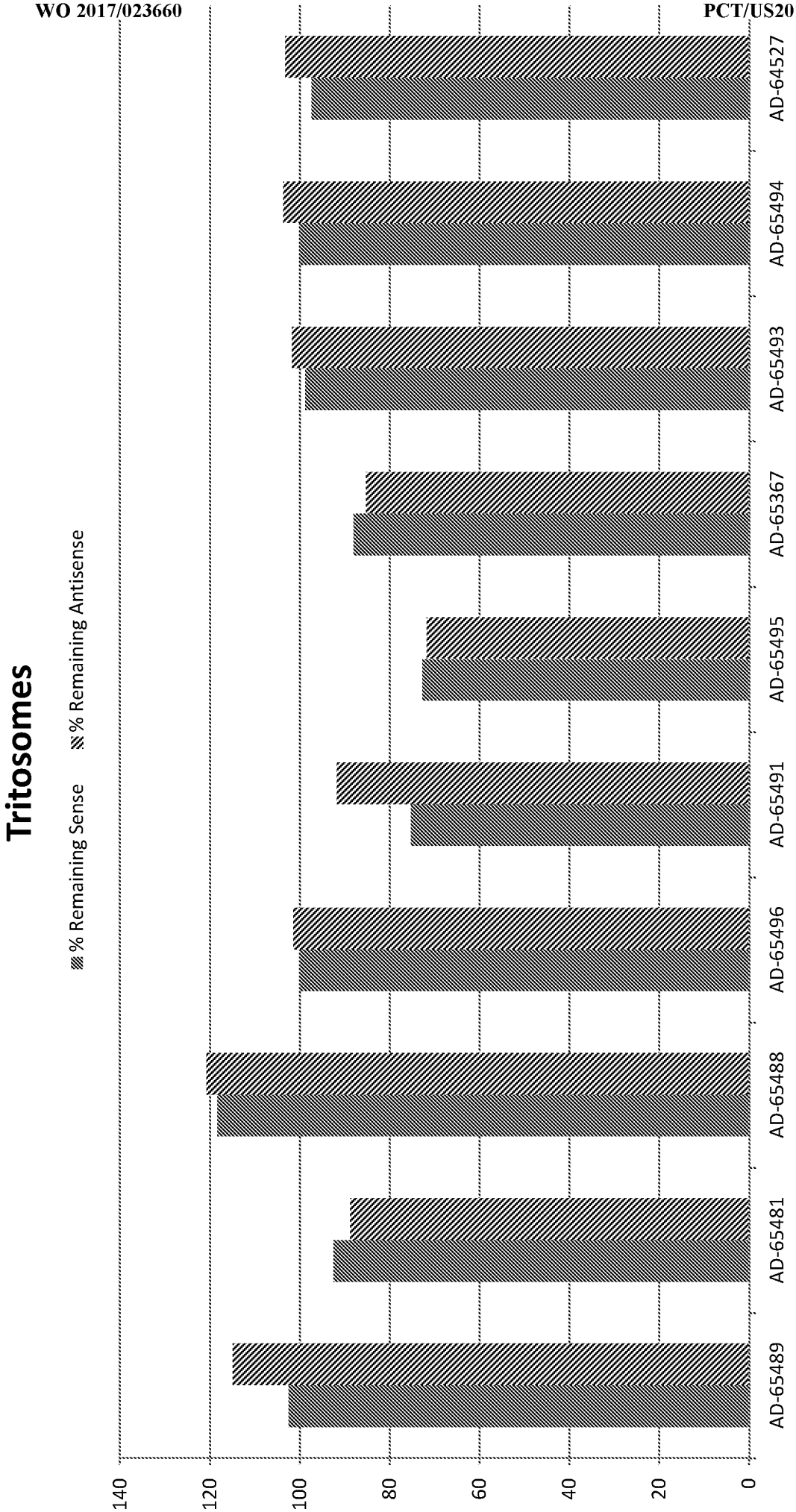

Tritosomes
% Remaining Sense
% Remaining Antisense
140
120
100
80
60
40
20
0
AD-65489
AD-65481
AD-65488
AD-65496
AD-65491
AD-65495
AD-65367
AD-65493
AD-65494
AD-64527

