
300
200
100
0
0
60
120
180
240
300
360
420
480
Time post dosing (minutes)

Figure 13

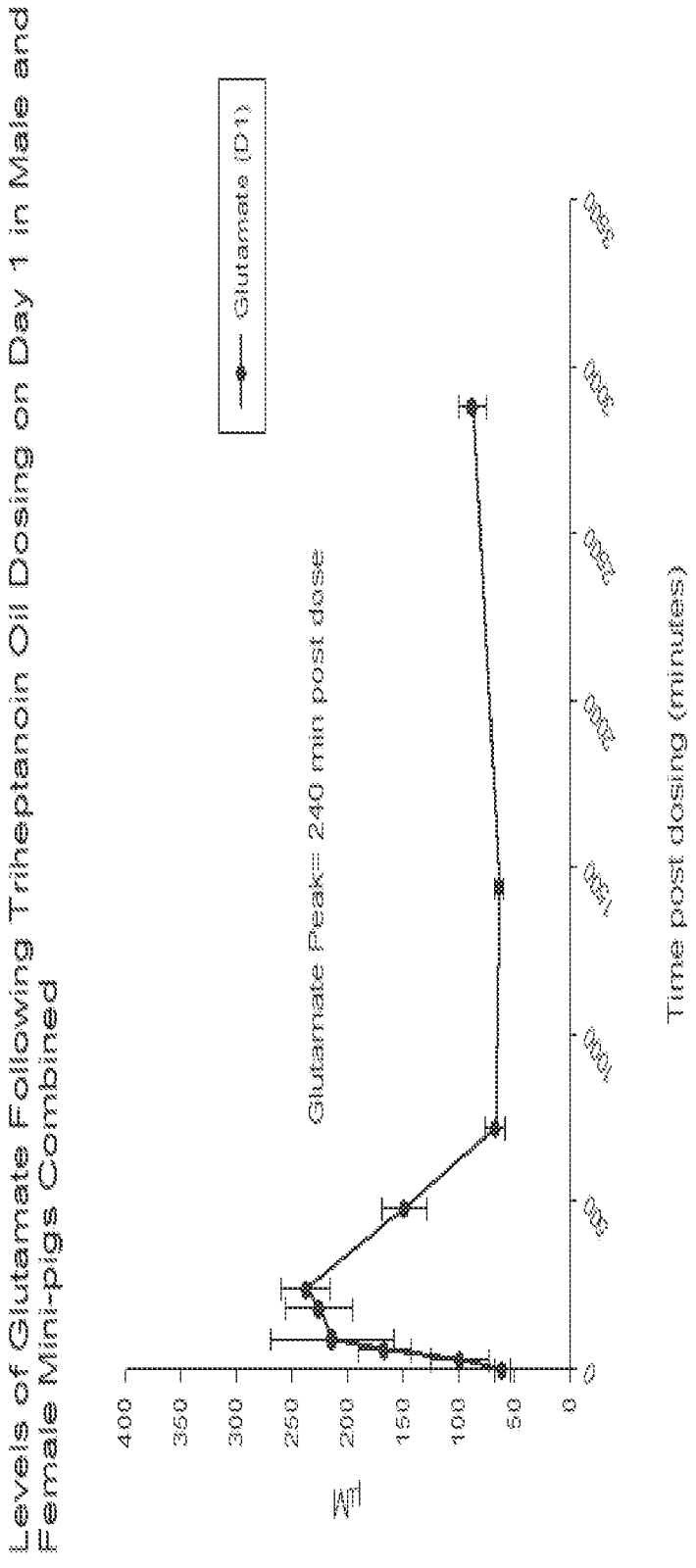

Levels of Glutamate Following Trihexyphenidyl Oil Dosing on Day 1 in Male and Female Mini-pigs Combined
Glutamate (D1)
Glutamate Peak= 240 min post dose
400
350
300
250
200
150
100
50
0
Time post dosing (minutes)

Figure 14

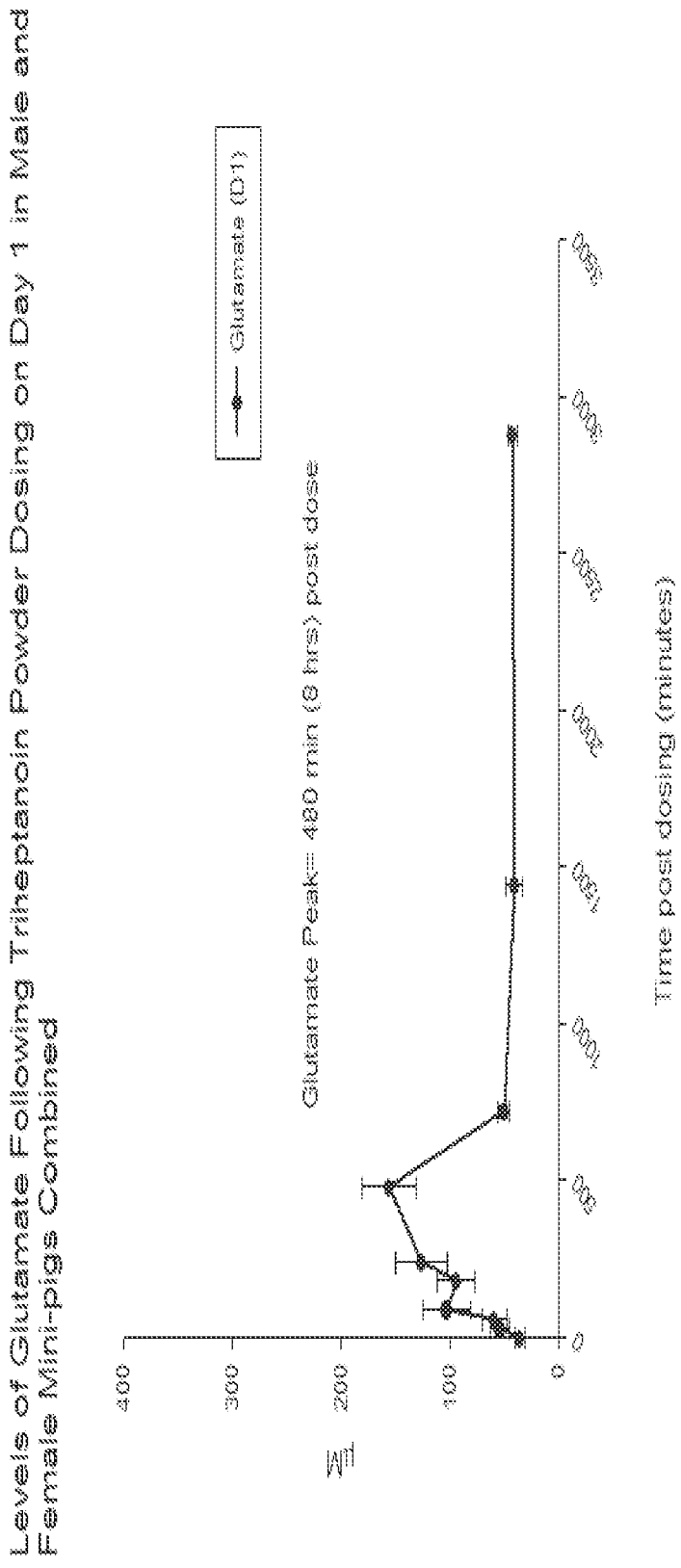

Levels of Glutamate Following Trihexyphenidyl Powder Dosing on Day 1 in Male and Female Mini-pigs Combined
Glutamate (D1)
Glutamate Peak= 480 min (8 hrs) post dose
400
300
200
100
0
0
60
120
180
240
300
360
420
480
Time post dosing (minutes)

Figure 15

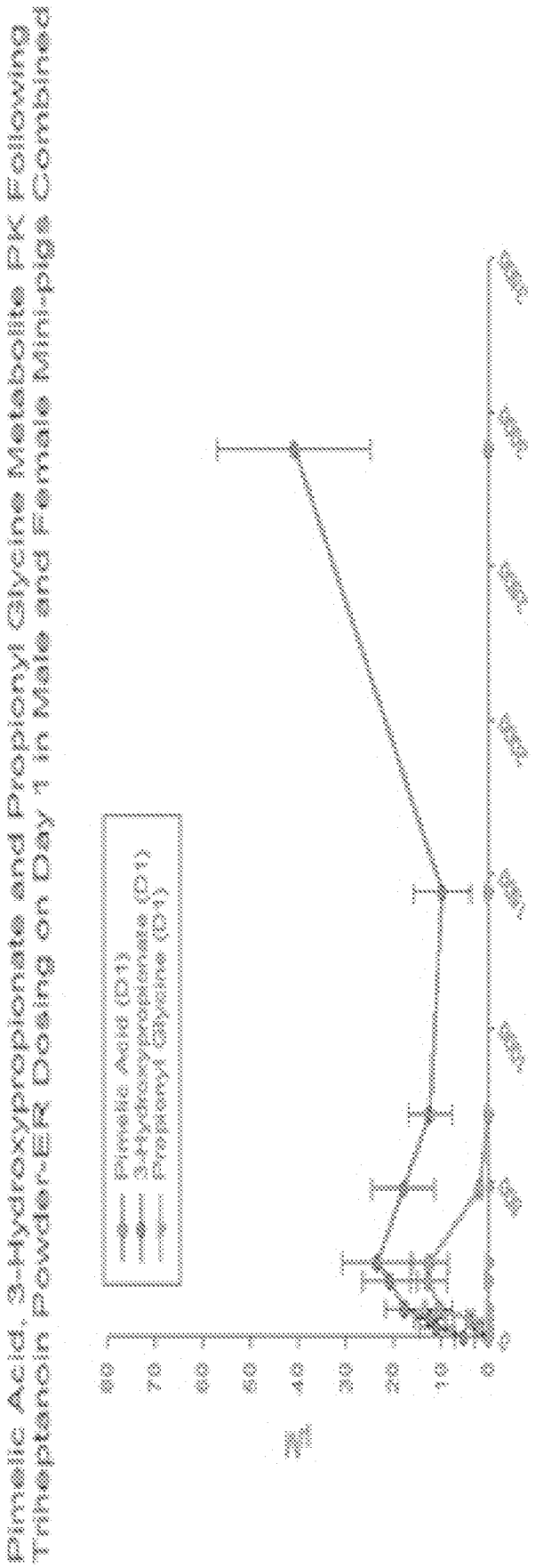

Pimelic Acid, 3-Hydroxypropionate and Propionyl Glycine Metabolite PK Following Trihexanoin Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Pimelic acid (ug/mL)
Time post dosing (minutes)
0
10
20
30
40
50
60
70
80
Pimelic acid (ug/mL)
3-Hydroxypropionic acid (ug/mL)
Propionyl glycine (ug/mL)

