Figure 1

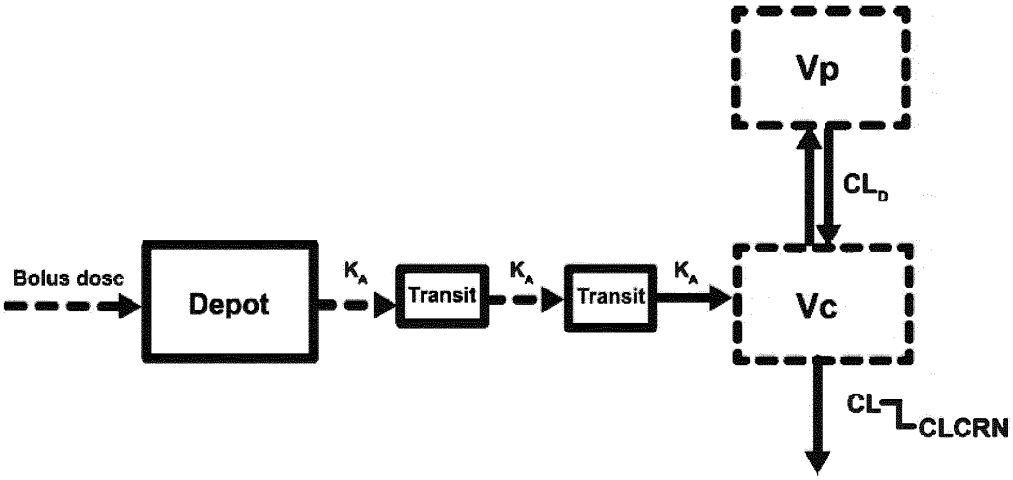


Figure 2a and b

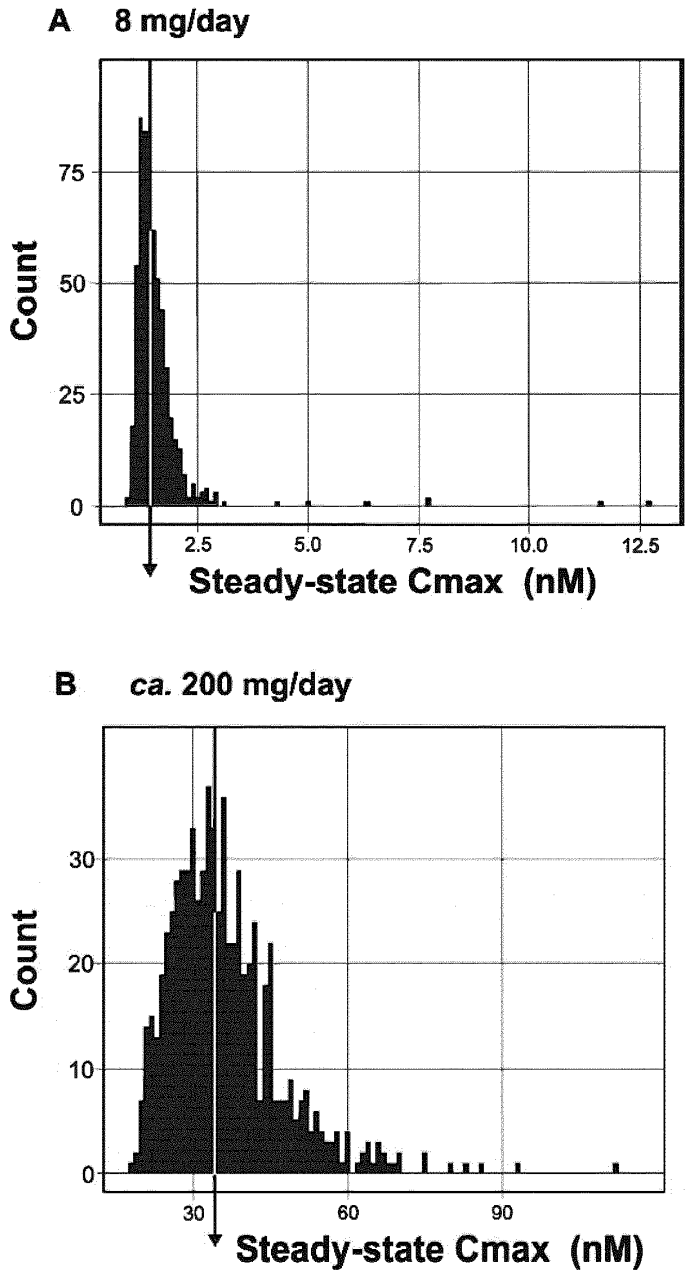


Figure 3a and 3b

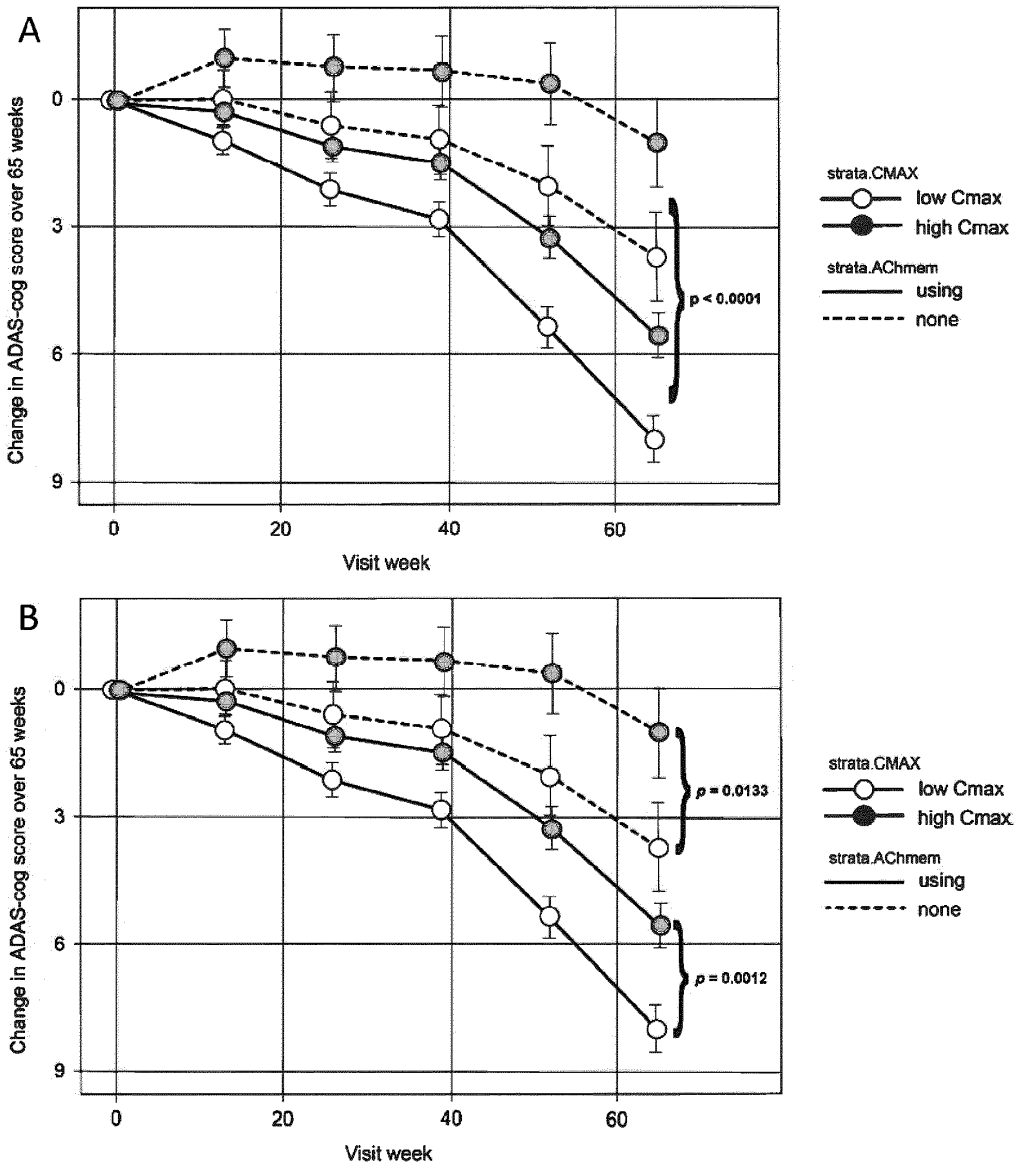


Figure 4

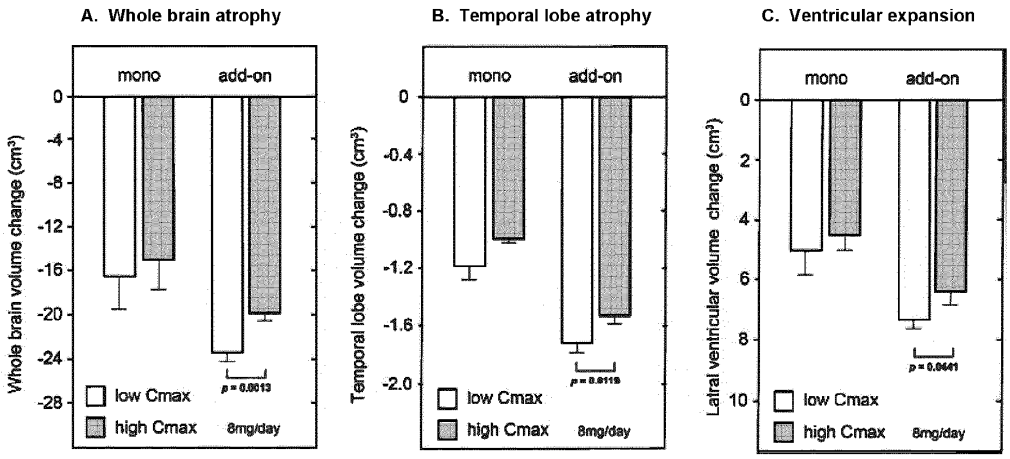


Figure 5