Figure 1

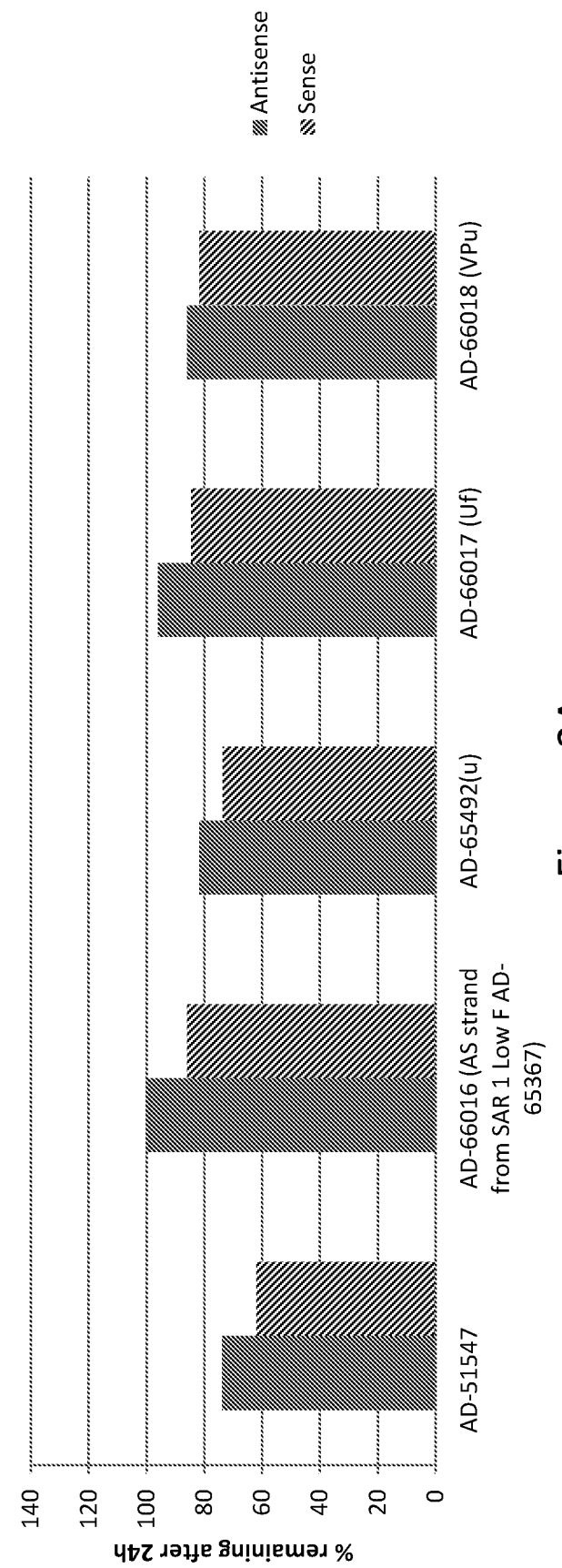


Figure 2A

Figure 2B

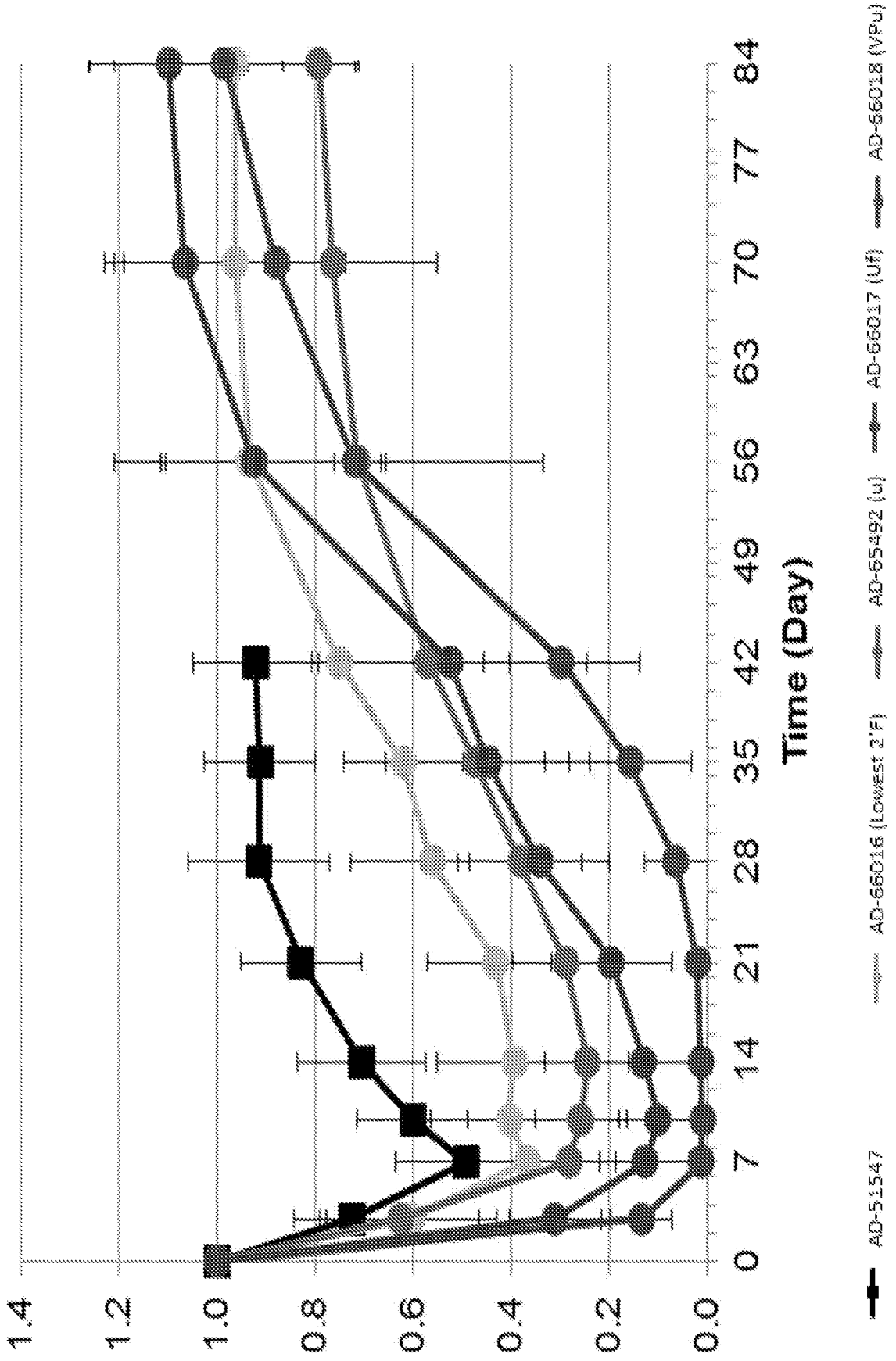

Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
7
14
21
28
35
42
49
56
63
70
77
84
Time (Day)
AD-51547
AD-66016 (Lowest 2'F)
AD-65492 (u)
AD-66017 (Uf)
AD-66018 (Vpu)

Figure 3

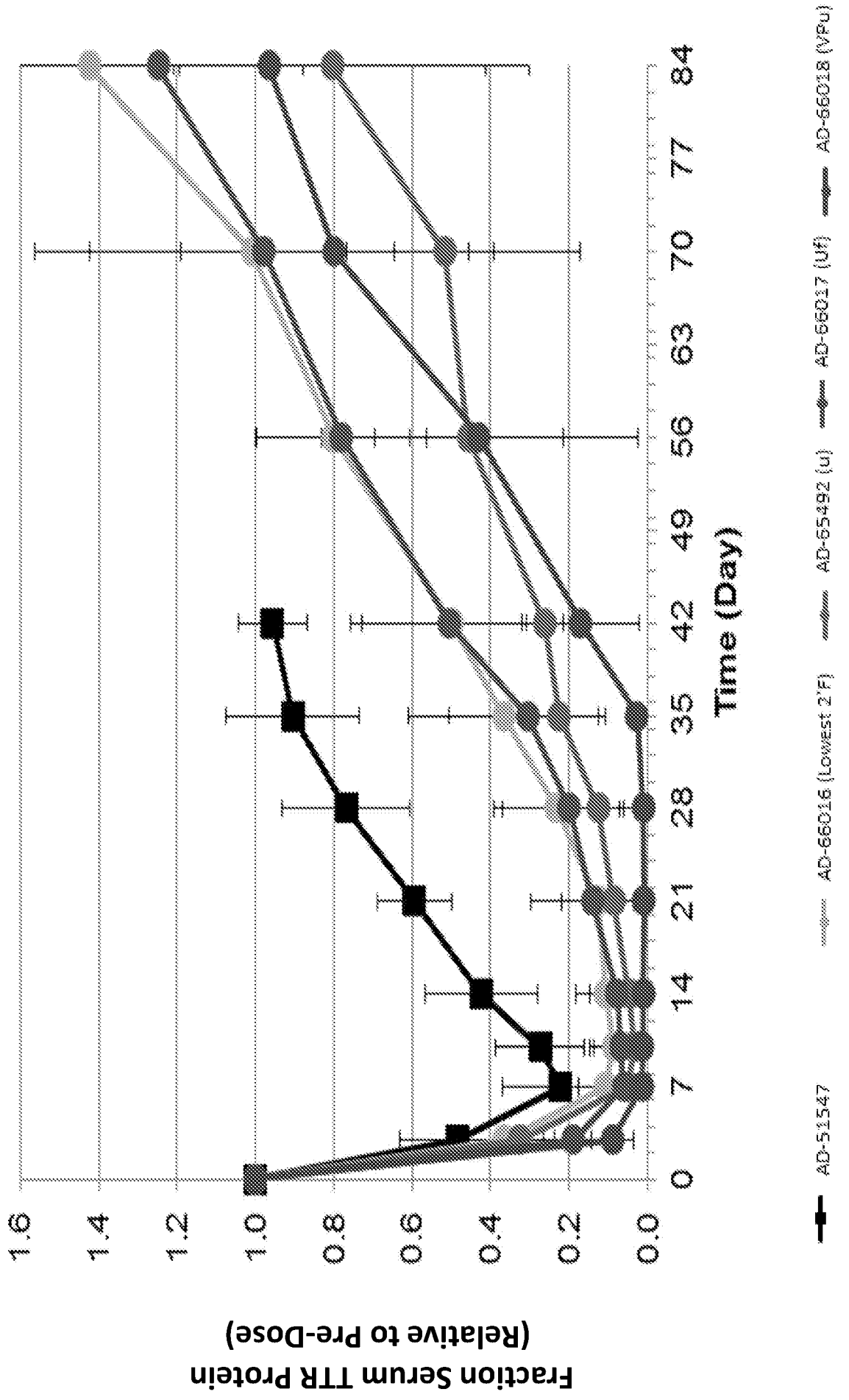

Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
7
14
21
28
35
42
49
56
63
70
77
84
Time (Day)
AD-51547
AD-66016 (Lowest 2'F)
AD-65492 (u)
AD-66017 (Uf)
AD-66018 (VPu)