Figure 16

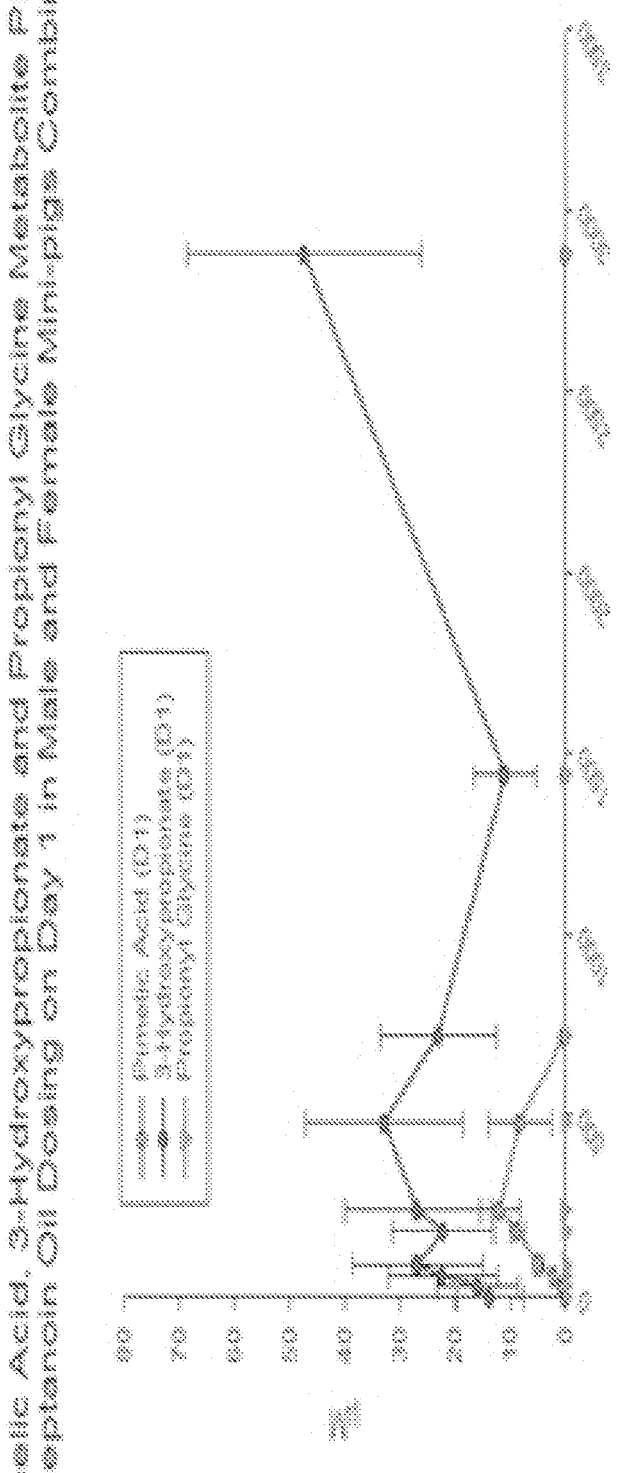

Palmitic Acid, 3-Hydroxypropionate and Propionyl Glycine Metabolite PK Following Triheptanoin Oil Dosing on Day 1 in Male and Female Mini-pigs Combined
Palmitic Acid (C16)
3-Hydroxypropionate (C3)
Propionyl Glycine (C3)
(C16 scaled down 10 fold)
Time post dosing (minutes)

Figure 17

Pimselle Acid, 3-Hydroxypropionate and Propionyl Glycine Metabolite PK Following Trihexanoin Powder Dosing on Day 1 in Male and Female Mini-pigs Combined
Pimselle acid (C11)
3-HP
Propionyl Glycine (C3)
Time post dosing (minutes)

Figure 18

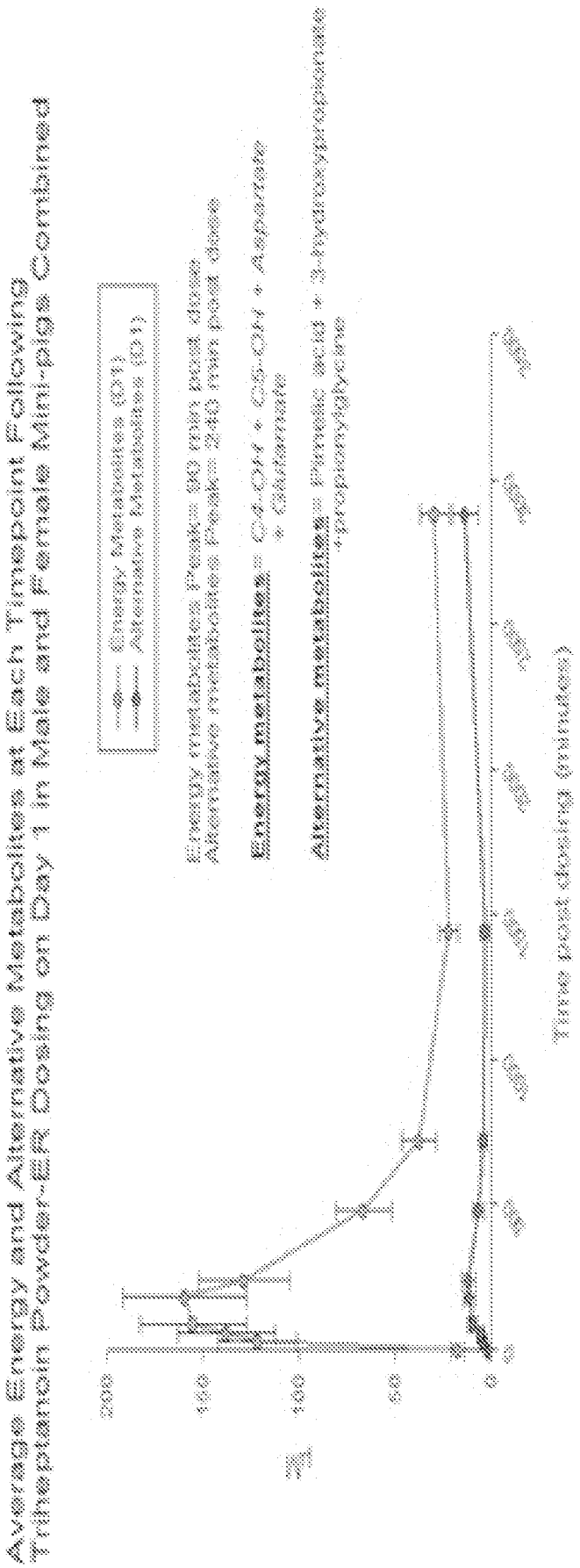

Average Energy and Alternative Metabolites at Each Timepoint Following Tritherapeutic Powder-ER Dosing on Day 1 in Male and Female Mini-pigs Combined
Energy Metabolites (kJ)
Alternative Metabolites (kJ)
Energy metabolites Peaks: 90 min post dose
Alternative metabolites Peaks: 240 min post dose
Energy metabolites = C4-OH + C5-OH + Aspartate + Glutamate
Alternative metabolites = Phenyl acid + 3-hydroxybutyrate + propionylcarnitine
Time (post dosing (minutes))

Figure 19

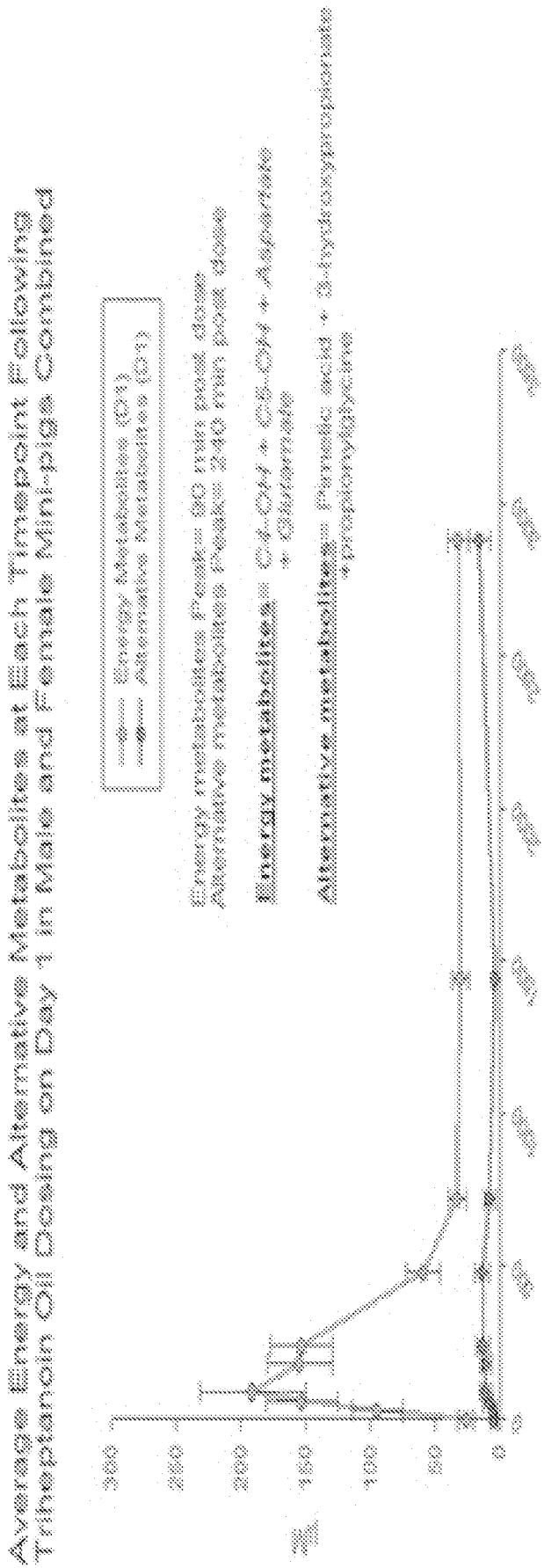

Average Energy and Alternative Metabolites at Each Timepoint Following Trihexanoin Oil Dosing on Day 1 in Male and Female Mini-pigs Combined
(n=8) Energy
(n=8) Energy metabolites
(n=8) Alternative energy
Energy metabolites Peak = 60 min post dose
Alternative energy Peak = 240 min post dose
Energy metabolites = C4-OH + C6-OH + Ketones + Glycerol
Alternative energy = Phenyl acid + 3-hydroxybutyrate + succinylacetone + succinylacetoacetate
Time post dosing (minutes)

Figure 20

Average Energy and Alternative Metabolites at Each Timepoint Following Triheptanoin Powder Dosing on Day 1 in Male and Female Mini-pigs Combined
Energy Metabolites
Alternative Metabolites (C01)
Energy metabolites: Peak = 60 min post dose
Alternative metabolites: Peak = 240 min post dose
Energy metabolites = C4-OH + C5-OH + Acetate + Glutamate
Alternative metabolites = Formic acid + 3-hydroxypropionate + pyroglutamate
Time post dosing (minutes)
mM
300
250
200
150
100
50
0
0
60
120
180
240
300
360
420
480
540
600
660
720
780
840
900
960
1020
1080
1140
1200
1260
1320
1380
1440