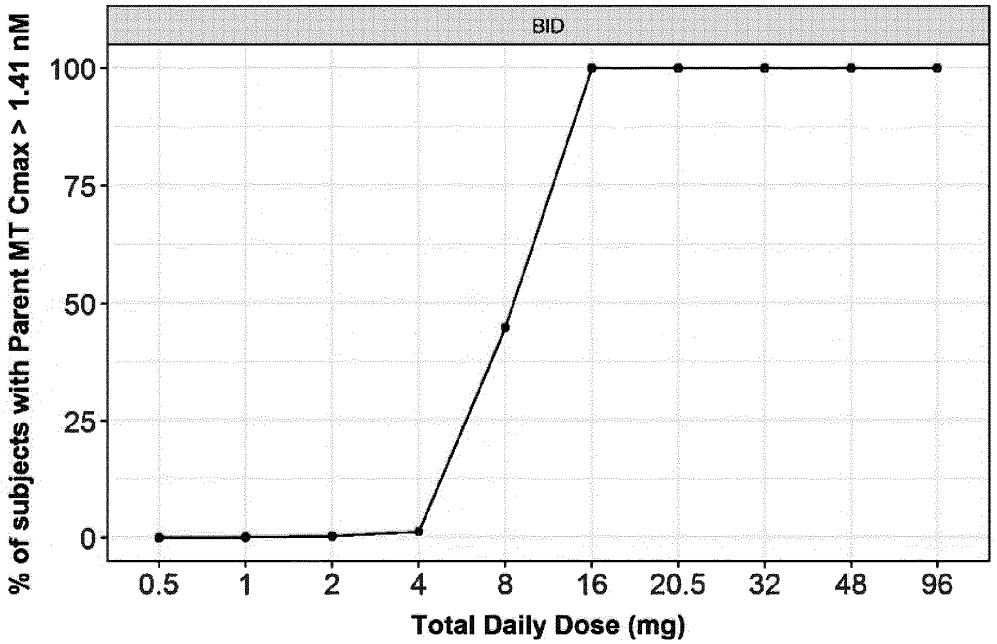


Figure 6

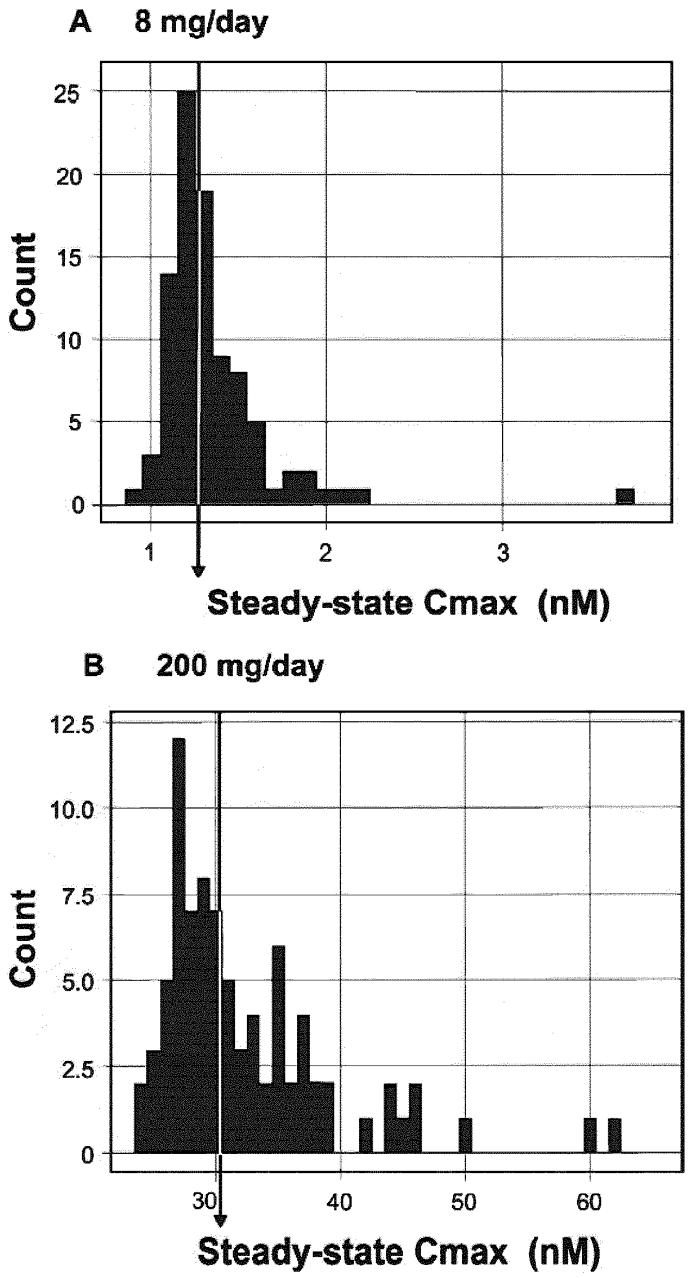

A 8 mg/day
Count
25
20
15
10
5
0
1
2
3
Steady-state Cmax (nM)
B 200 mg/day
Count
12.5
10.0
7.5
5.0
2.5
0
30
40
50
60
Steady-state Cmax (nM)