Figure 4

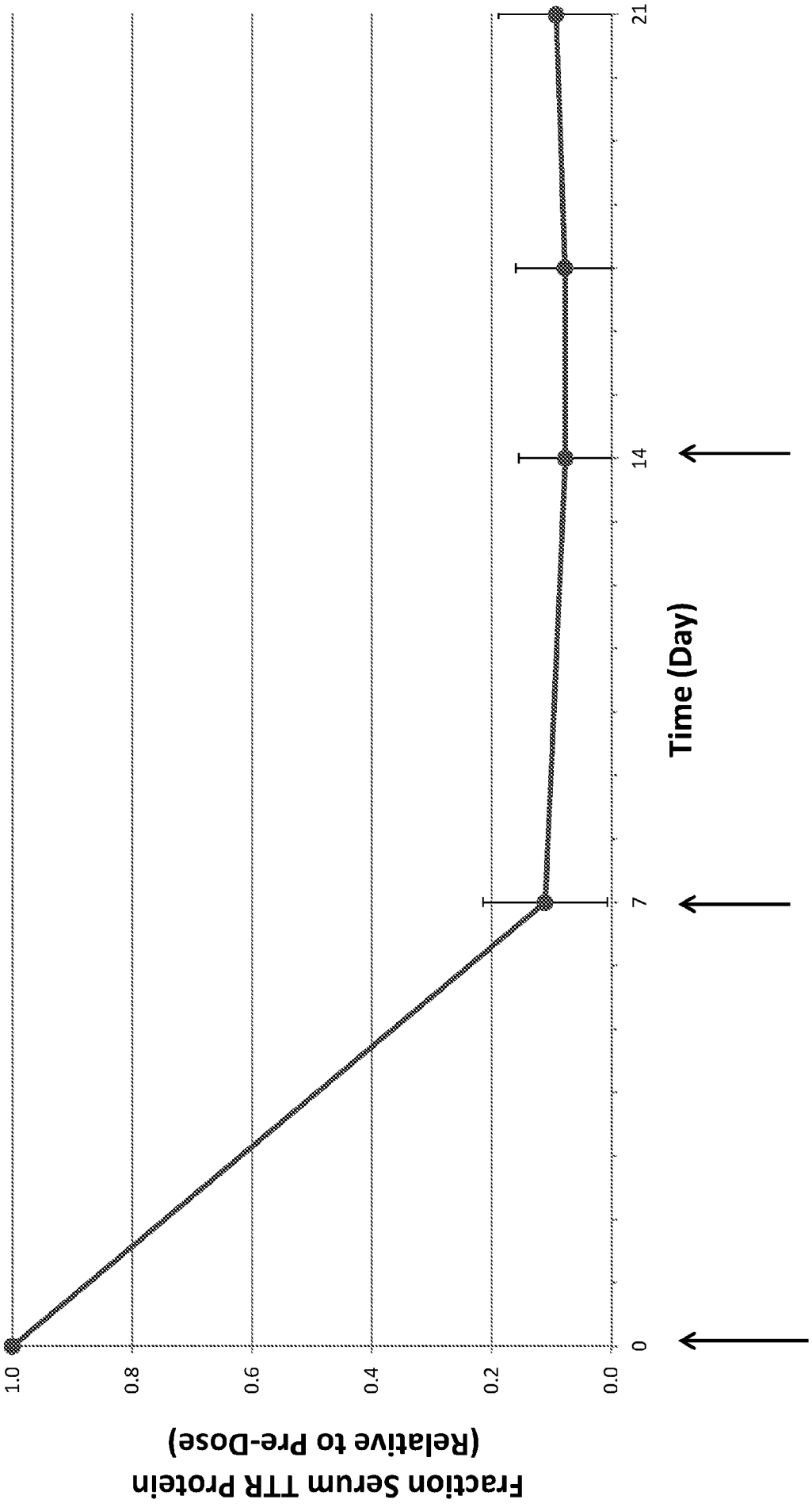

Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.0
0.8
0.6
0.4
0.2
0.0
0
7
14
21
Time (Day)

Figure 5

Figure 6A

QMx4 @ 0.3mg/kg

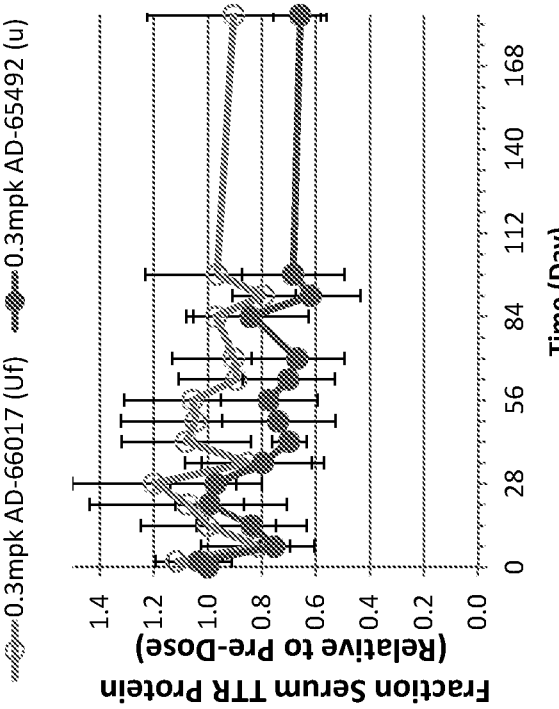


Figure 6B

QMx4 @ 1mg/kg

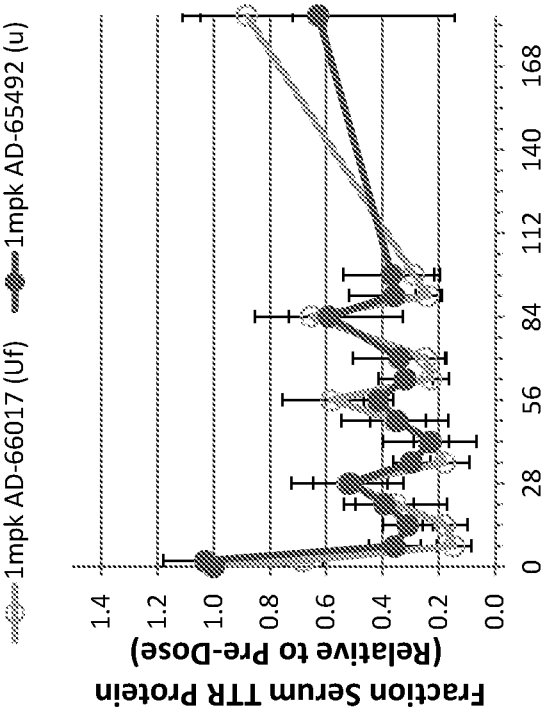
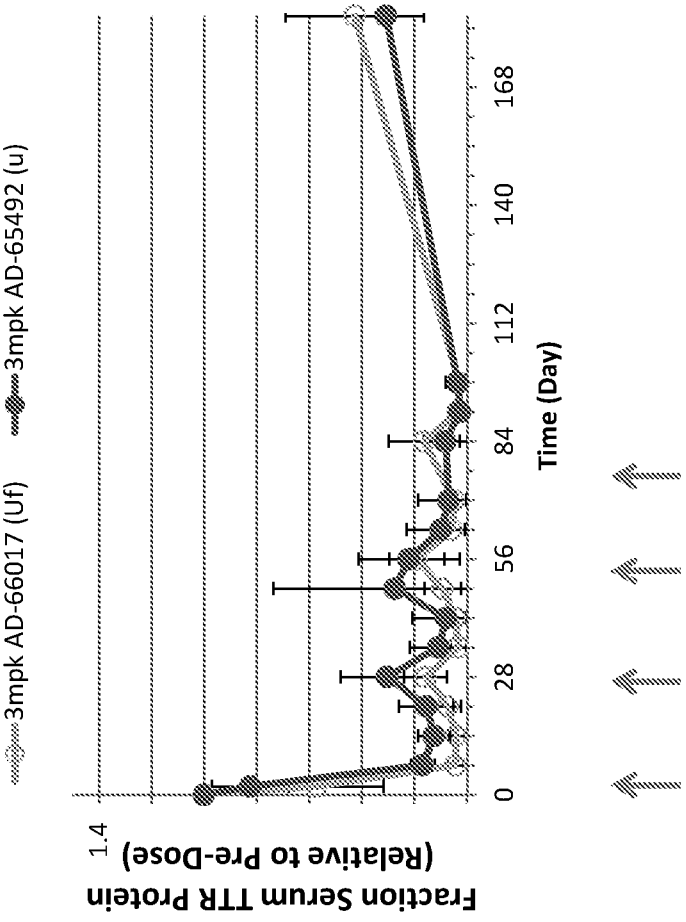
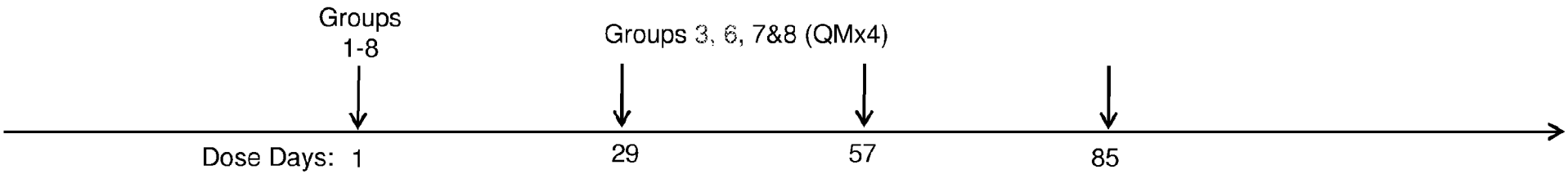