Figure 21

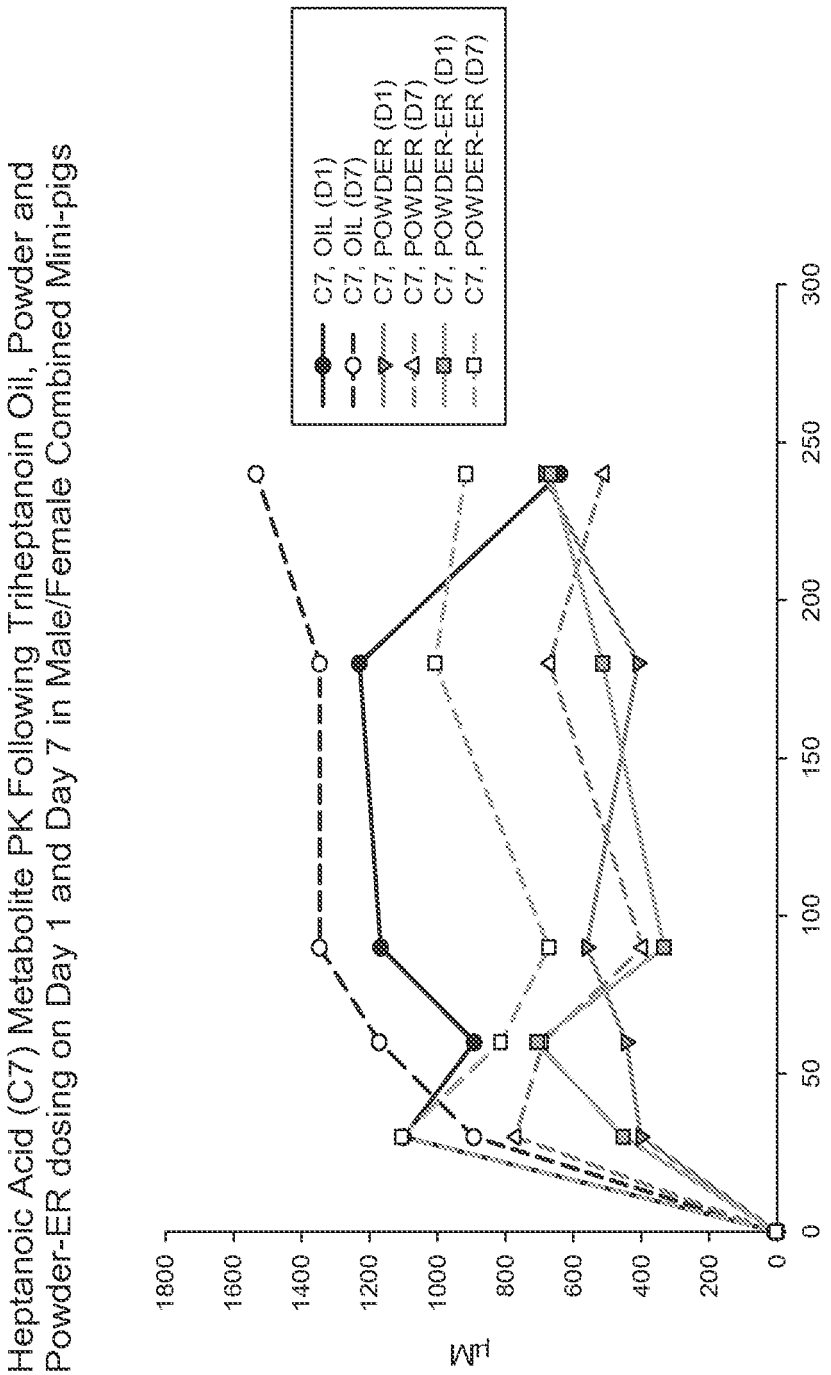

Heptanoic Acid (C7) Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
C7, OIL (D1)
C7, OIL (D7)
C7, POWDER (D1)
C7, POWDER (D7)
C7, POWDER-ER (D1)
C7, POWDER-ER (D7)
µM
1800
1600
1400
1200
1000
800
600
400
200
0
0
50
100
150
200
250
300
Time post dosing

Figure 22

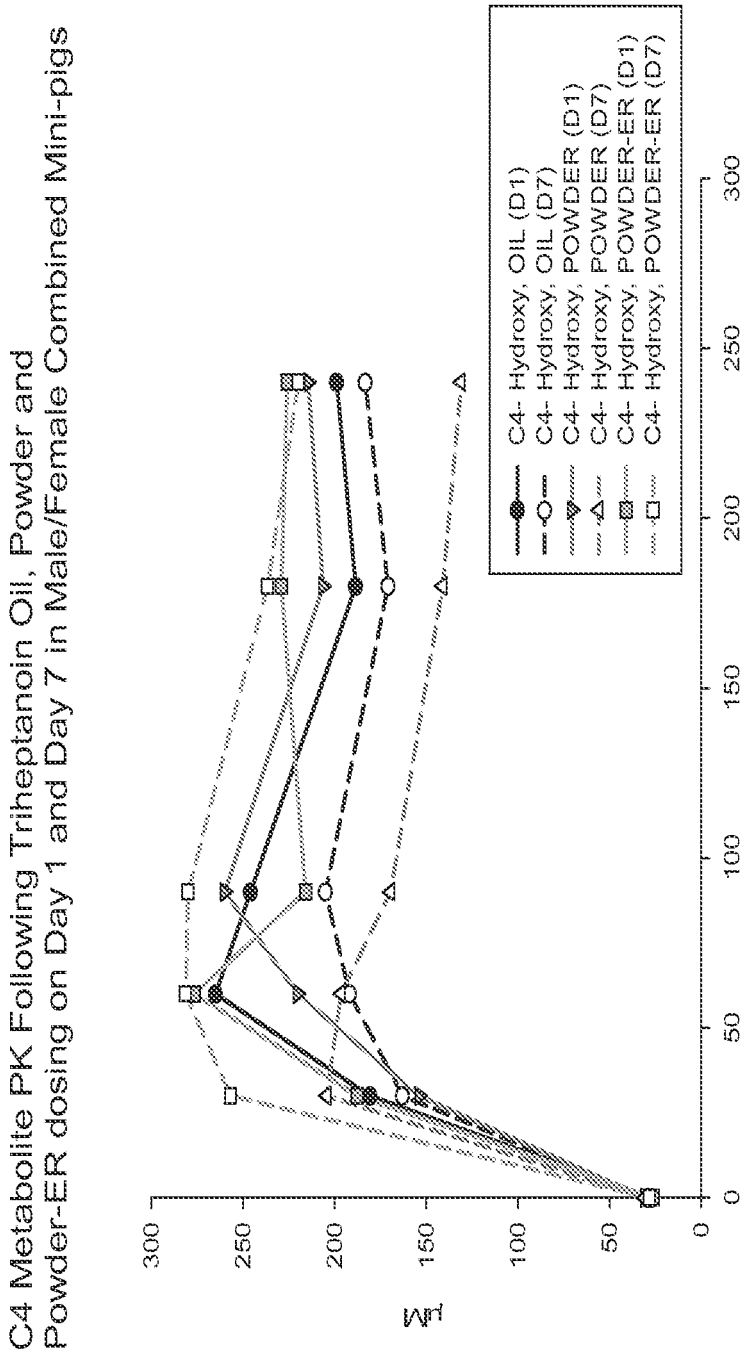

C4 Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
C4- Hydroxy, OIL (D1)
C4- Hydroxy, OIL (D7)
C4- Hydroxy, POWDER (D1)
C4- Hydroxy, POWDER (D7)
C4- Hydroxy, POWDER-ER (D1)
C4- Hydroxy, POWDER-ER (D7)
Time post dosing
0
50
100
150
200
250
300

Figure 23

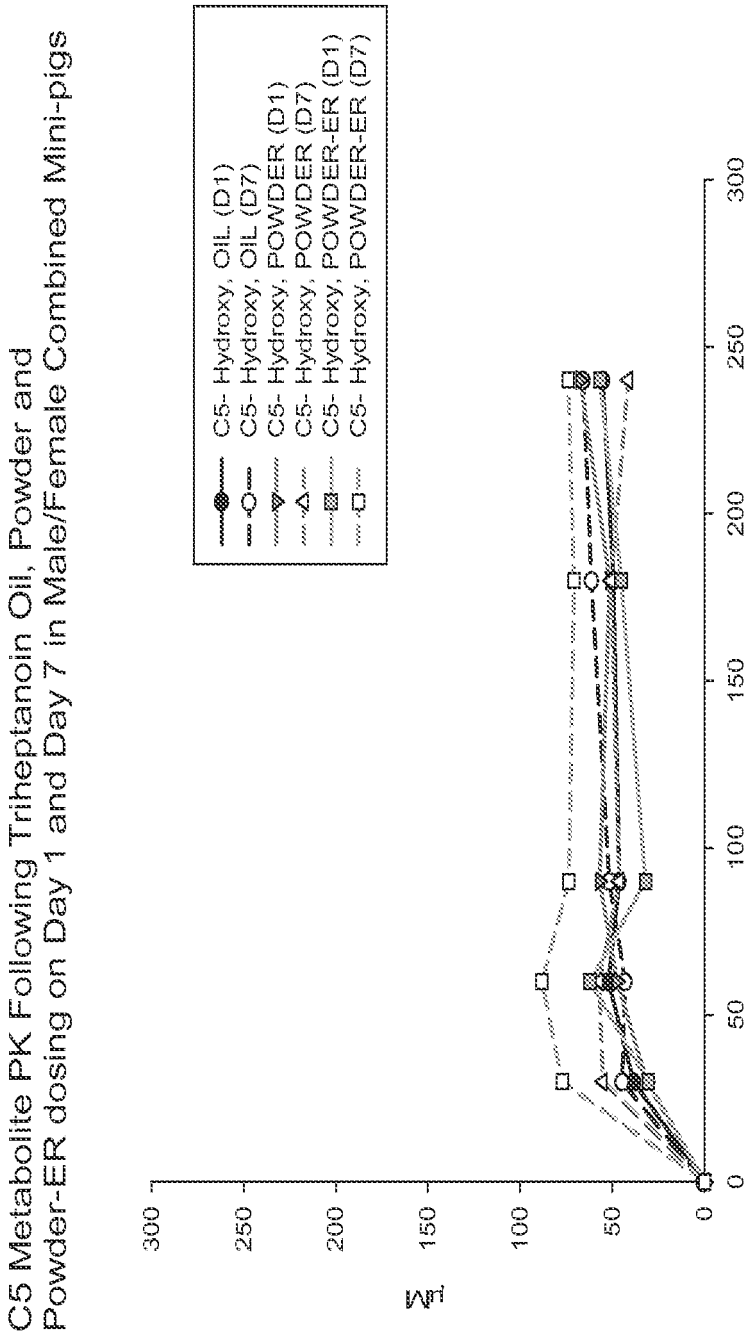

C5 Metabolite PK Following Triheptanoin Oil, Powder and
Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
C5- Hydroxy, OIL (D1)
C5- Hydroxy, OIL (D7)
C5- Hydroxy, POWDER (D1)
C5- Hydroxy, POWDER (D7)
C5- Hydroxy, POWDER-ER (D1)
C5- Hydroxy, POWDER-ER (D7)
uM
300
250
200
150
100
50
0
0
50
100
150
200
250
300
Time post dosing