Figure 7

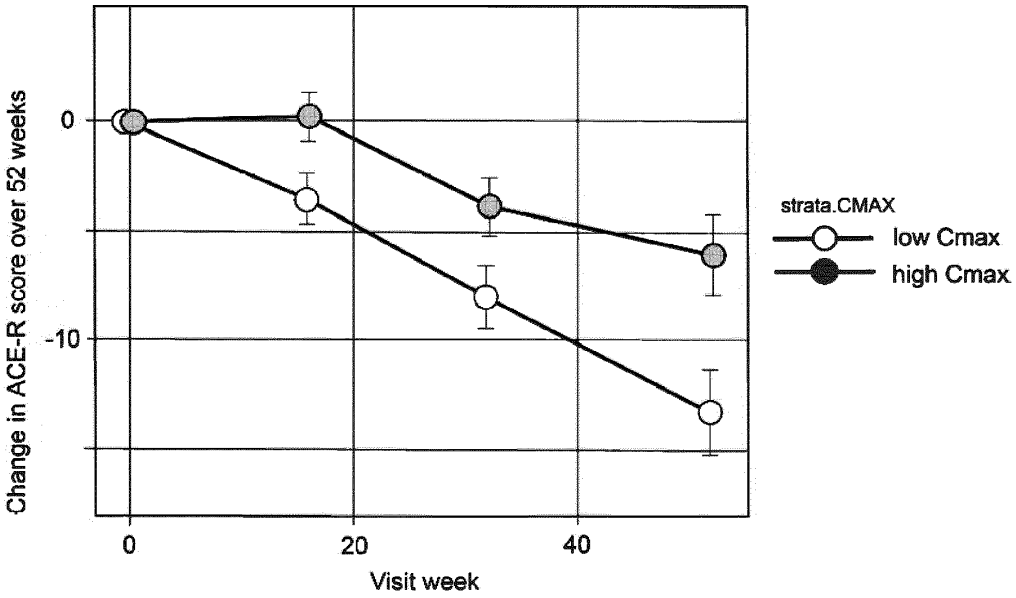


Figure 8

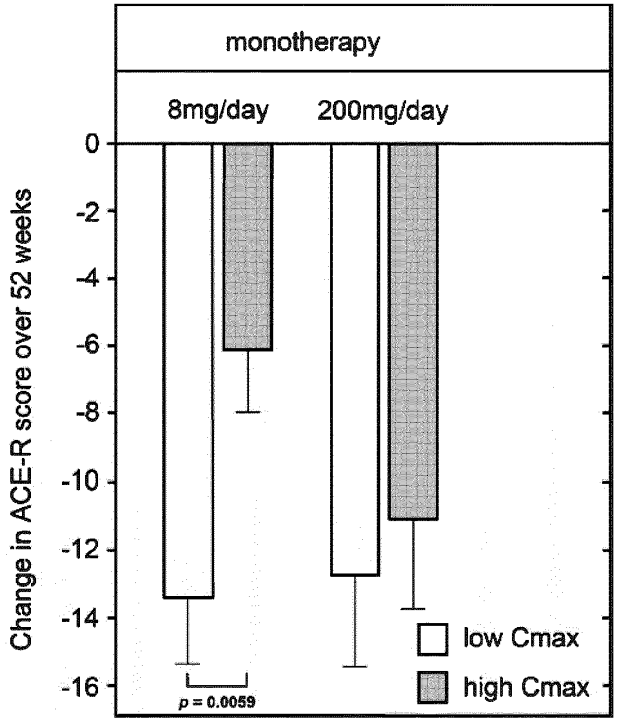


Figure 9

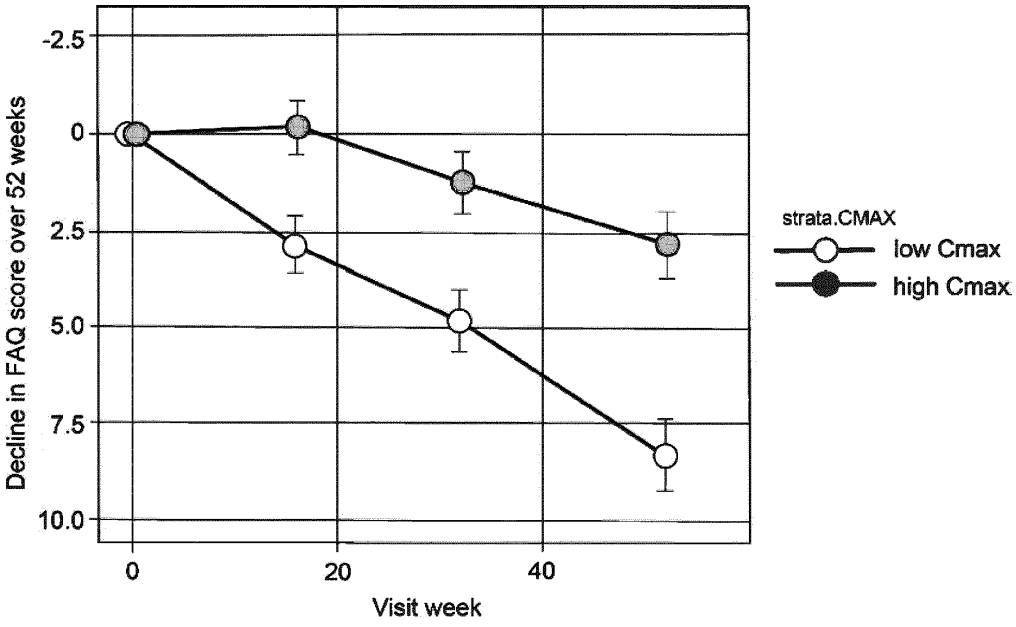


Figure 10

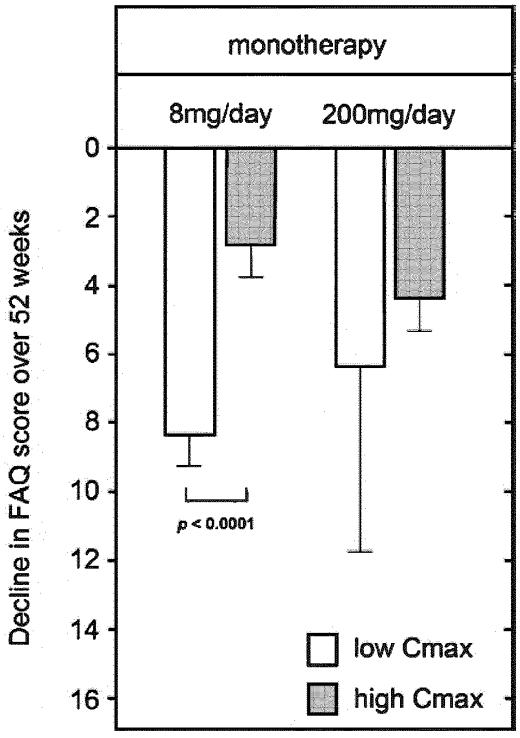
