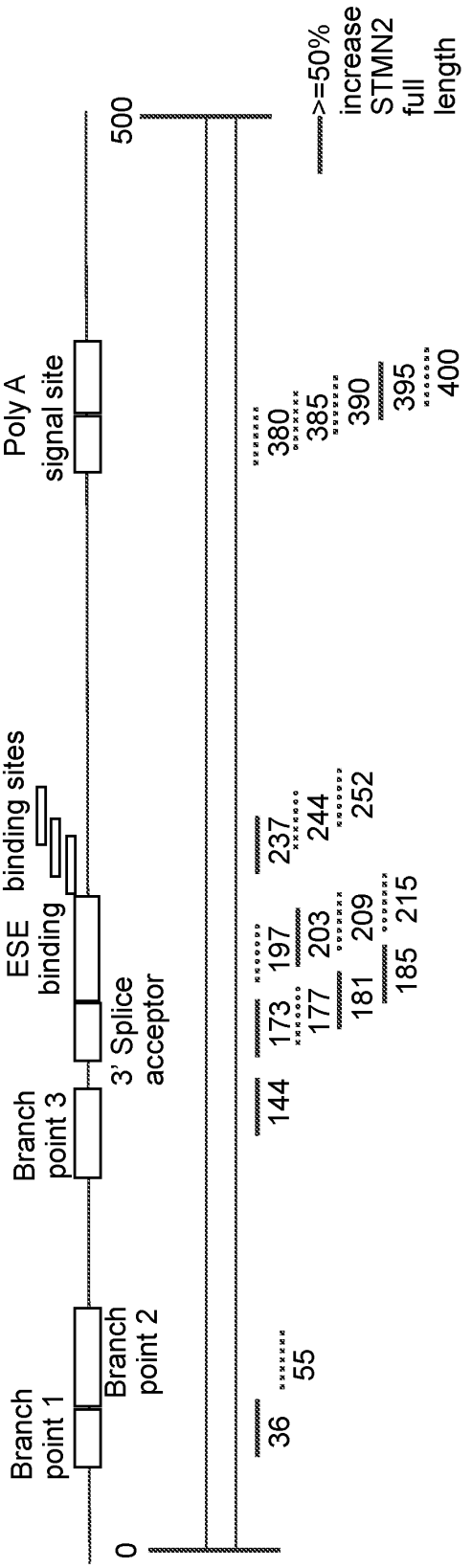

Branch point 1
Branch point 2
Branch point 3
3' Splice acceptor
ESE binding
TDP43 binding sites
Poly A signal site
0
500
36
55
144
173
177
181
185
197
203
209
215
237
244
252
380
385
390
395
400
>=50% increase STMN2 full length

FIG. 1A

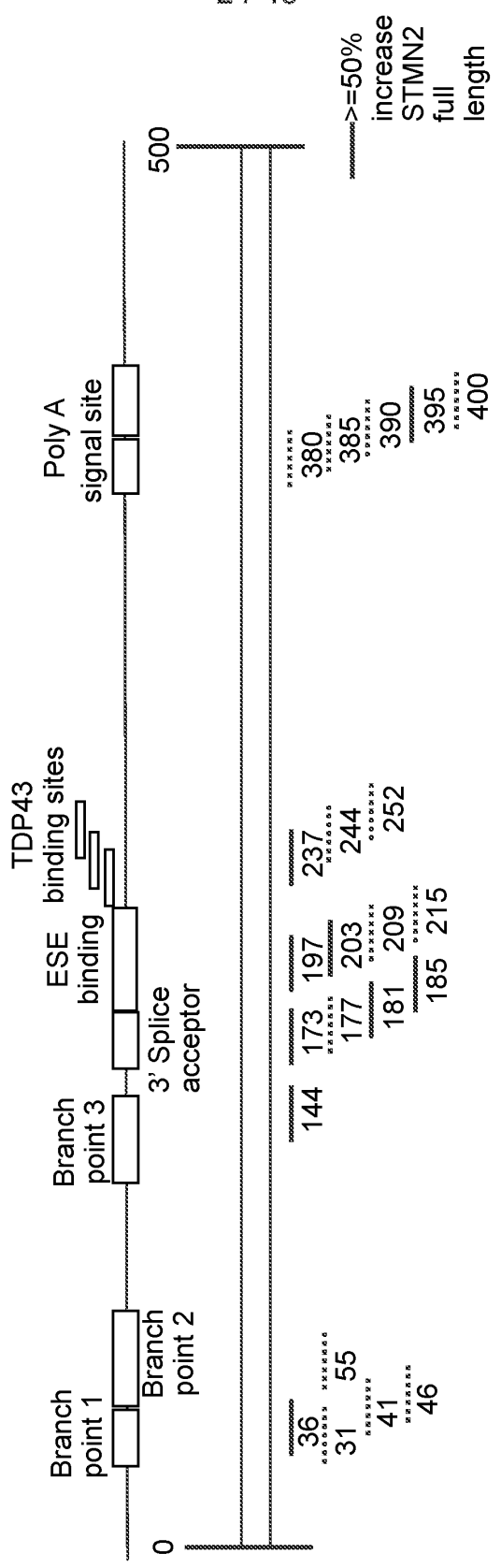

0
500
Branch point 1
Branch point 2
Branch point 3
3' Splice acceptor
ESE binding
TDP43 binding sites
Poly A signal site
>=50% increase STMN2 full length
36
31
55
41
46
144
173
197
177
203
181
209
185
215
237
244
252
380
385
390
395
400