Figure 24

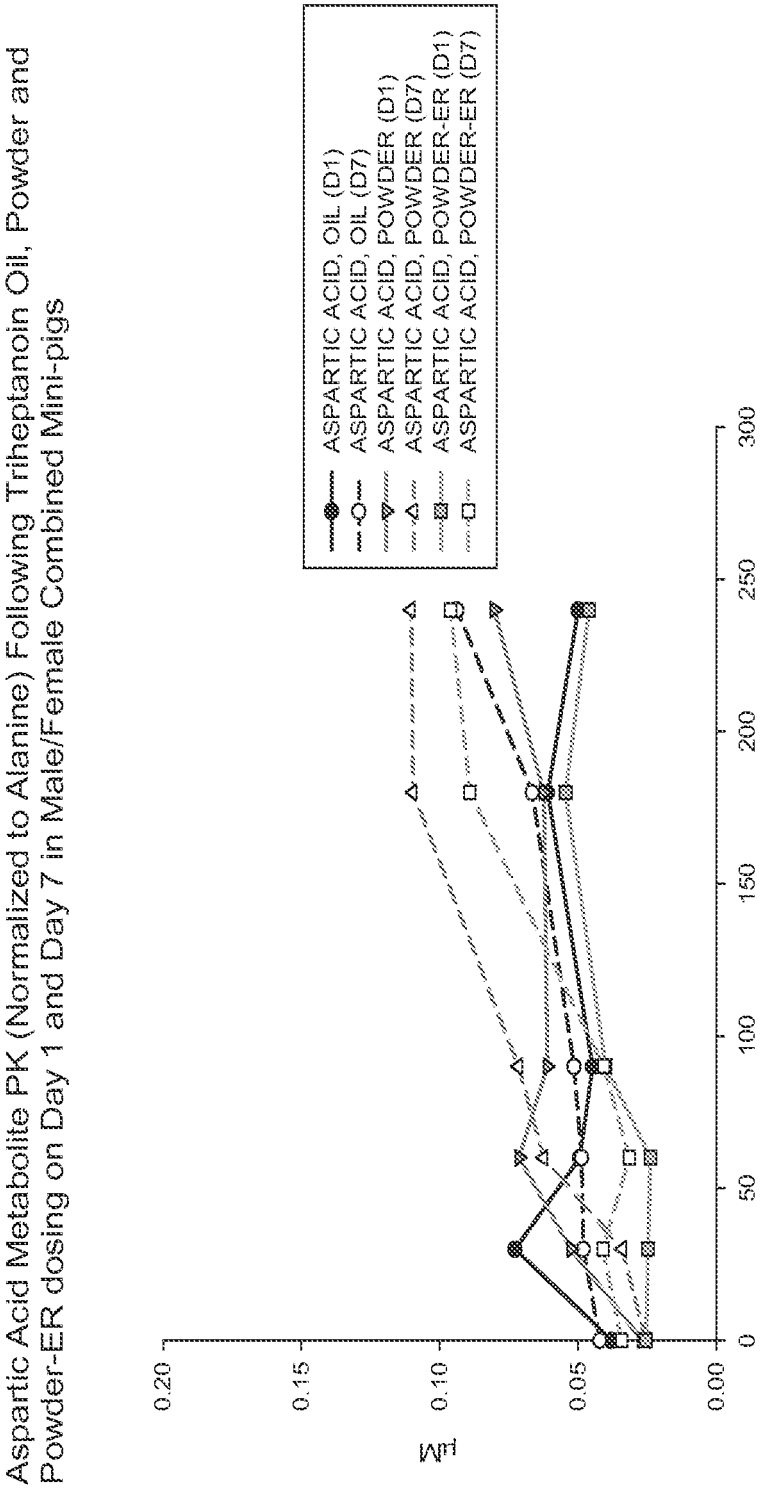

Aspartic Acid Metabolite PK (Normalized to Alanine) Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
ASPARTIC ACID, OIL (D1)
ASPARTIC ACID, OIL (D7)
ASPARTIC ACID, POWDER (D1)
ASPARTIC ACID, POWDER (D7)
ASPARTIC ACID, POWDER-ER (D1)
ASPARTIC ACID, POWDER-ER (D7)
μM
0.20
0.15
0.10
0.05
0.00
0
50
100
150
200
250
300
Time post dosing

Figure 25

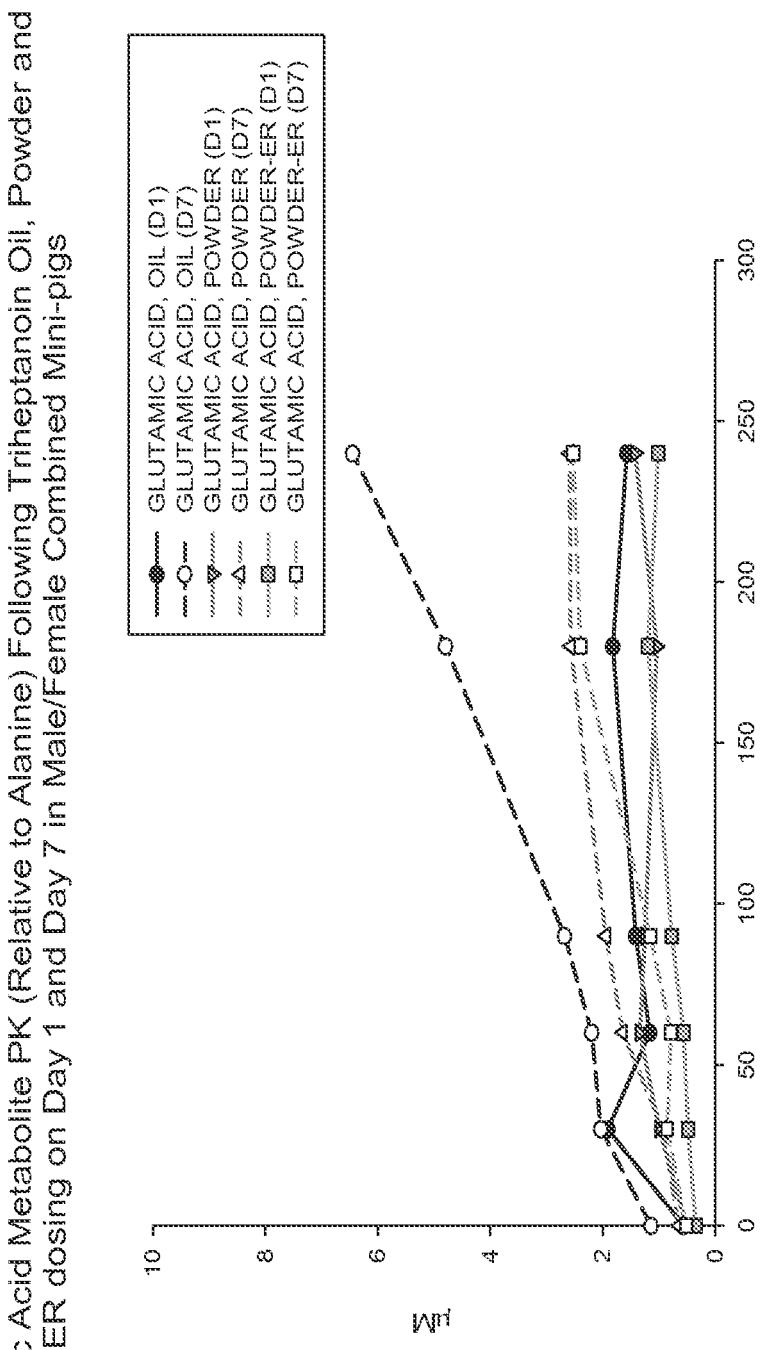

Glutamic Acid Metabolite PK (Relative to Alanine) Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
GLUTAMIC ACID, OIL (D1)
GLUTAMIC ACID, OIL (D7)
GLUTAMIC ACID, POWDER (D1)
GLUTAMIC ACID, POWDER (D7)
GLUTAMIC ACID, POWDER-ER (D1)
GLUTAMIC ACID, POWDER-ER (D7)
μM
0
2
4
6
8
10
0
50
100
150
200
250
300
Time post dosing

Figure 26

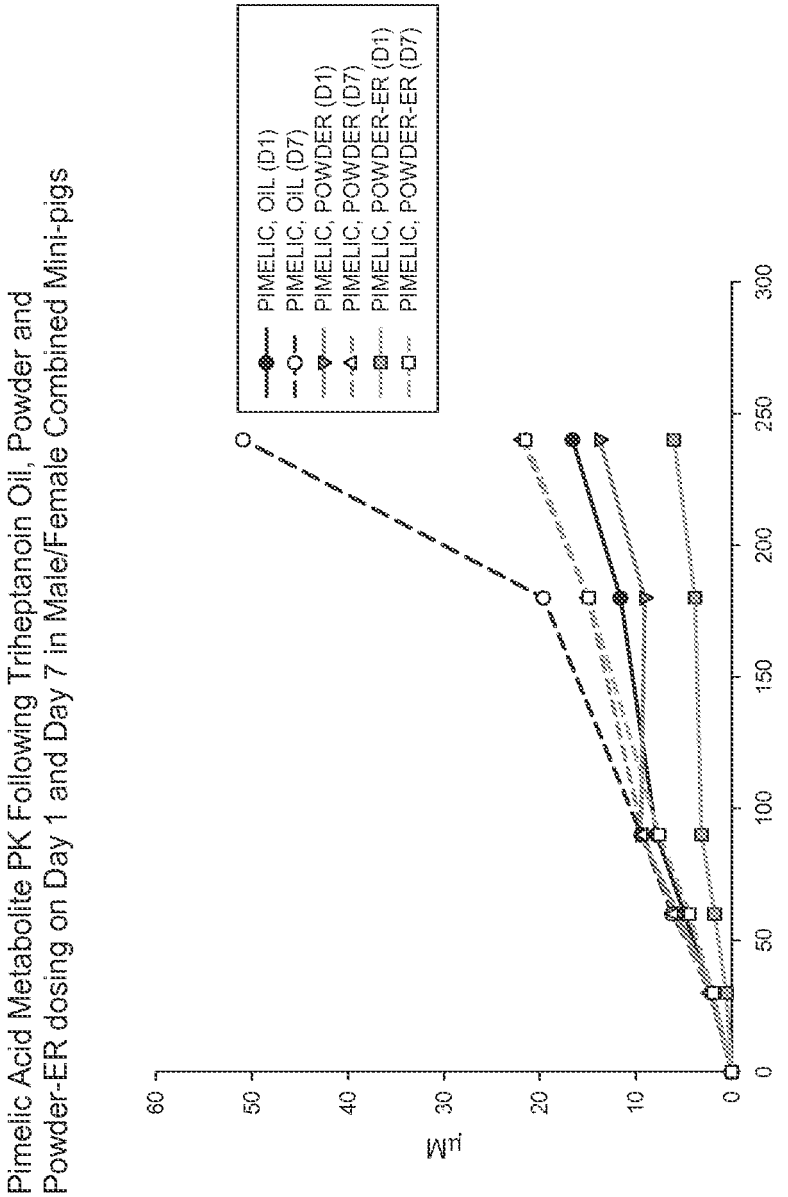

Pimelic Acid Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
PIMELIC, OIL (D1)
PIMELIC, OIL (D7)
PIMELIC, POWDER (D1)
PIMELIC, POWDER (D7)
PIMELIC, POWDER-ER (D1)
PIMELIC, POWDER-ER (D7)
µM
0
10
20
30
40
50
60
0
50
100
150
200
250
300
Time post dosing