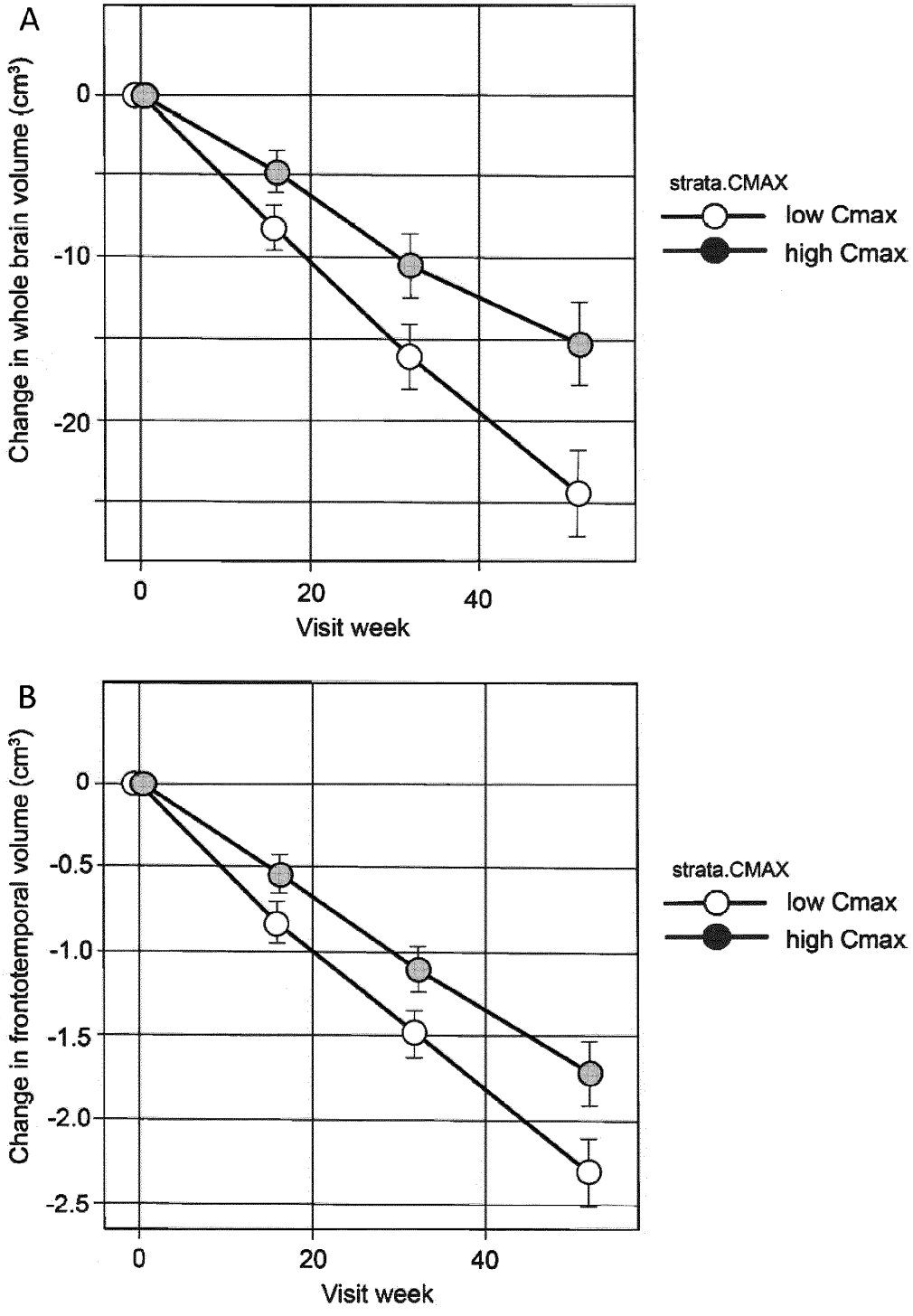


Figure 11a, b and c



C

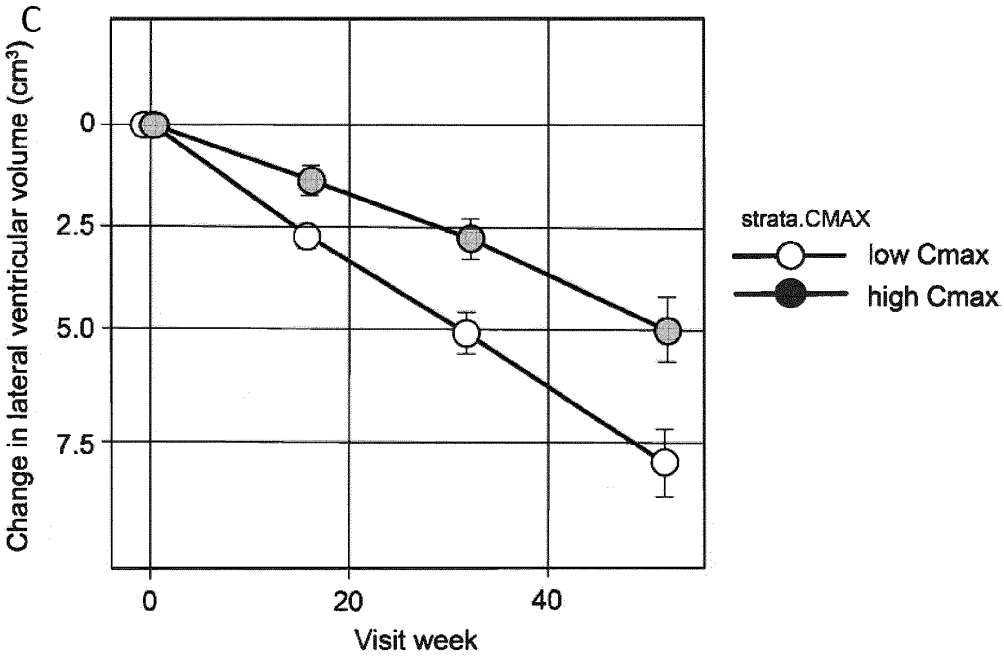

Change in lateral ventricular volume (cm³)
0
2.5
5.0
7.5
0
20
40
Visit week
strata.CMAX
low Cmax
high Cmax