Figure 6C

QMx4 @ 3mg/kg





Test Article	Group Number	n	Dose day	Dose level (mg/kg)	Dose Volume (mL/kg)	Re dose days	Re-dose level (mg/kg)
AD-65492	1	3	1	0.3	2	N/A	N/A
AD-65492	2	3	1	1	2	N/A	N/A
AD-65492	3	3	1	3	2	29, 57, 85	3
AD-66017	4	3	1	0.3	2	N/A	N/A
AD-66017	5	3	1	1	2	N/A	N/A
AD-66017	6	3	1	3	2	29, 57, 85	3
AD-65492	7	3	1	1	2	29, 57, 85	1
AD-66017	8	3	1	1	2	29, 57, 85	1

Figure 7

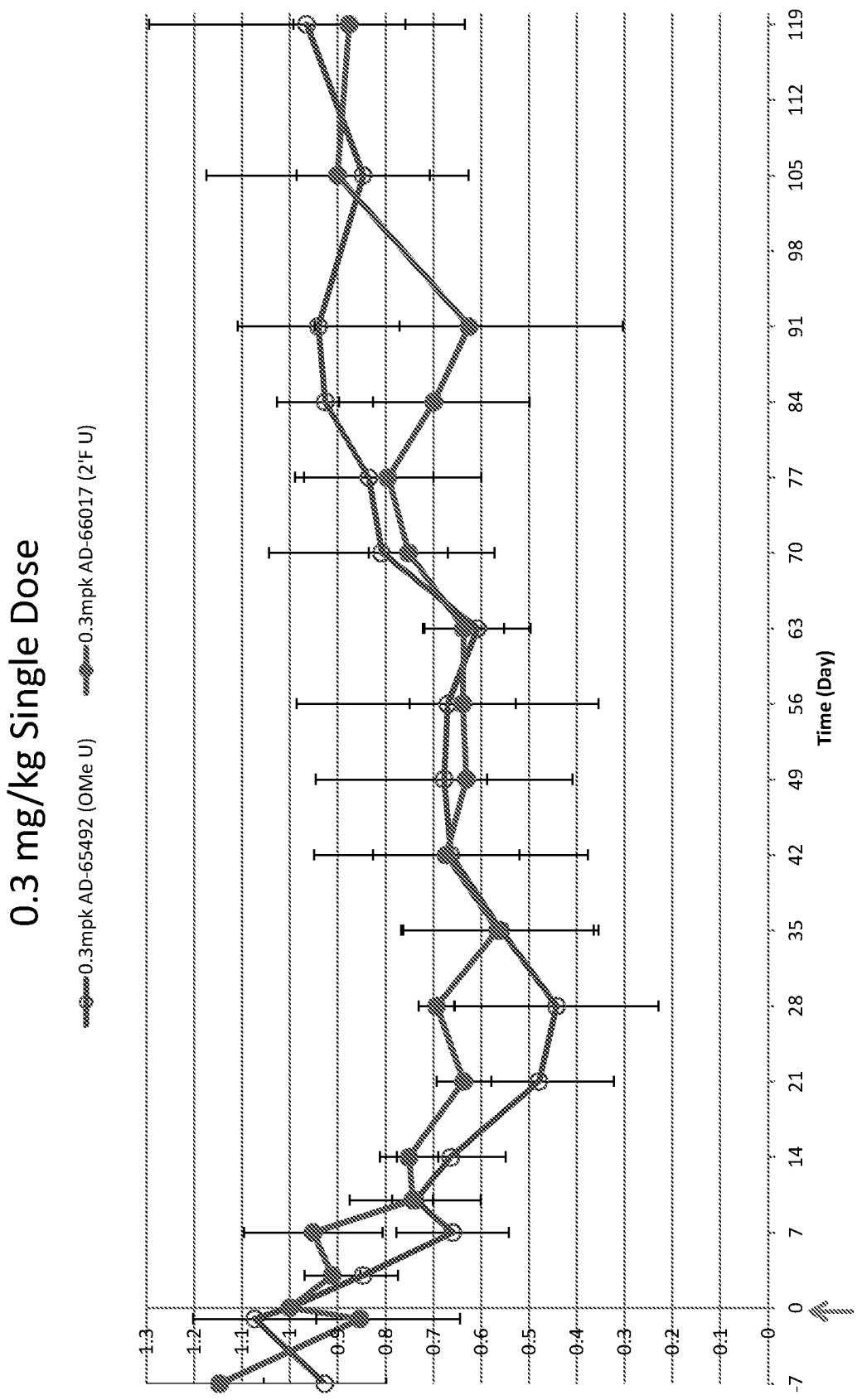

0.3 mg/kg Single Dose
0.3mpk AD-65492 (OMe U)
0.3mpk AD-66017 (2'F U)
Fraction Serum TTR Protein
(Relative to Pre-Dose)
Time (Day)
-7
0
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3