FIG. 1B

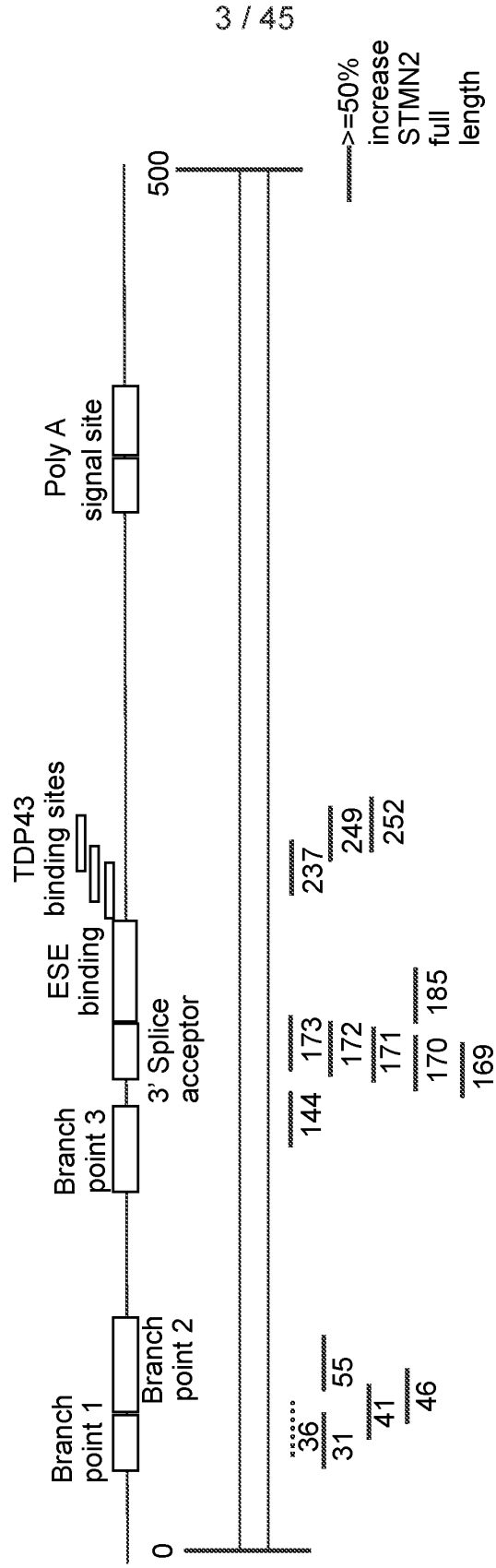

Branch point 1
Branch point 2
Branch point 3
3' Splice acceptor
ESE binding
TDP43 binding sites
Poly A signal site
0
500
36
31
55
41
46
144
173
172
171
170
185
169
237
249
252
>=50% increase STMN2 full length