Figure 12

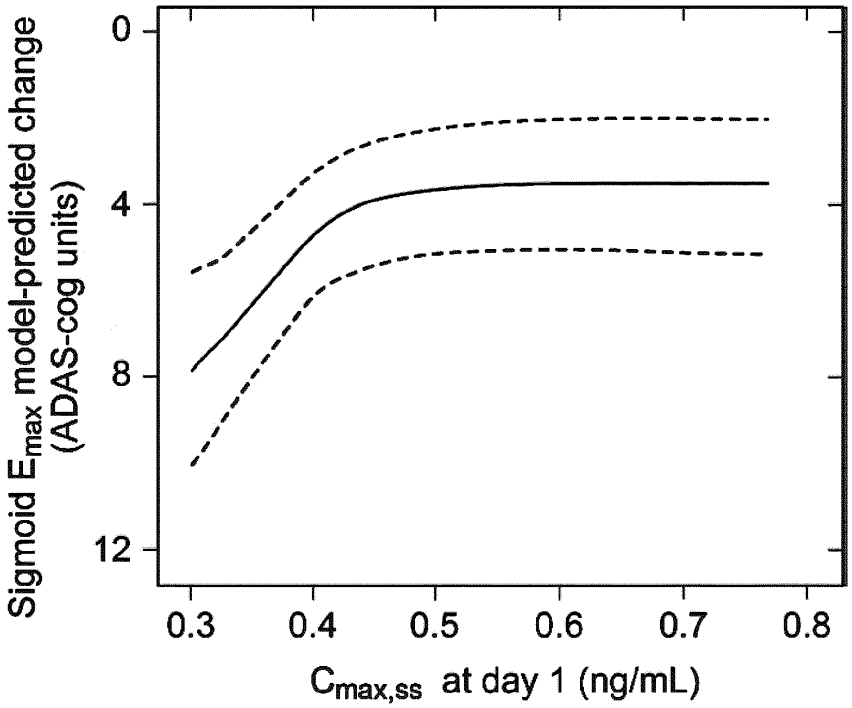

Sigmoid E_{max} model-predicted change (ADAS-cog units)
0
4
8
12
0.3
0.4
0.5
0.6
0.7
0.8
$C_{max,ss}$ at day 1 (ng/mL)

Figure 13

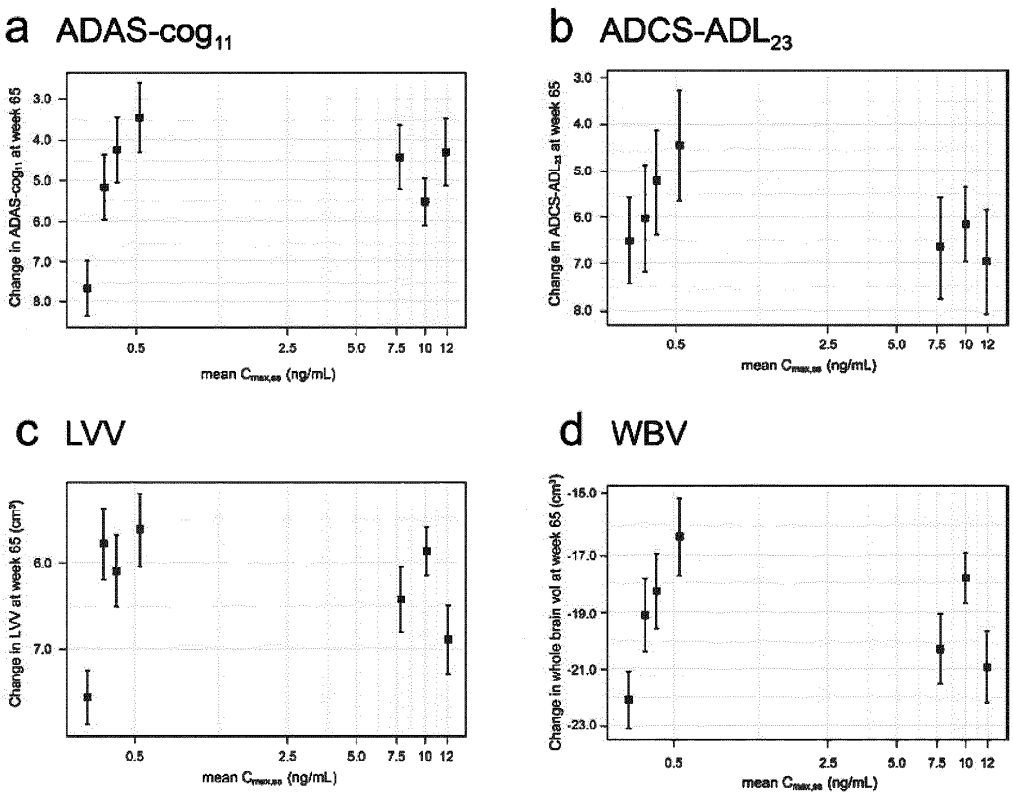

a ADAS-cog11
Change in ADAS-cog11 at week 65
3.0
4.0
5.0
6.0
7.0
8.0
0.5
2.5
5.0
7.5
10
12
mean Cmax,ss (ng/mL)
b ADCS-ADL23
Change in ADCS-ADL23 at week 65
3.0
4.0
5.0
6.0
7.0
8.0
0.5
2.5
5.0
7.5
10
12
mean Cmax,ss (ng/mL)
c LVV
Change in LVV at week 65 (cm³)
6.0
7.0
0.5
2.5
5.0
7.5
10
12
mean Cmax,ss (ng/mL)
d WBV
Change in whole brain vol at week 65 (cm³)
-15.0
-17.0
-19.0
-21.0
-23.0
0.5
2.5
5.0
7.5
10
12
mean Cmax,ss (ng/mL)

Figure 14

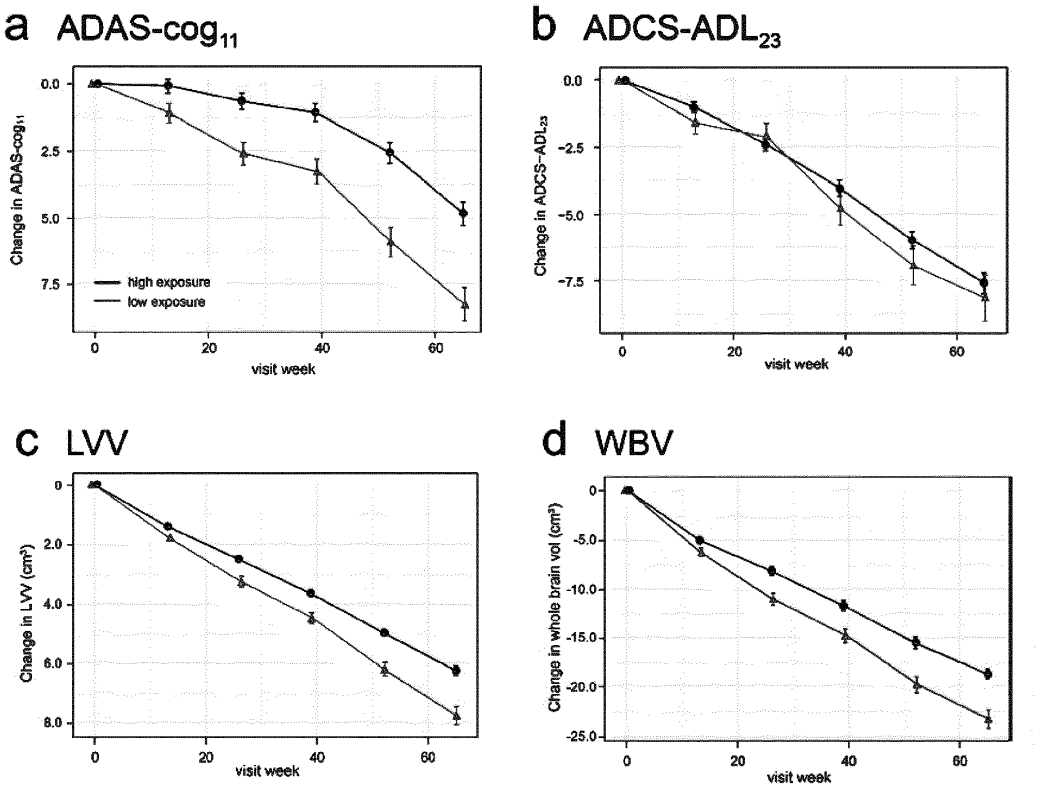

a ADAS-cog11
Change in ADAS-cog11
0.0
2.5
5.0
7.5
high exposure
low exposure
0
20
40
60
visit week
b ADCS-ADL23
Change in ADCS-ADL23
0.0
-2.5
-5.0
-7.5
visit week
c LVV
Change in LVV (cm³)
0
2.0
4.0
6.0
8.0
visit week
d WBV
Change in whole brain vol (cm³)
0
-5.0
-10.0
-15.0
-20.0
-25.0
visit week