Figure 27

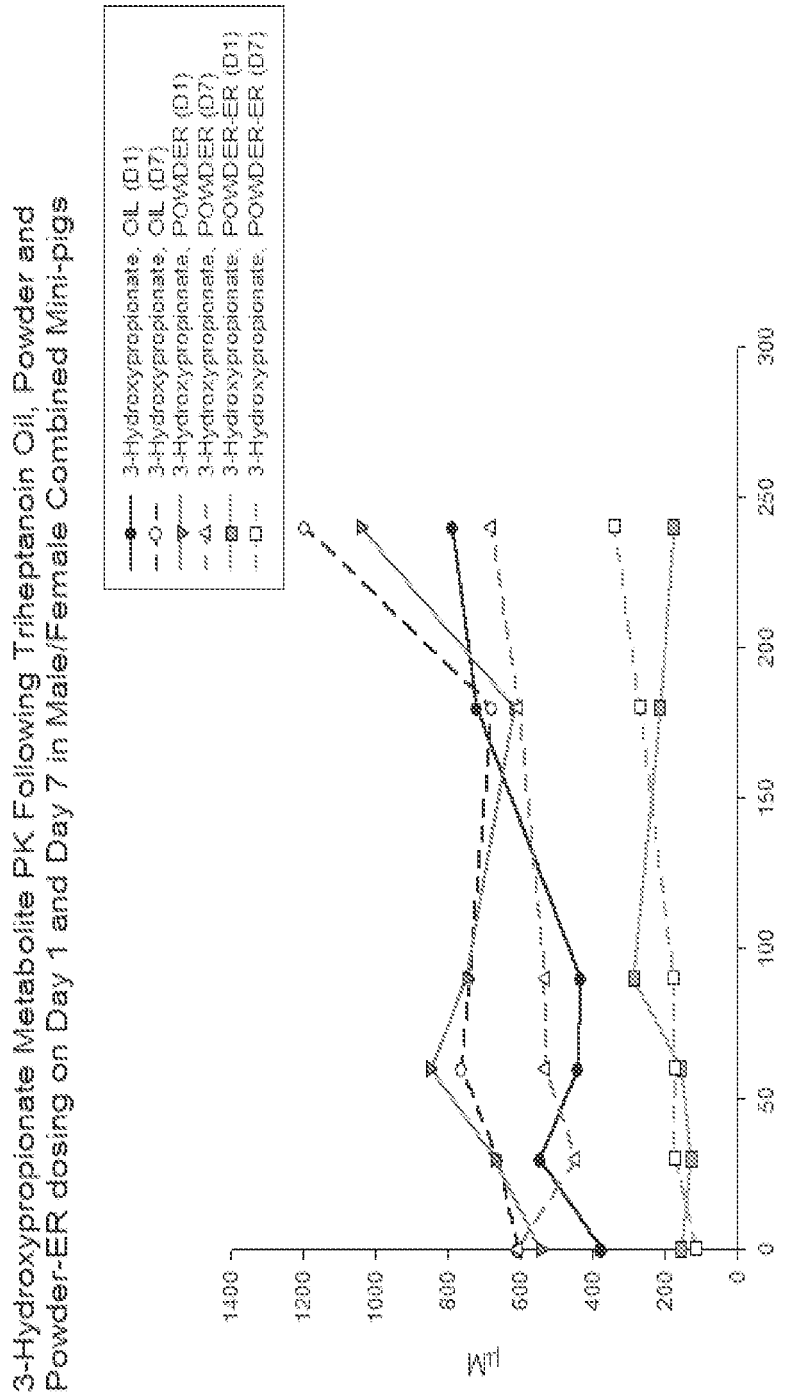

3-Hydroxypropionate Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
3-Hydroxypropionate, OIL (D1)
3-Hydroxypropionate, OIL (D7)
3-Hydroxypropionate, POWDER (D1)
3-Hydroxypropionate, POWDER (D7)
3-Hydroxypropionate, POWDER-ER (D1)
3-Hydroxypropionate, POWDER-ER (D7)
µM
1400
1200
1000
800
600
400
200
0
0
50
100
150
200
250
300
Time post dosing

Figure 28

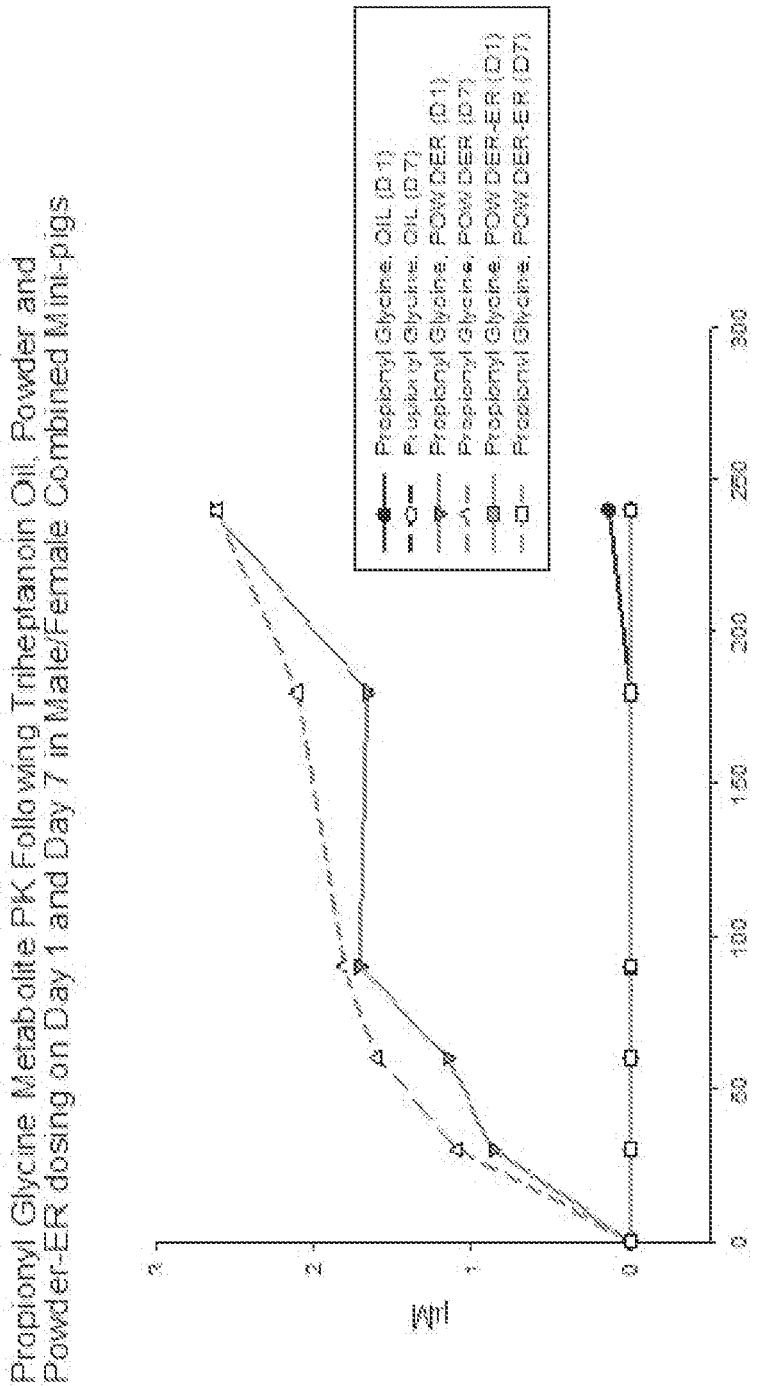

Propionyl Glycine Metabolite PK Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
Propionyl Glycine, OIL (D1)
Propionyl Glycine, OIL (D7)
Propionyl Glycine, POWDER (D1)
Propionyl Glycine, POWDER (D7)
Propionyl Glycine, POWDER-ER (D1)
Propionyl Glycine, POWDER-ER (D7)
µg/ml
0
1
2
3
0
50
100
150
200
250
300
Time post dosing

Figure 29

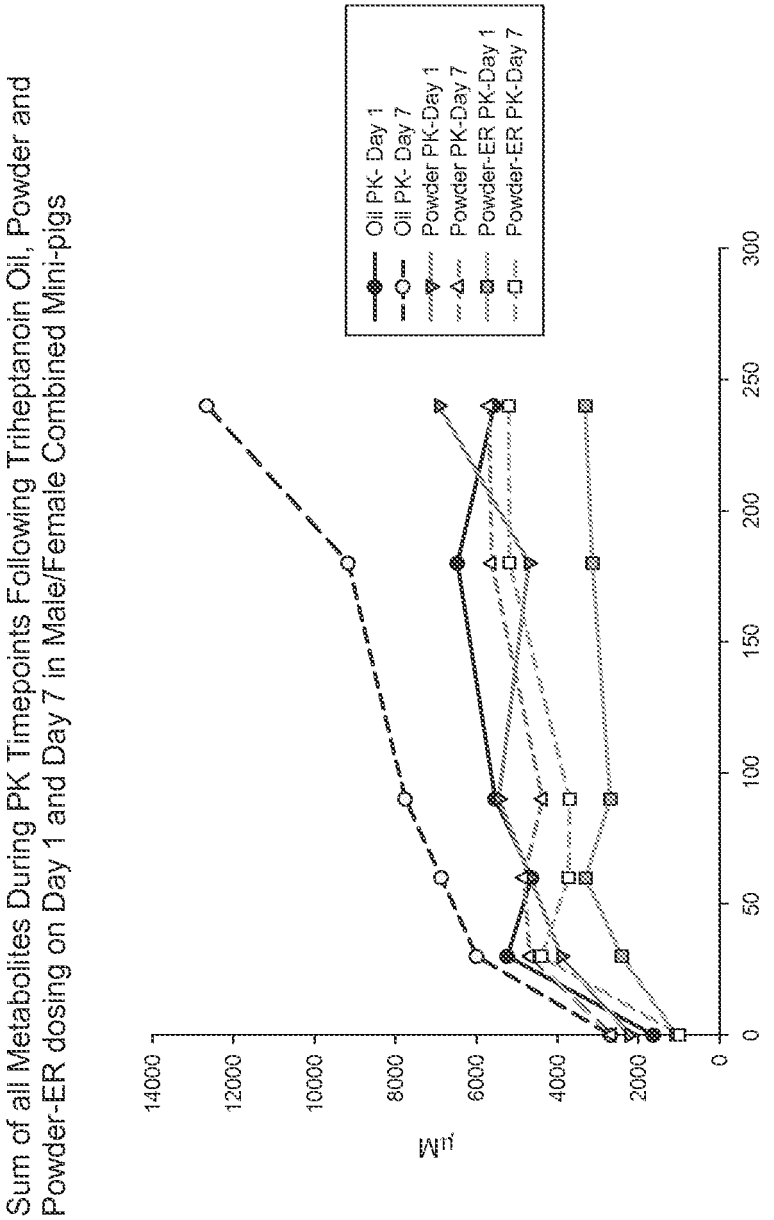

Sum of all Metabolites During PK Timepoints Following Triheptanoin Oil, Powder and Powder-ER dosing on Day 1 and Day 7 in Male/Female Combined Mini-pigs
Oil PK- Day 1
Oil PK- Day 7
Powder PK-Day 1
Powder PK-Day 7
Powder-ER PK-Day 1
Powder-ER PK-Day 7
μM
14000
12000
10000
8000
6000
4000
2000
0
0
50
100
150
200
250
300
Time post dosing