Figure 8A

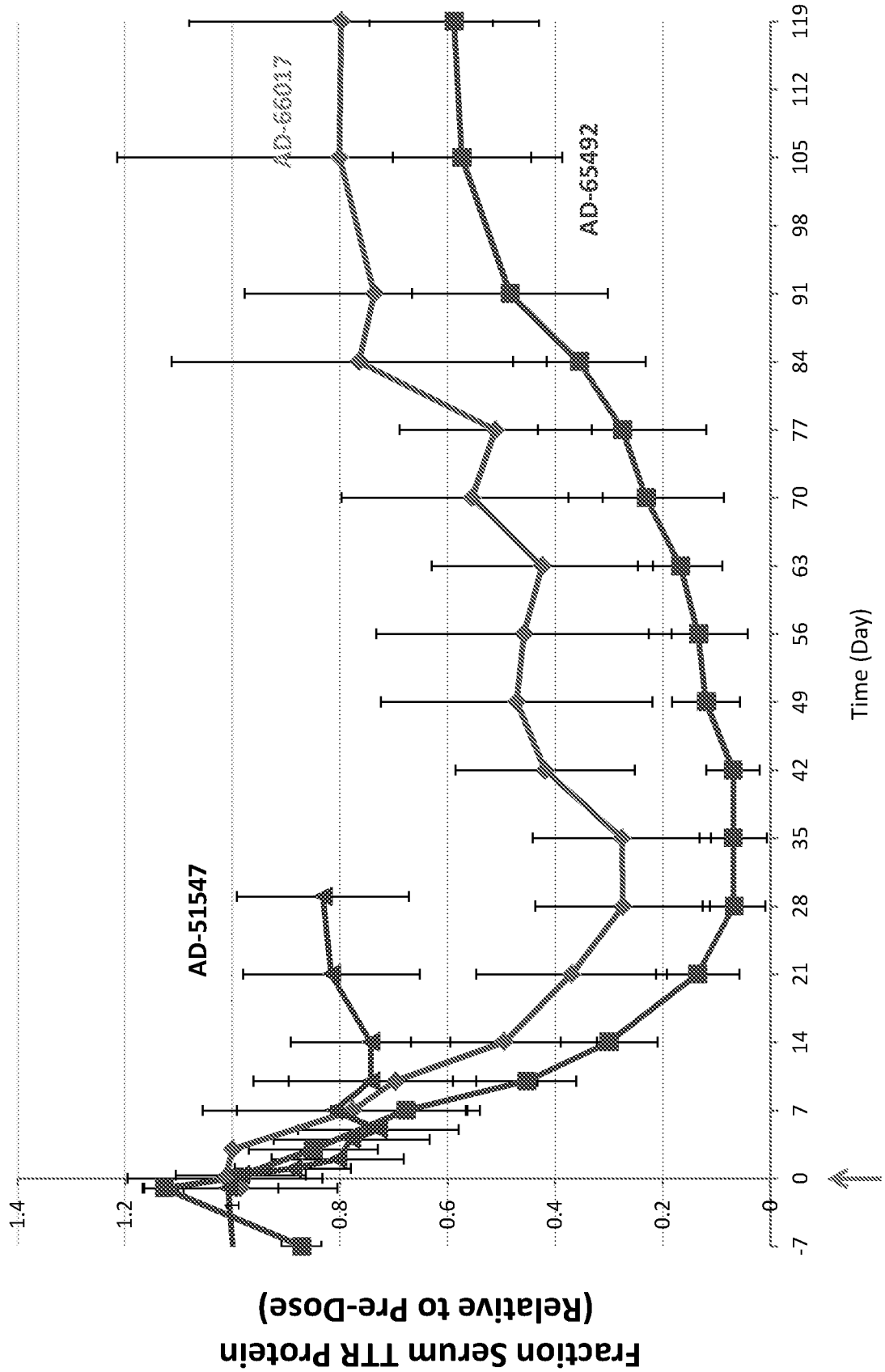

Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.4
1.2
0.8
0.6
0.4
0.2
0
-7
0
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119
Time (Day)
AD-51547
AD-66017
AD-65492

Figure 8B

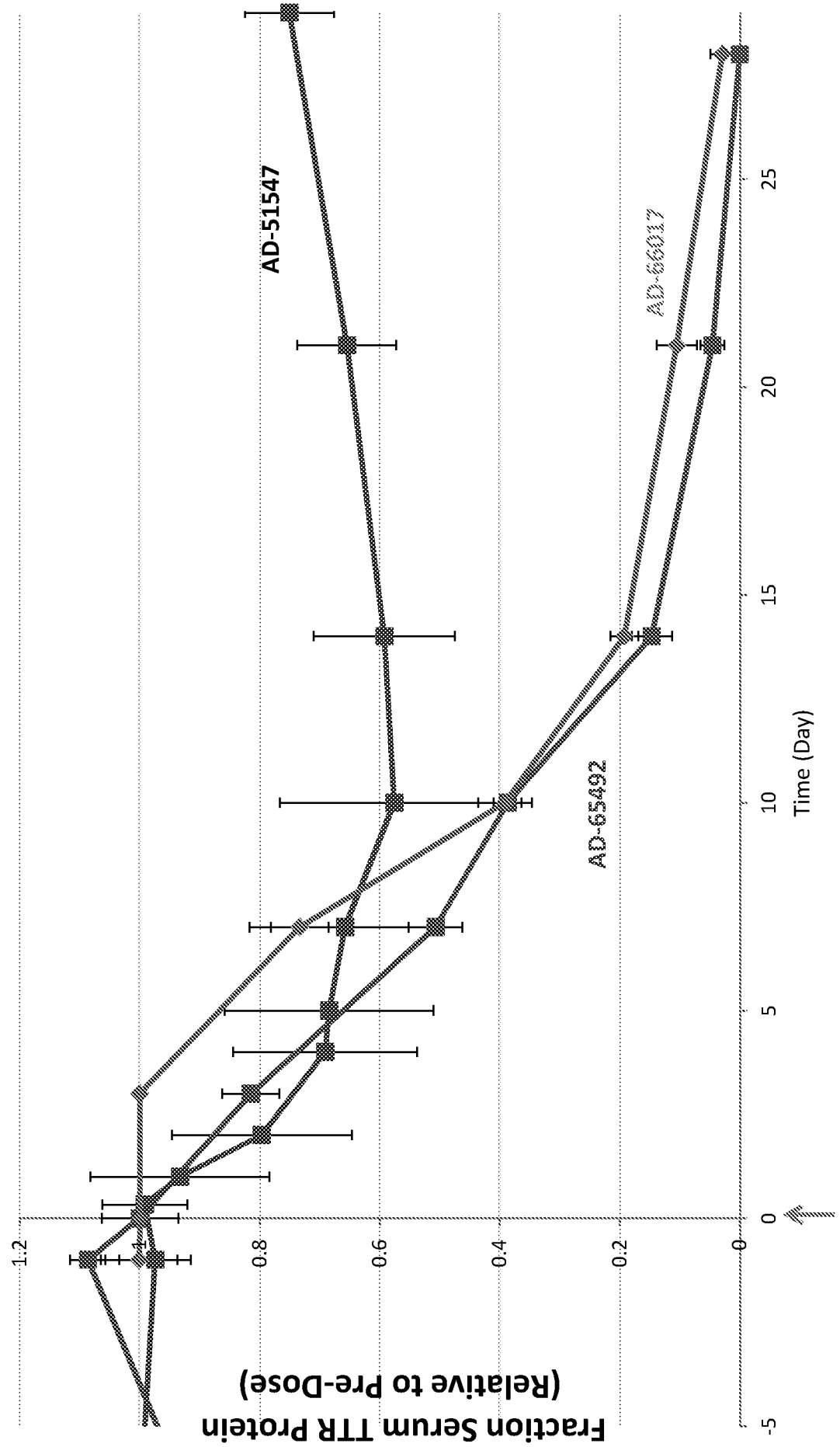

Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.2
1
0.8
0.6
0.4
0.2
0
-5
0
5
10
15
20
25
Time (Day)
AD-51547
AD-66017
AD-65492