Figure 15

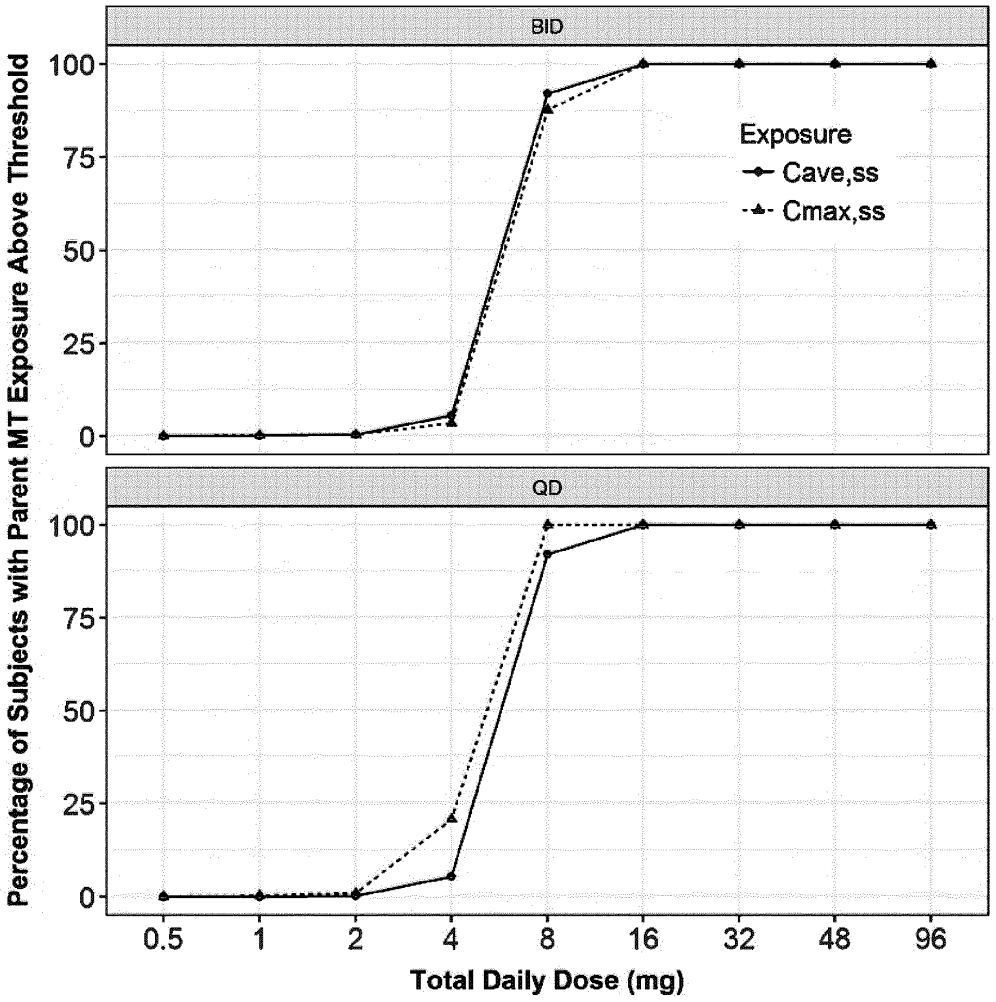

BID
QD
Exposure
Cave,ss
Cmax,ss
Percentage of Subjects with Parent MT Exposure Above Threshold
100
75
50
25
0
0.5
1
2
4
8
16
32
48
96
Total Daily Dose (mg)

Figure 16

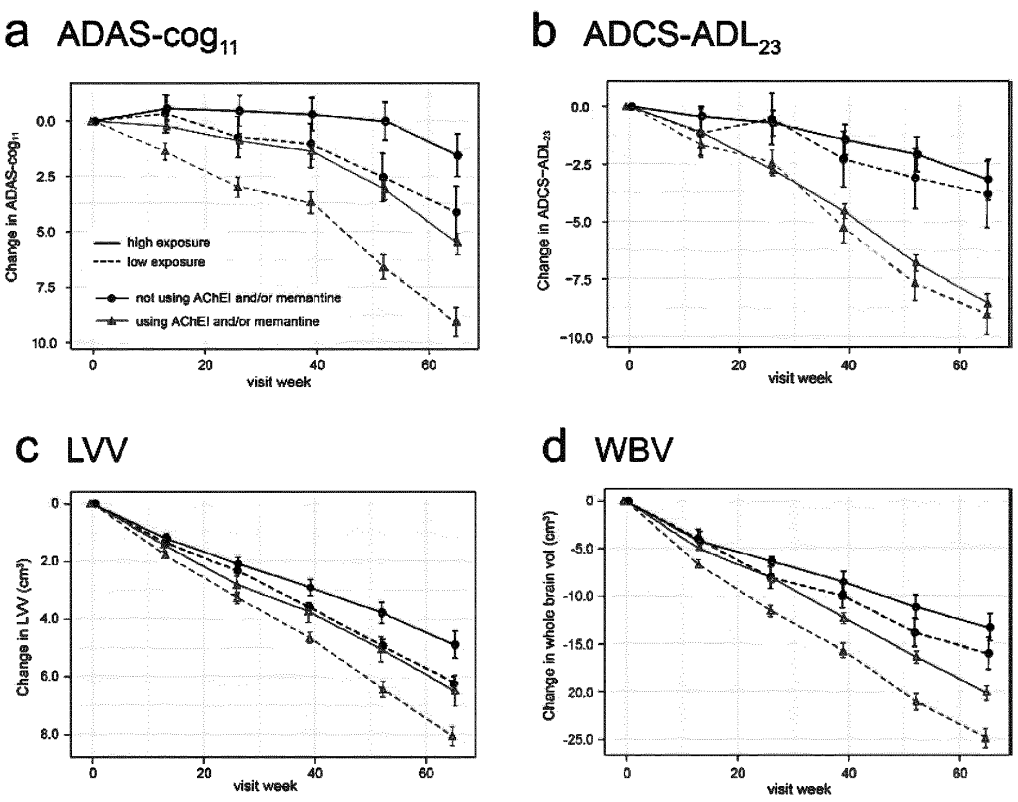

a ADAS-cog11
Change in ADAS-cog11
0.0
2.5
5.0
7.5
10.0
high exposure
low exposure
not using AChEI and/or memantine
using AChEI and/or memantine
0
20
40
60
visit week
b ADCS-ADL23
Change in ADCS−ADL23
0.0
−2.5
−5.0
−7.5
−10.0
visit week
c LVV
Change in LVV (cm³)
0
2.0
4.0
6.0
8.0
visit week
d WBV
Change in whole brain vol (cm³)
0
-5.0
-10.0
-15.0
20.0
-25.0
visit week