Figure 30

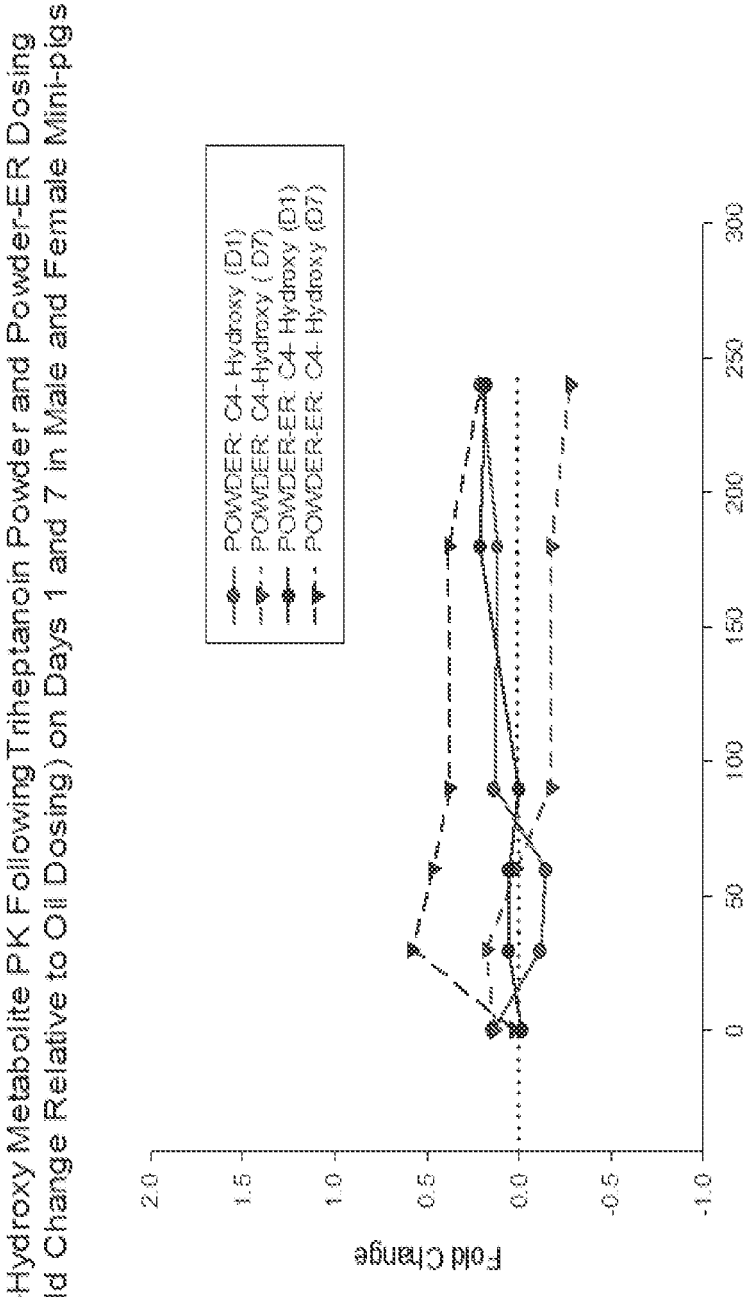

C4-Hydroxy Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER: C4-Hydroxy (D1)
POWDER: C4-Hydroxy (D7)
POWDER-ER: C4-Hydroxy (D1)
POWDER-ER: C4-Hydroxy (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 31

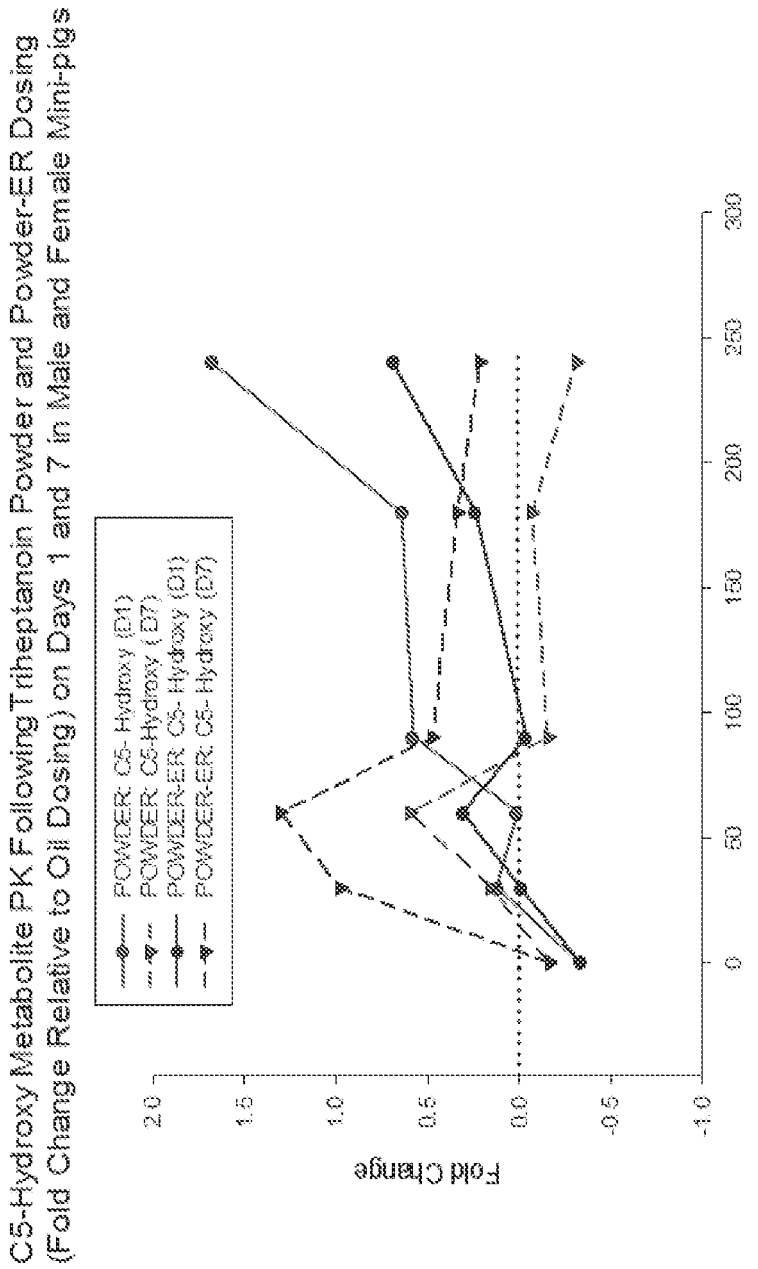

C5-Hydroxy Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER: C5- Hydroxy (D1)
POWDER: C5-Hydroxy (D7)
POWDER-ER: C5- Hydroxy (D1)
POWDER-ER: C5- Hydroxy (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 32

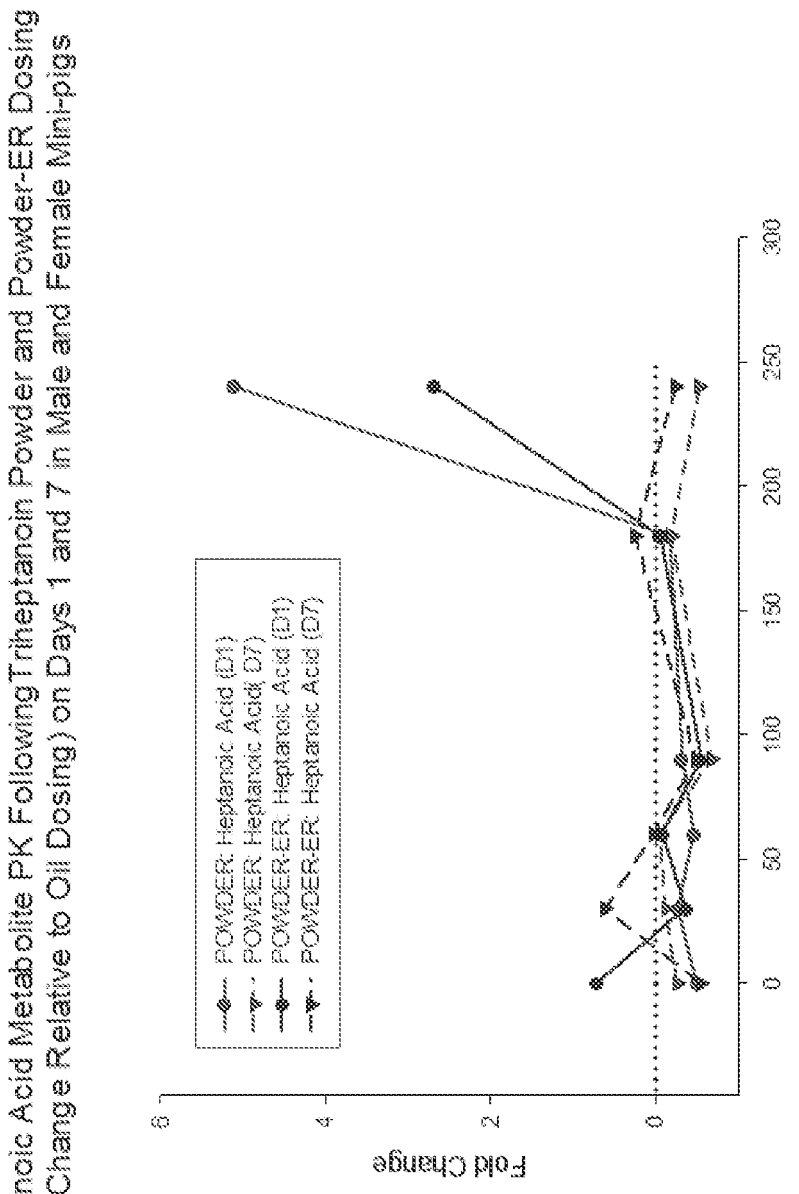

Heptanoic Acid Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER Heptanoic Acid (D1)
POWDER Heptanoic Acid(D7)
POWDER-ER Heptanoic Acid (D1)
POWDER-ER Heptanoic Acid (D7)
Fold Change
0
2
4
6
0
50
100
150
200
250
300
Time post dosing

Figure 33

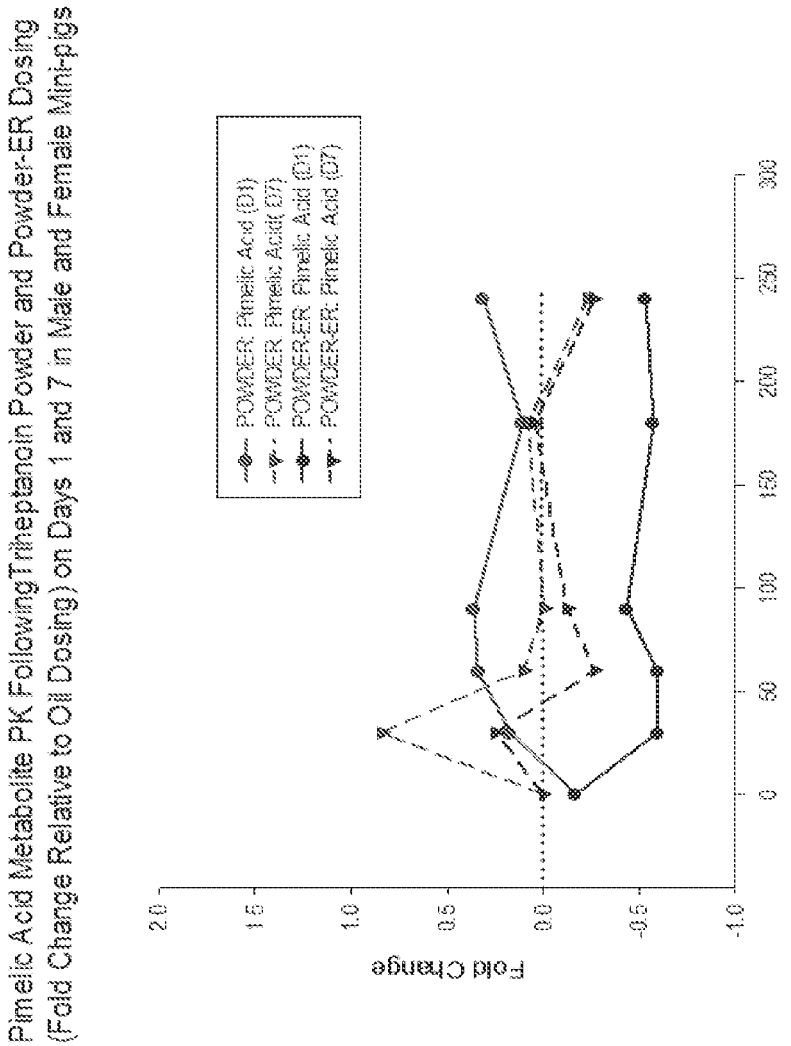

Pimelic Acid Metabolite PK Following Trilleptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER Pimelic Acid (D1)
POWDER Pimelic Acid (D7)
POWDER-ER Pimelic Acid (D1)
POWDER-ER Pimelic Acid (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 34