Figure 8C

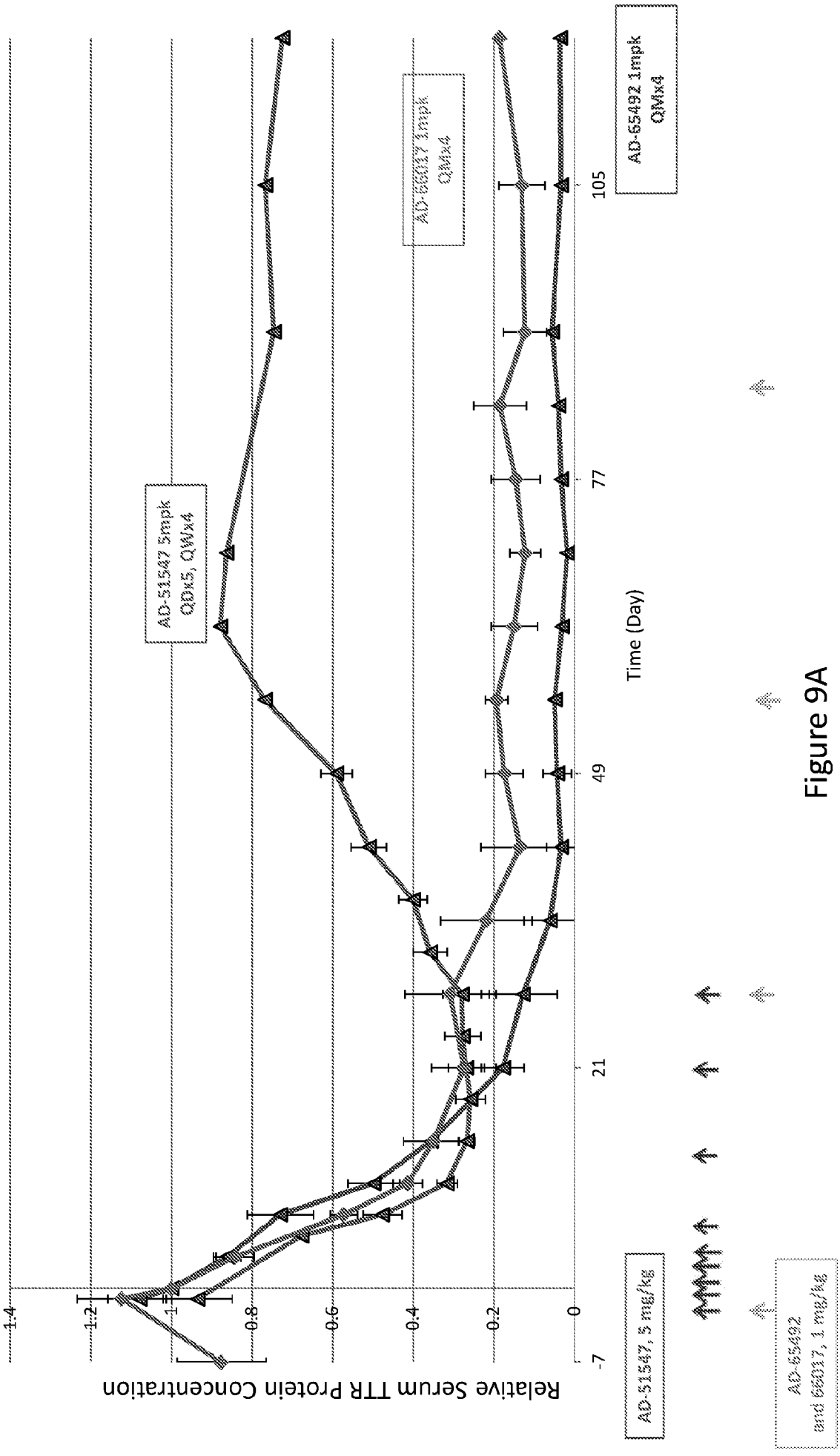

Relative Serum TTR Protein Concentration
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-7
21
49
77
105
Time (Day)
AD-51547 5mpk QDx5, QWx4
AD-66017 1mpk QWx4
AD-65492 1mpk QWx4
AD-51547, 5 mg/kg
AD-65492 and 66017, 1 mg/kg

Figure 9A

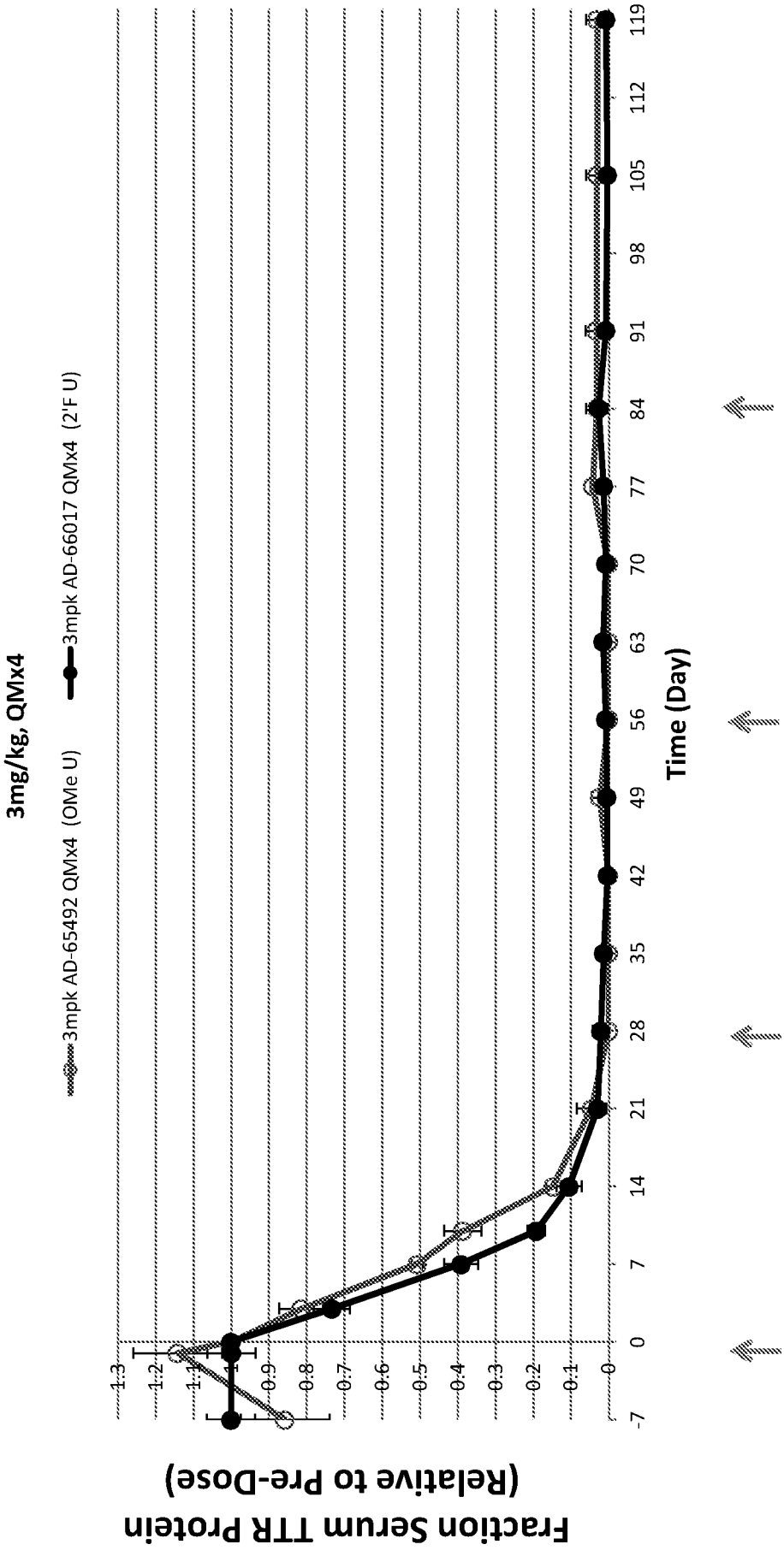

3mg/kg, QMx4
3mpk AD-65492 QMx4 (OMe U)
3mpk AD-66017 QMx4 (2'F U)
Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-7
0
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119
Time (Day)