Figure 17

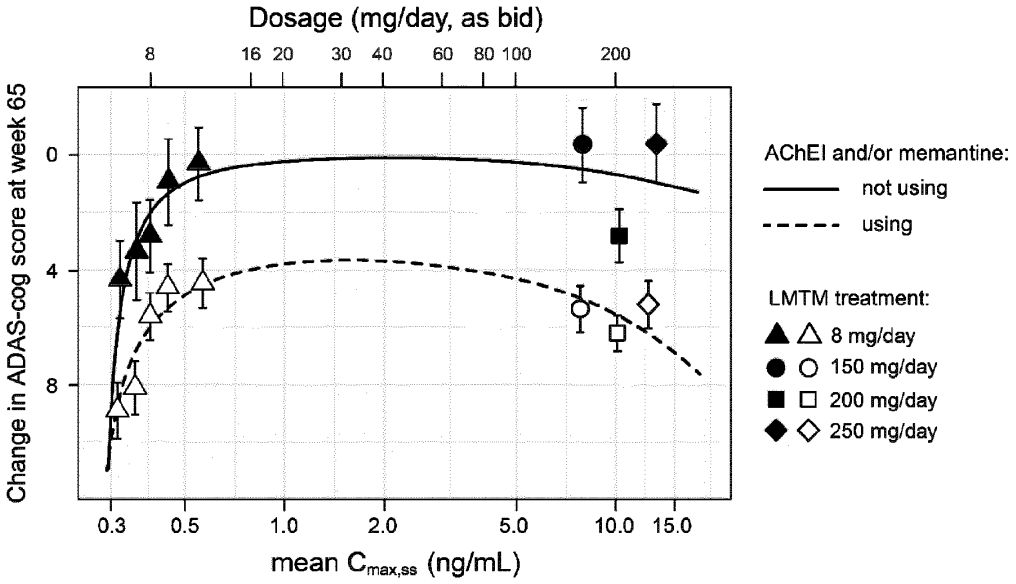

Dosage (mg/day, as bid)
8
16 20
30
40
60
80 100
200
Change in ADAS-cog score at week 65
0
4
8
0.3
0.5
1.0
2.0
5.0
10.0 15.0
mean $C_{max,ss}$ (ng/mL)
AChEI and/or memantine:
not using
using
LMTM treatment:
8 mg/day
150 mg/day
200 mg/day
250 mg/day

Figure 18

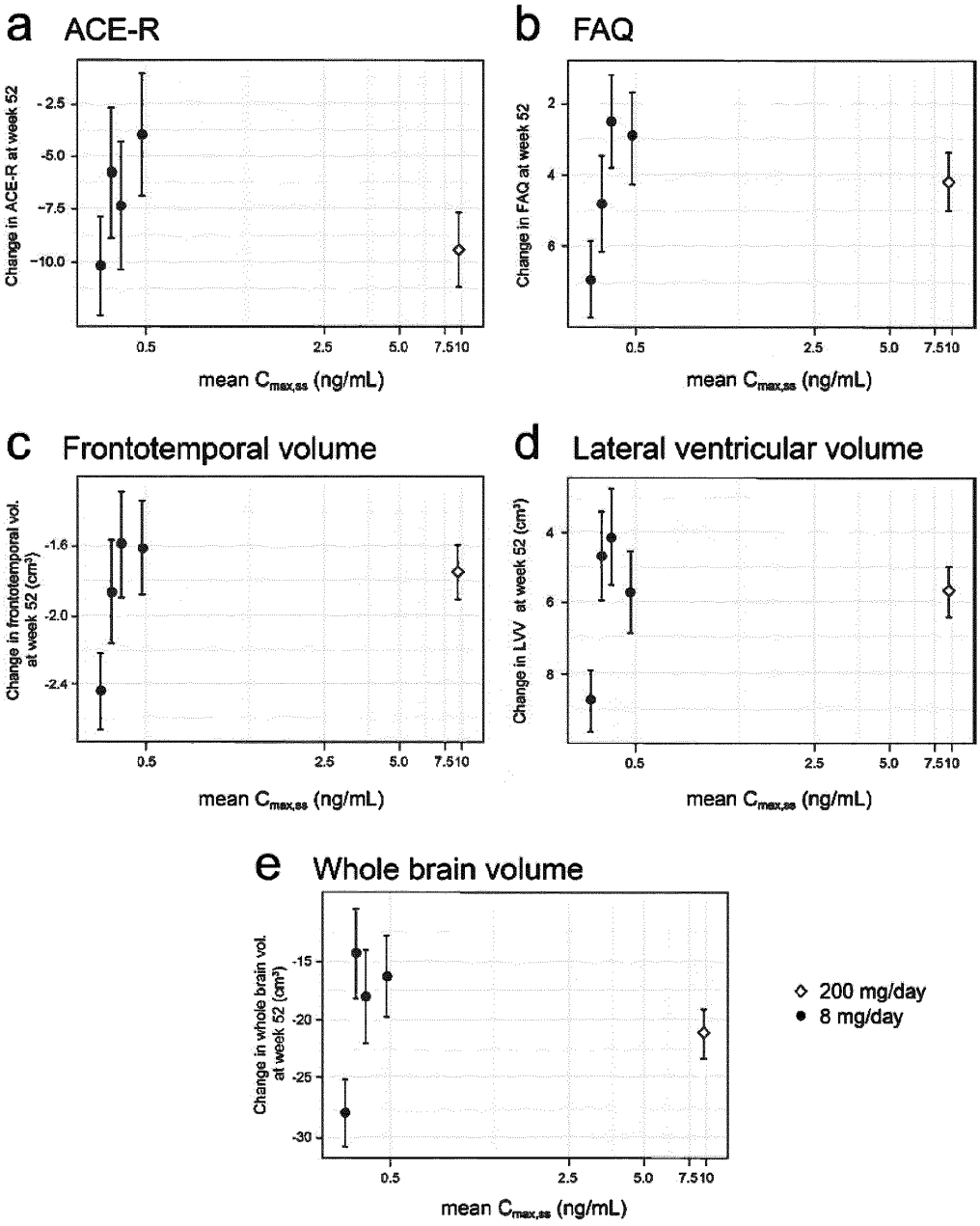

a ACE-R
Change in ACE-R at week 52
-2.5
-5.0
-7.5
-10.0
0.5
2.5
5.0
7.510
mean $C_{max,ss}$ (ng/mL)
b FAQ
Change in FAQ at week 52
2
4
6
0.5
2.5
5.0
7.510
mean $C_{max,ss}$ (ng/mL)
c Frontotemporal volume
Change in frontotemporal vol. at week 52 (cm³)
-1.6
-2.0
-2.4
0.5
2.5
5.0
7.510
mean $C_{max,ss}$ (ng/mL)
d Lateral ventricular volume
Change in LVV at week 52 (cm³)
4
6
8
0.5
2.5
5.0
7.510
mean $C_{max,ss}$ (ng/mL)
e Whole brain volume
Change in whole brain vol. at week 52 (cm³)
-15
-20
-25
-30
0.5
2.5
5.0
7.510
mean $C_{max,ss}$ (ng/mL)
◇ 200 mg/day
● 8 mg/day