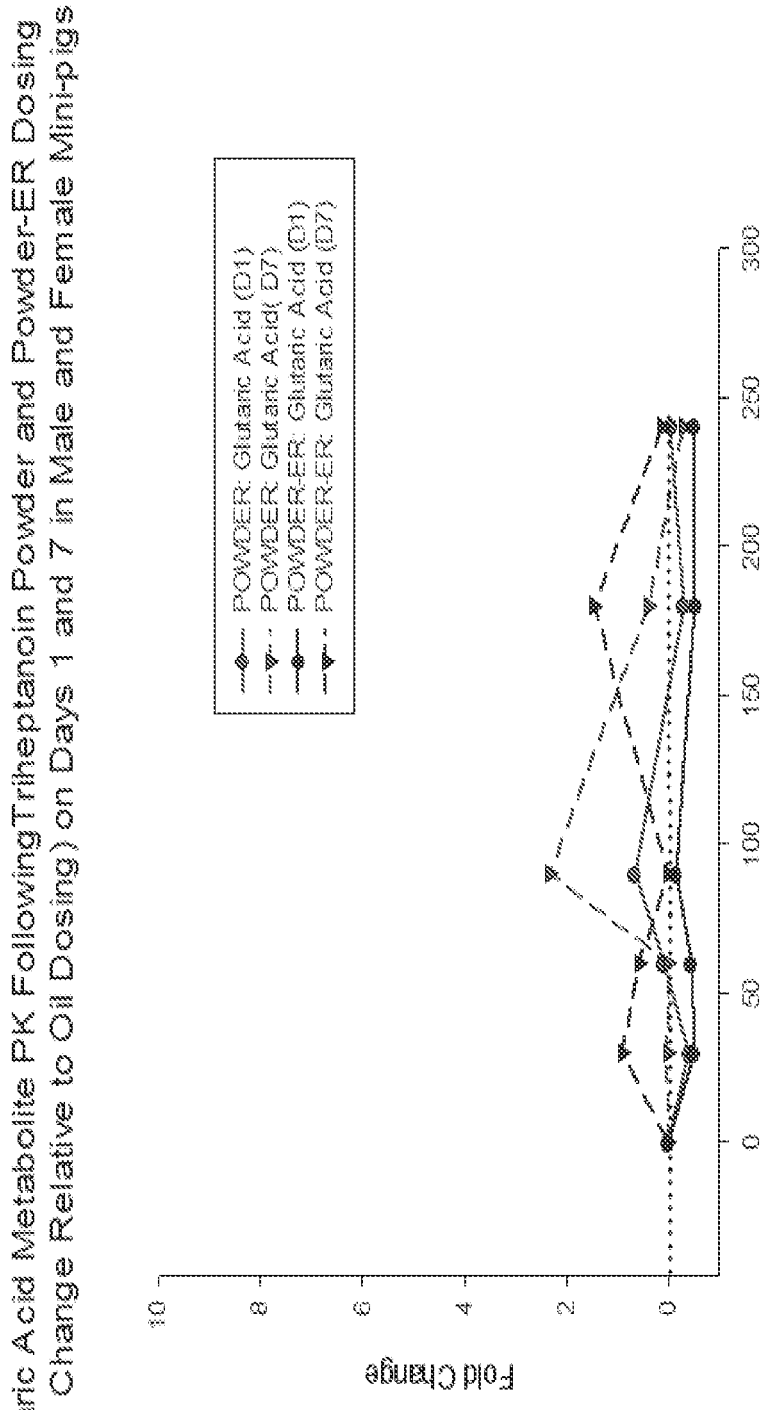

Glutaric Acid Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER: Glutaric Acid (D1)
POWDER: Glutaric Acid(D7)
POWDER-ER: Glutaric Acid (D1)
POWDER-ER: Glutaric Acid (D7)
Fold Change
0
2
4
6
8
10
0
50
100
150
200
250
300
Time post dosing

Figure 35

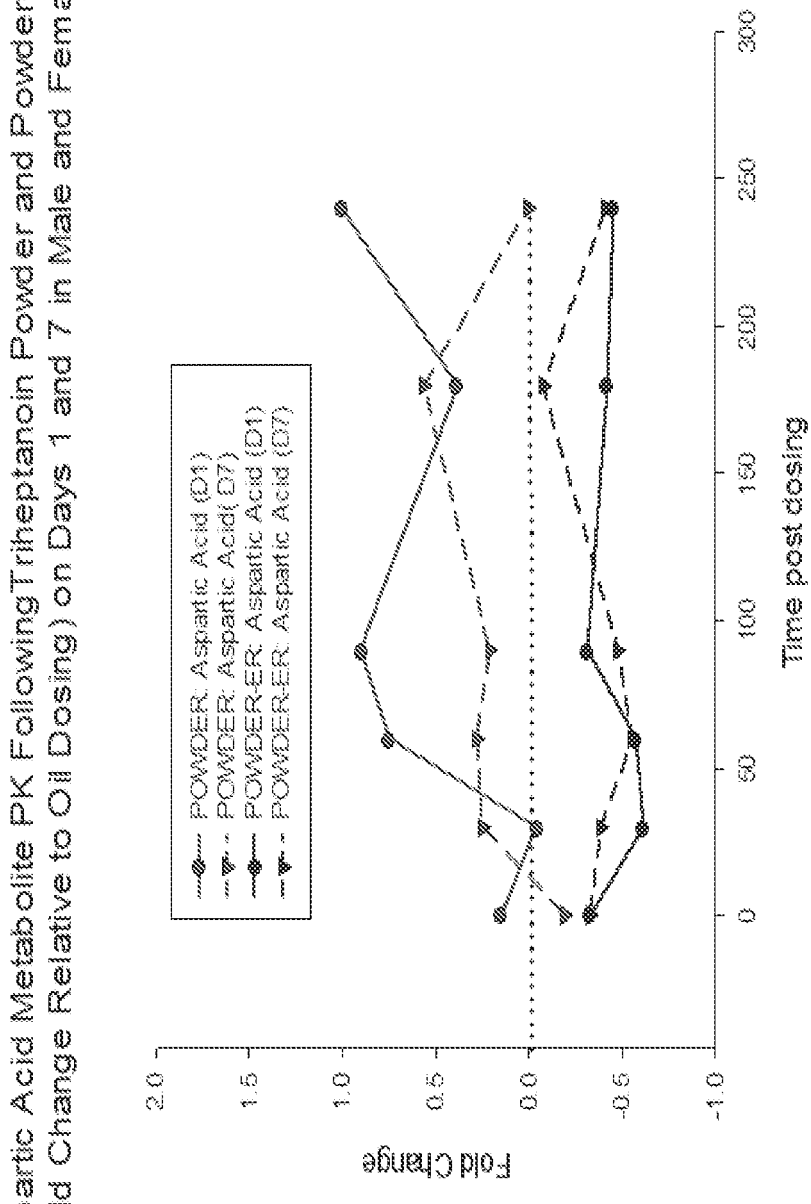

Aspartic Acid Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER: Aspartic Acid (D1)
POWDER: Aspartic Acid(D7)
POWDER-ER: Aspartic Acid (D1)
POWDER-ER: Aspartic Acid (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 36

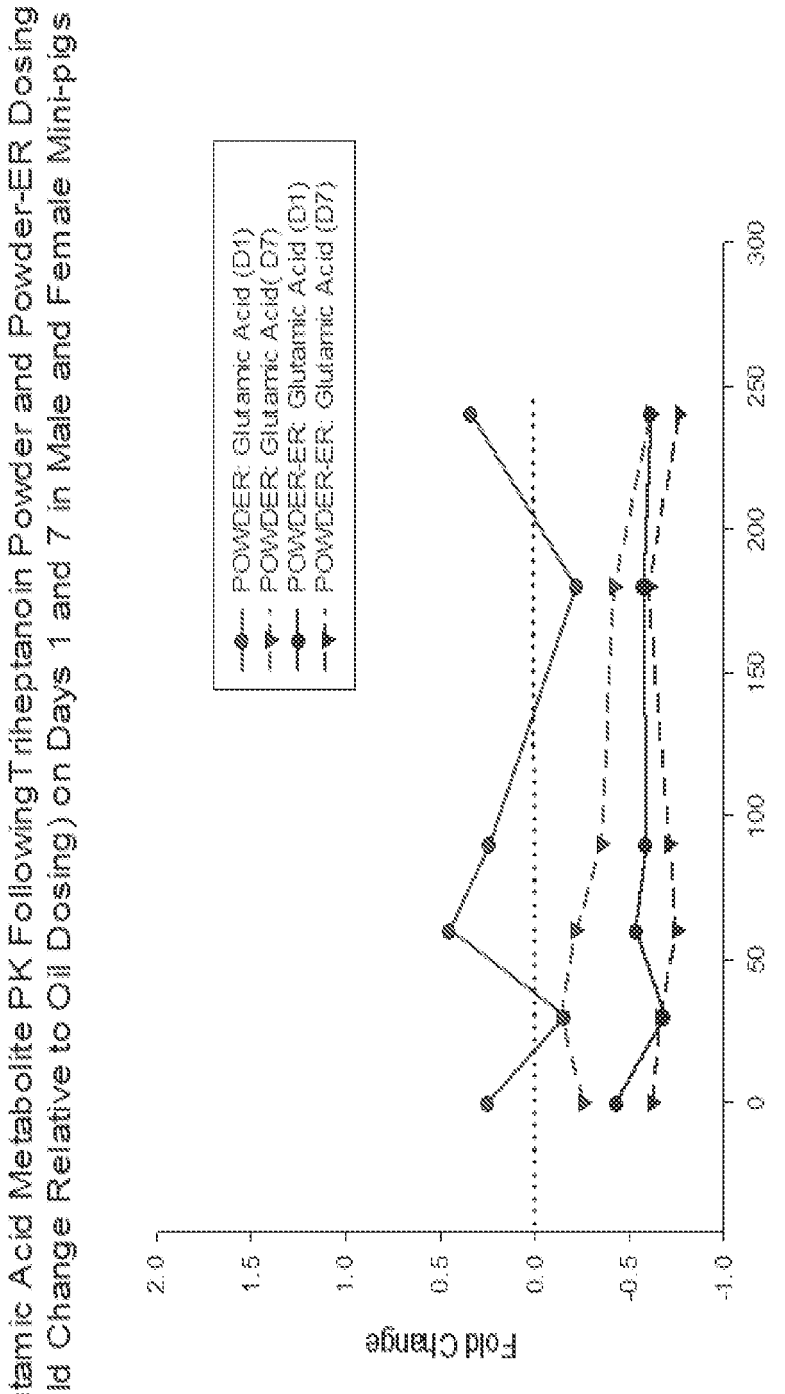

Glutamic Acid Metabolite PK Following Trheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER Glutamic Acid (D1)
POWDER Glutamic Acid(D7)
POWDER-ER Glutamic Acid (D1)
POWDER-ER Glutamic Acid (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 37