Figure 9B

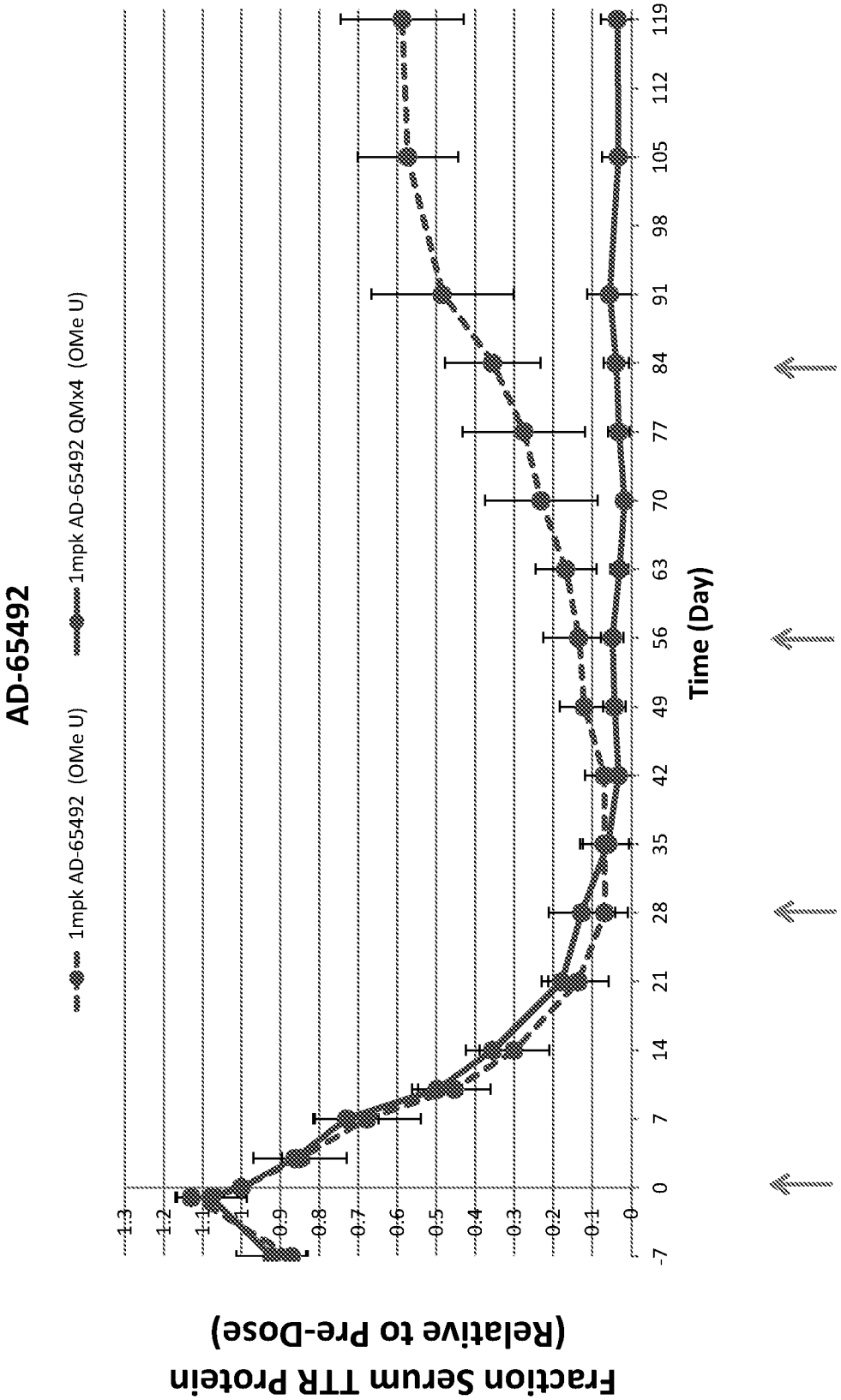

AD-65492
1mpk AD-65492 (OMe U)
1mpk AD-65492 QMx4 (OMe U)
Fraction Serum TTR Protein
(Relative to Pre-Dose)
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-7
0
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119
Time (Day)

Figure 10A

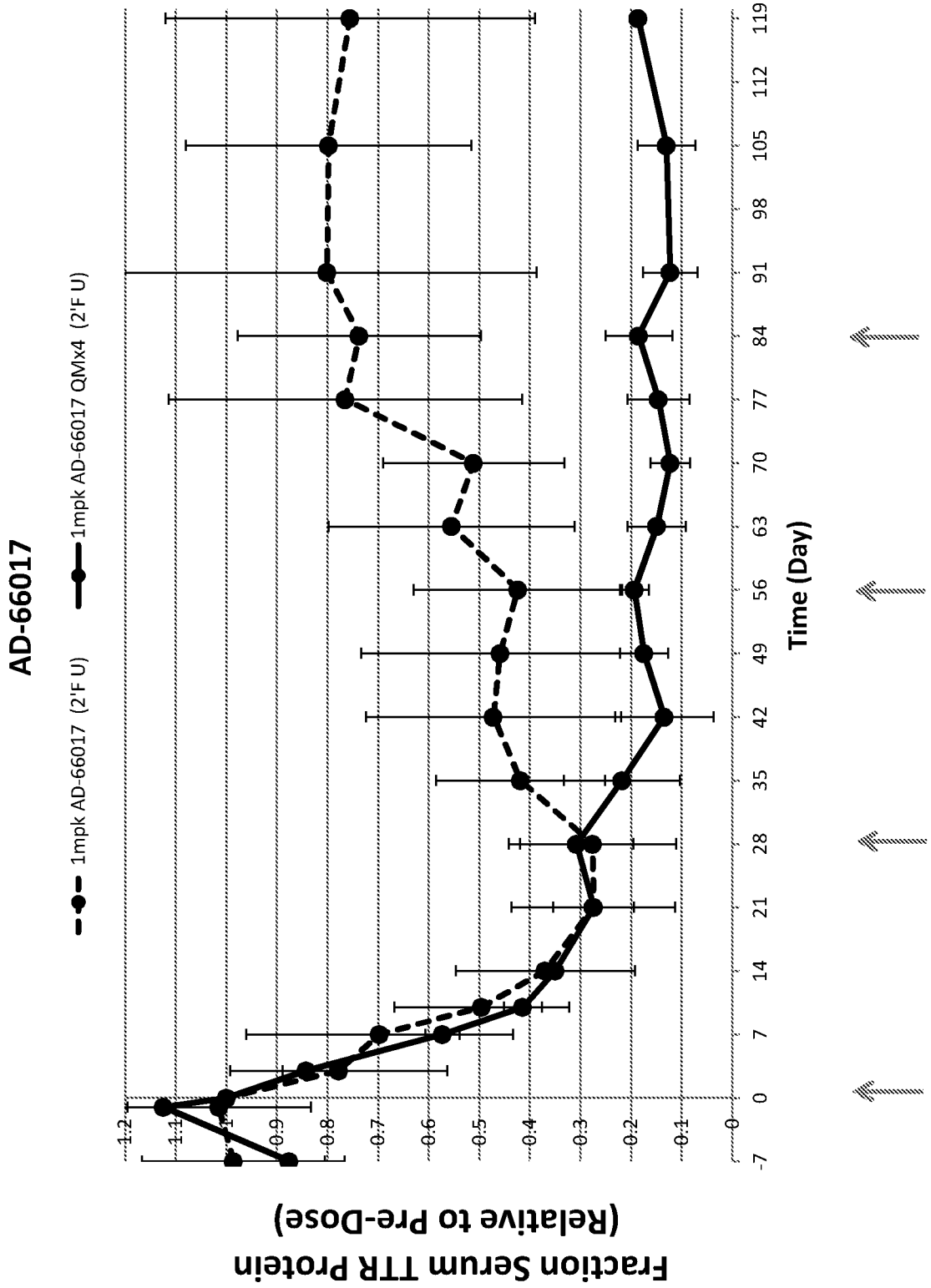

AD-66017
1mpk AD-66017 (2'F U)
1mpk AD-66017 QMx4 (2'F U)
Fraction Serum TTR Protein
(Relative to Pre-Dose)
Time (Day)
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-7
0
7
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
119