Figure 19

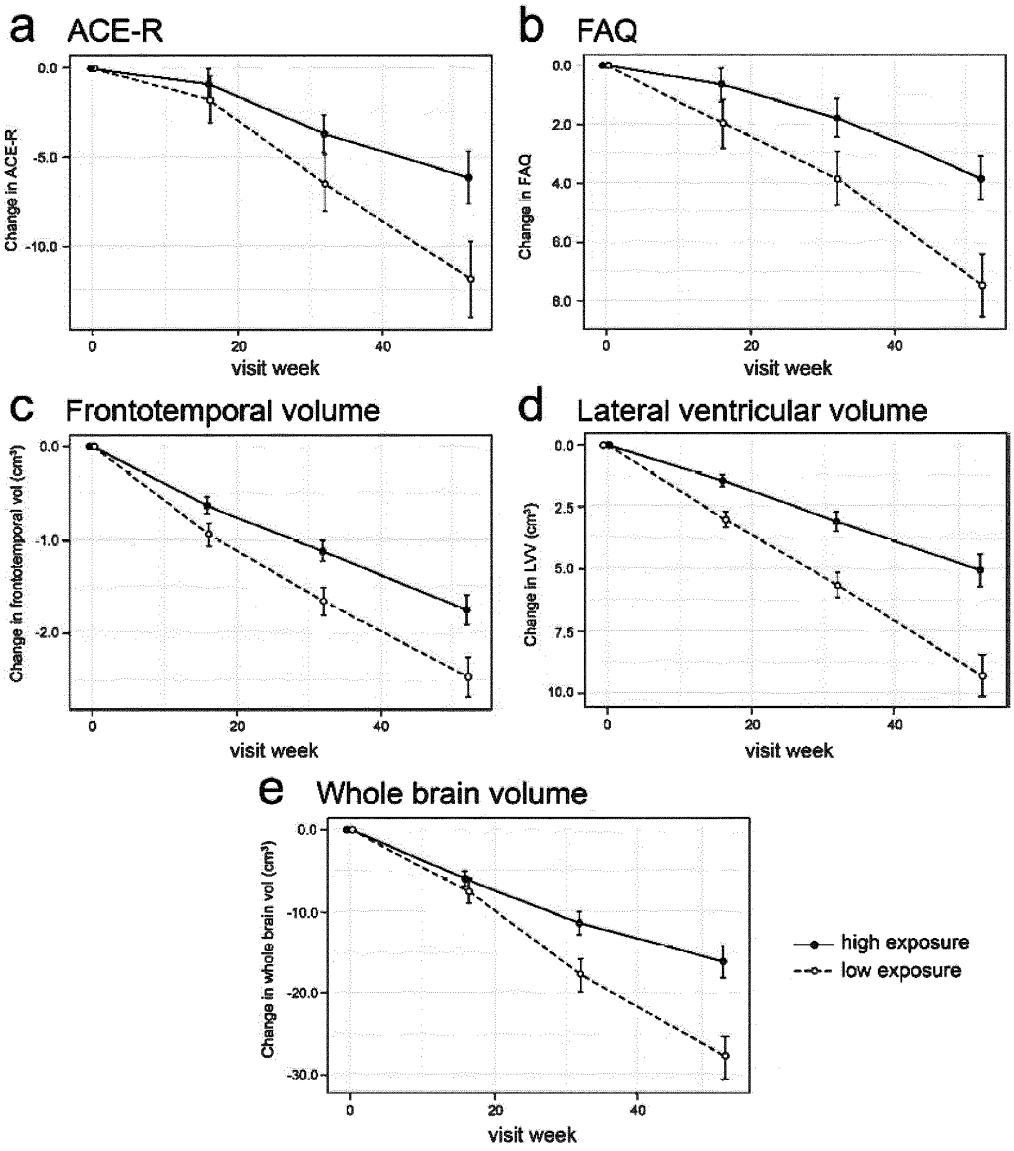
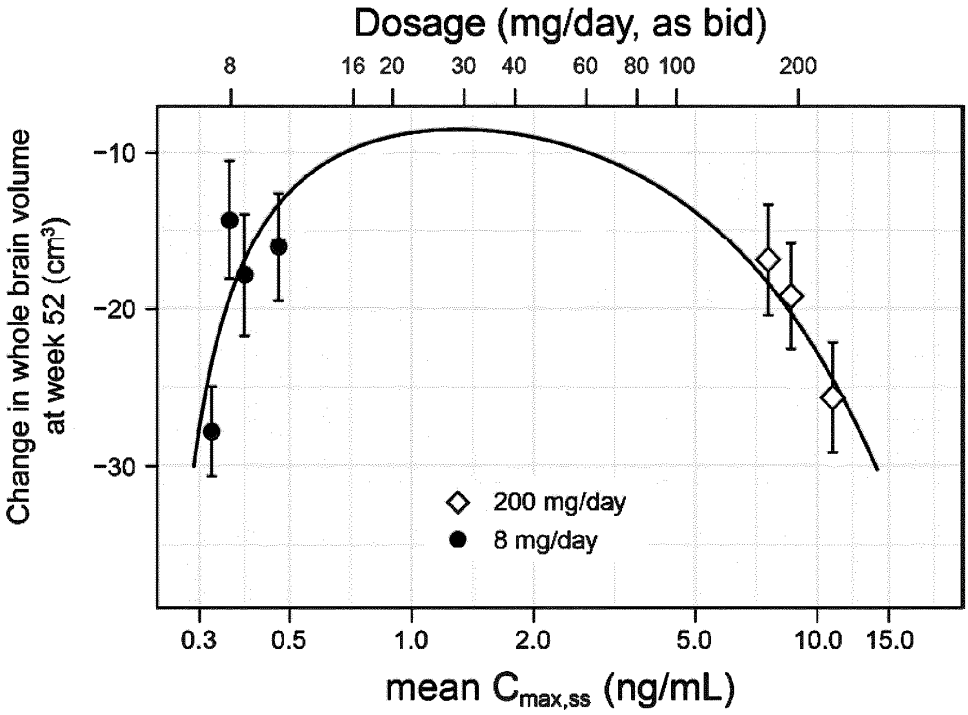

a ACE-R
Change in ACE-R
0.0
-5.0
-10.0
0
20
40
visit week
b FAQ
Change in FAQ
0.0
2.0
4.0
6.0
8.0
0
20
40
visit week
c Frontotemporal volume
Change in frontotemporal vol (cm³)
0.0
-1.0
-2.0
0
20
40
visit week
d Lateral ventricular volume
Change in LVV (cm³)
0.0
2.5
5.0
7.5
10.0
0
20
40
visit week
e Whole brain volume
Change in whole brain vol (cm³)
0.0
-10.0
-20.0
-30.0
0
20
40
visit week
high exposure
low exposure

Figure 20


Dosage (mg/day, as bid)
8
16 20
30
40
60
80 100
200
Change in whole brain volume at week 52 (cm³)
−10
−20
−30
200 mg/day
8 mg/day
0.3
0.5
1.0
2.0
5.0
10.0
15.0
mean $C_{max,ss}$ (ng/mL)