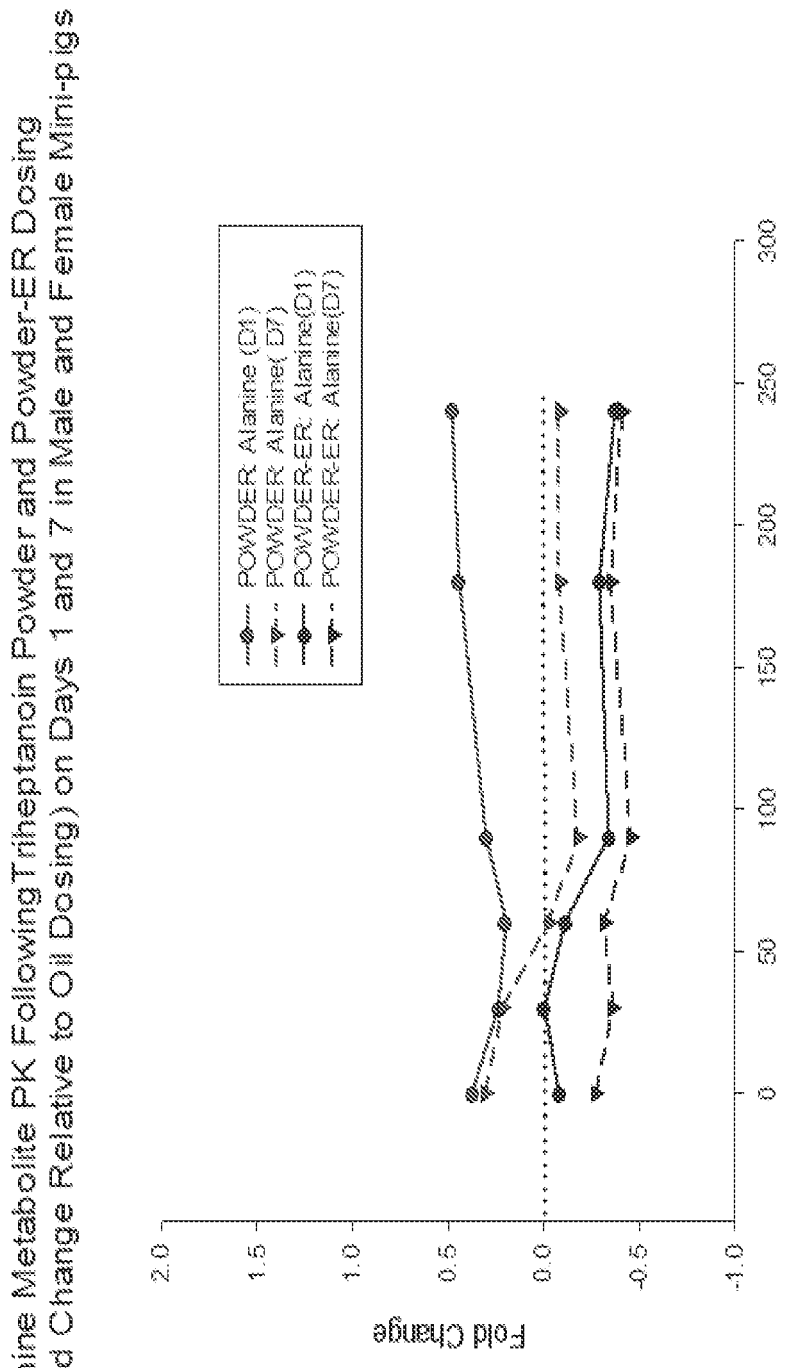

Alanine Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER Alanine (D1)
POWDER Alanine(D7)
POWDER-ER Alanine(D1)
POWDER-ER Alanine(D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 38

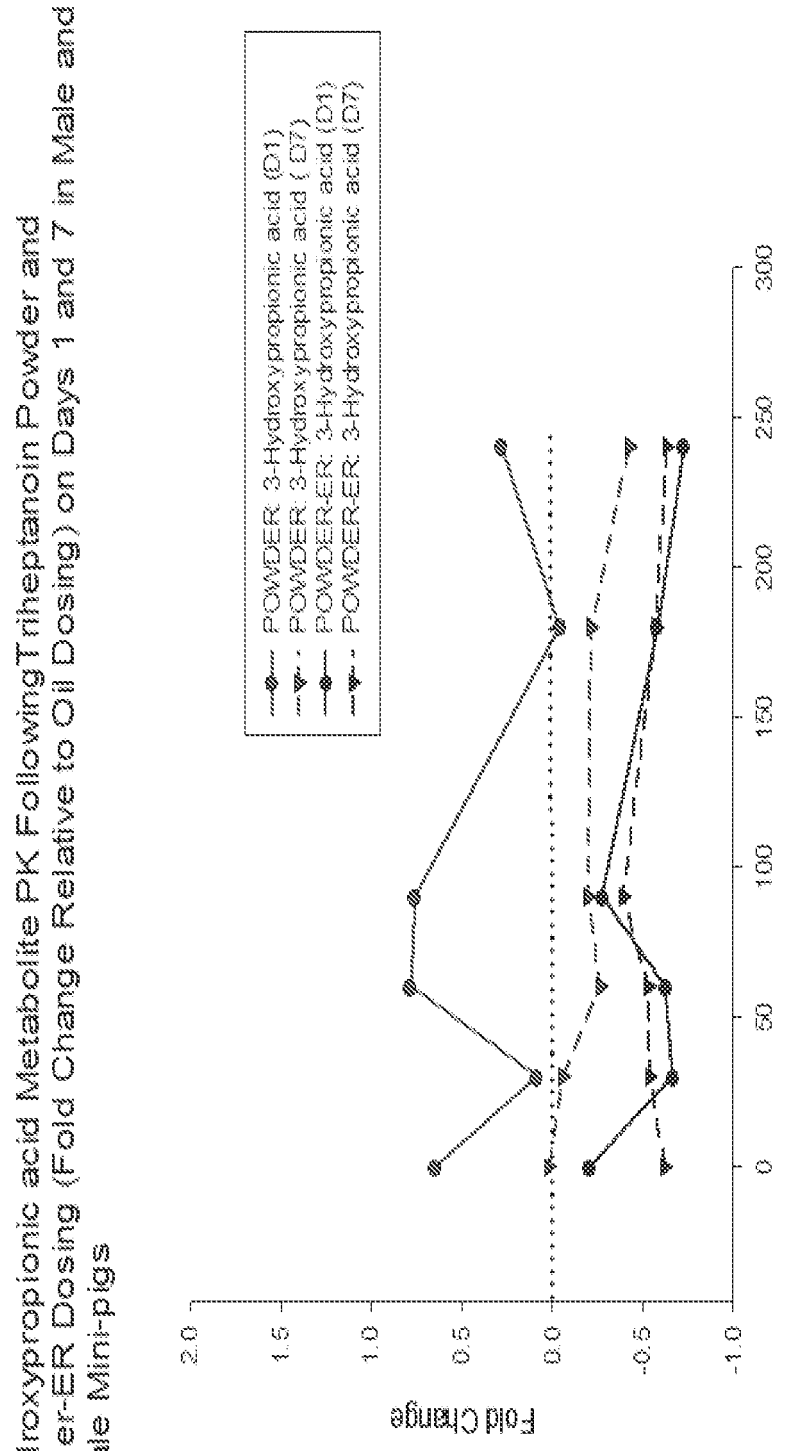

3-Hydroxypropionic acid Metabolite PK Following Triheptanoin Powder and Powder-ER Dosing (Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER: 3-Hydroxypropionic acid (D1)
POWDER: 3-Hydroxypropionic acid (D7)
POWDER-ER: 3-Hydroxypropionic acid (D1)
POWDER-ER: 3-Hydroxypropionic acid (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 39

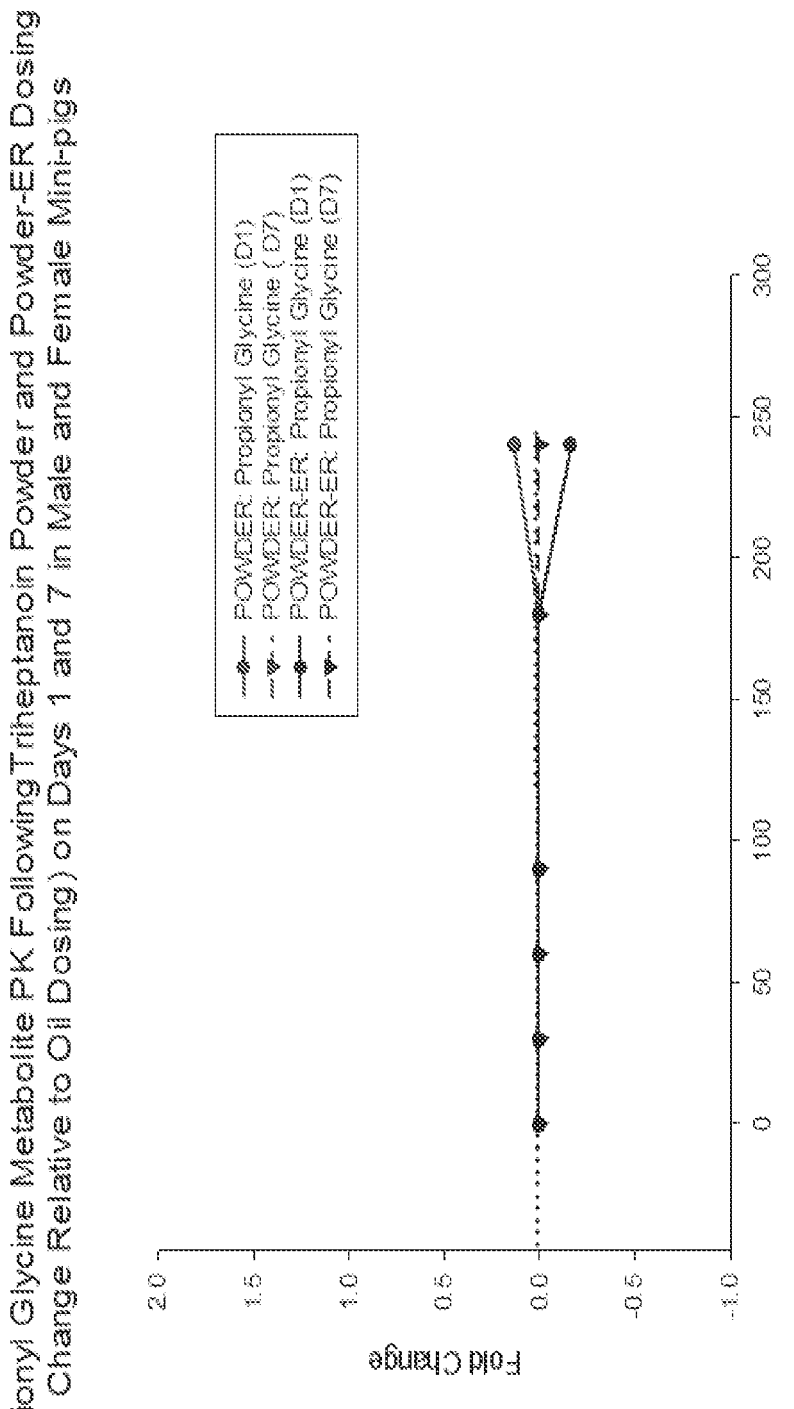

Propionyl Glycine Metabolite PK Following Trheptanoin Powder and Powder-ER Dosing
(Fold Change Relative to Oil Dosing) on Days 1 and 7 in Male and Female Mini-pigs
POWDER: Propionyl Glycine (D1)
POWDER: Propionyl Glycine (D7)
POWDER-ER: Propionyl Glycine (D1)
POWDER-ER: Propionyl Glycine (D7)
Fold Change
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Time post dosing

Figure 40