Figure 10B

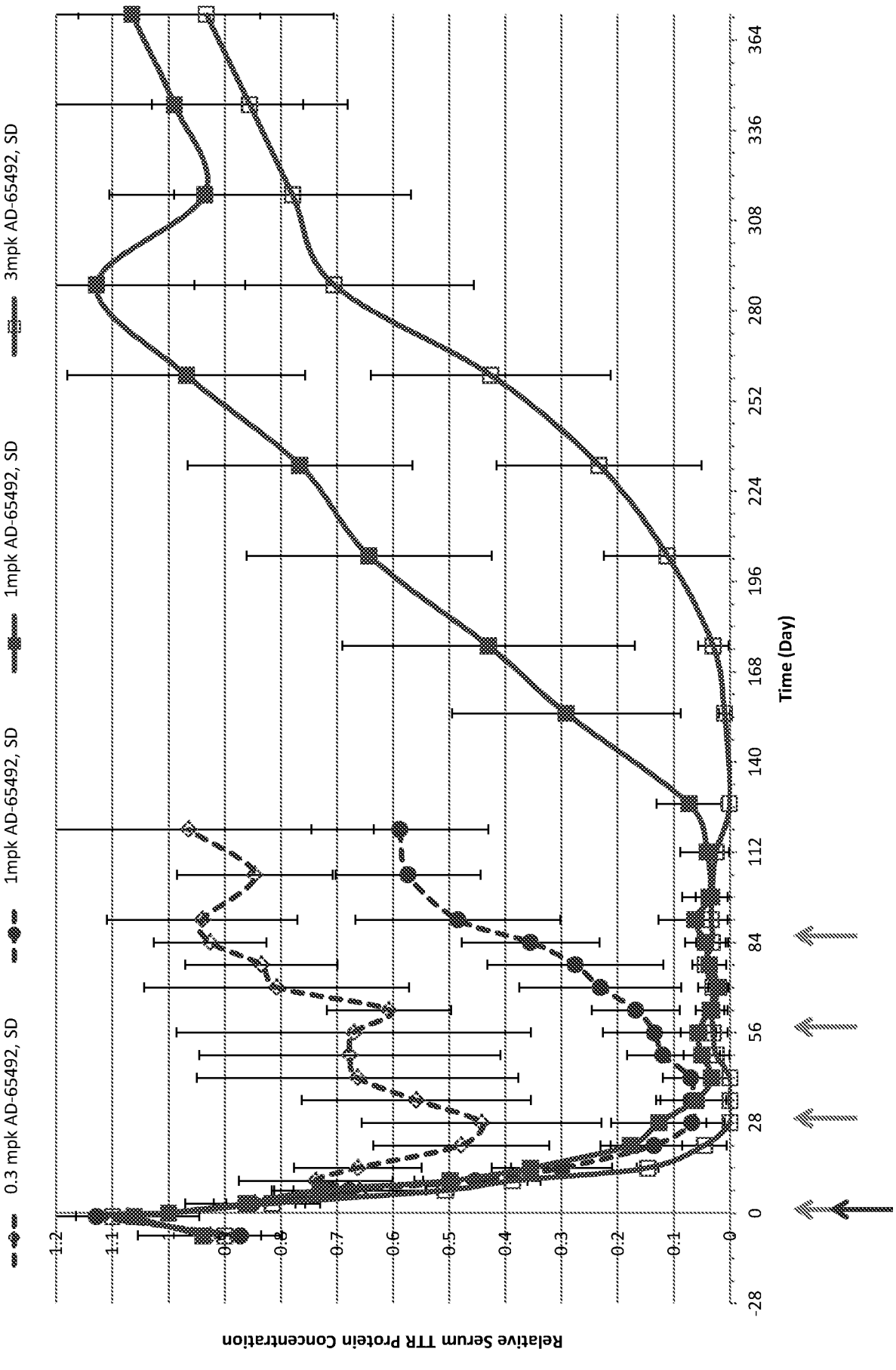
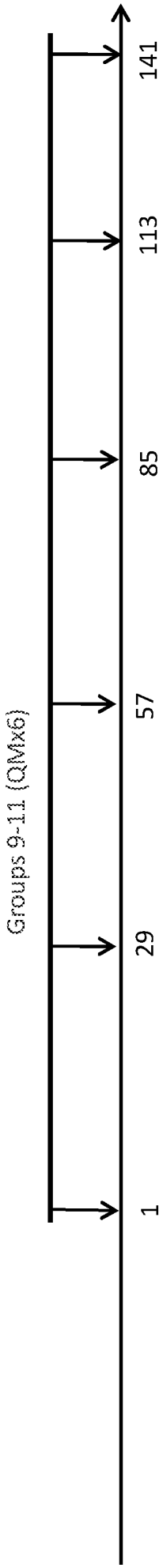

0.3 mpk AD-65492, SD
1mpk AD-65492, SD
1mpk AD-65492, SD
3mpk AD-65492, SD
Relative Serum TTR Protein Concentration
Time (Day)
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-28
0
28
56
84
112
140
168
196
224
252
280
308
336
364

Figure 11



Test Article	Group Number	n	Dose day	Dose level (mg/kg)	Dose Volume (mL/kg)	Re-dose days	Re-dose level (mg/kg)
AD-65492	9	4	1	0.3	2	29, 57, 85, 113, 141	0.3
AD-65492	10	4	1	0.6	2	29, 57, 85, 113, 141	0.6
AD-65492	11	4	1	1	2	29, 57, 85, 113, 141	0.3

Figure 12

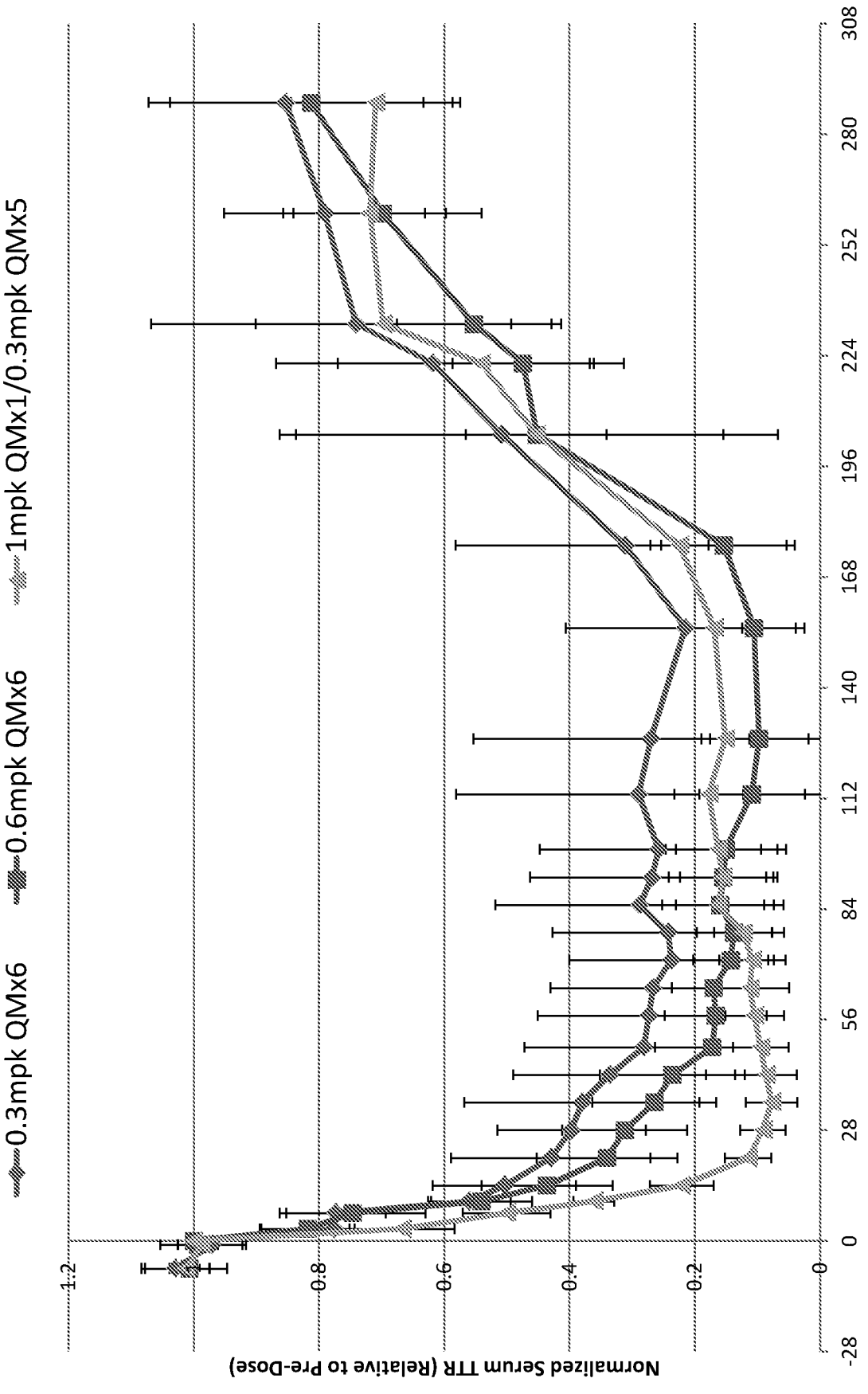

0.3mpk QMx6
0.6mpk QMx6
1mpk QMx1/0.3mpk QMx5
Normalized Serum TTR (Relative to Pre-Dose)
1.2
0.8
0.6
0.4
0.2
0
-28
0
28
56
84
112
140
168
196
224
252
280
308
Days

Figure 13