FIG. 1C

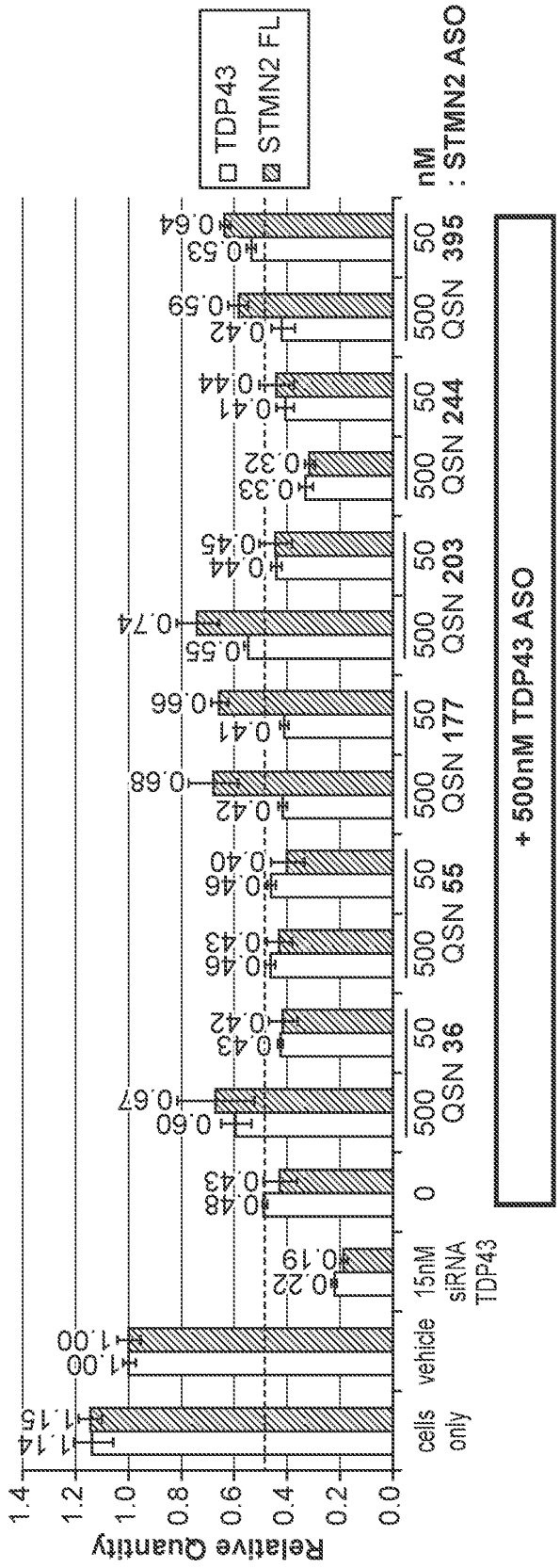

TDP43
STMN2 FL
nM : STMN2 ASO
Relative Quantity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
cells only
vehicle
15nM siRNA TDP43
0
QSN 36
QSN 55
QSN 177
QSN 203
QSN 244
QSN 395
50
500
+ 500nM TDP43 ASO
1.14
1.15
1.00
1.00
0.22
0.19
0.48
0.43
0.60
0.67
0.43
0.42
0.46
0.43
0.46
0.40
0.42
0.68
0.41
0.66
0.55
0.74
0.44
0.45
0.33
0.32
0.41
0.44
0.42
0.59
0.53
0.64

FIG. 2

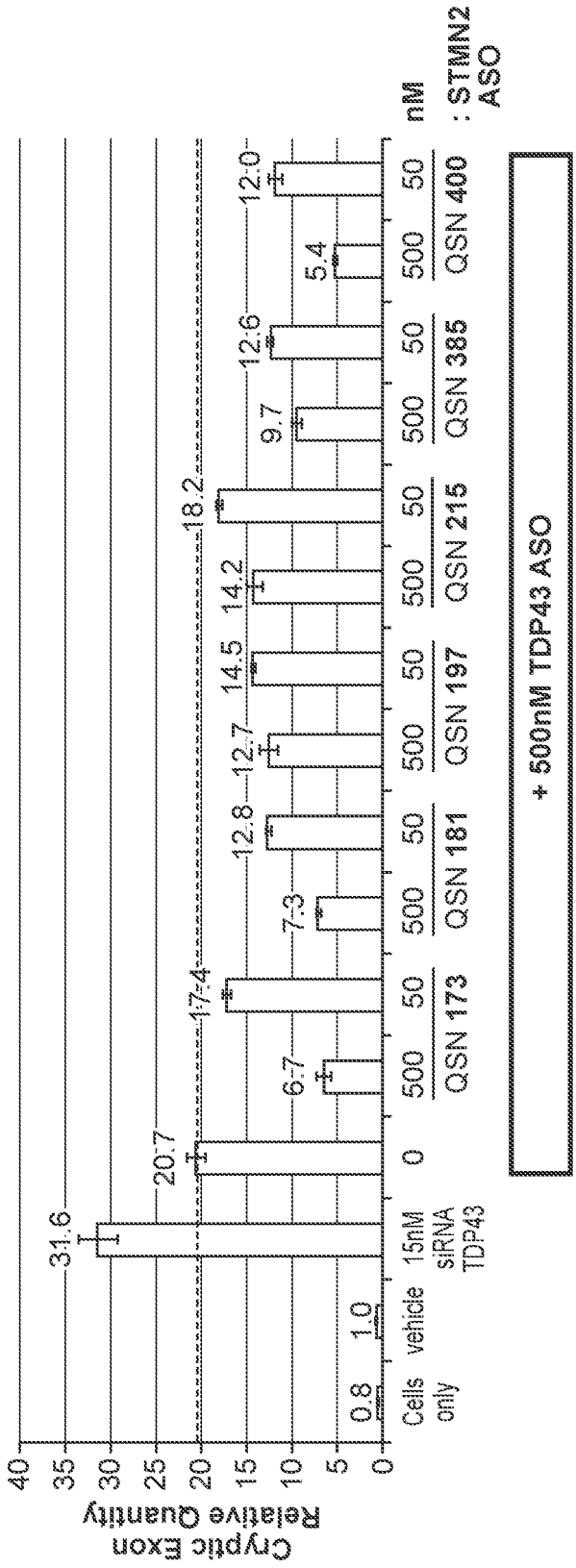

Cryptic Exon Relative Quantity
0
5
10
15
20
25
30
35
40
0.8
1.0
31.6
20.7
17.4
6.7
7.3
12.8
12.7
14.5
14.2
18.2
9.7
12.6
5.4
12.0
Cells only
vehicle
15nM siRNA TDP43
0
500
50
500
50
500
50
500
50
500
50
500
50
nM
QSN 173
QSN 181
QSN 197
QSN 215
QSN 385
QSN 400
: STMN2 ASO
+ 500nM TDP43 ASO

FIG. 3

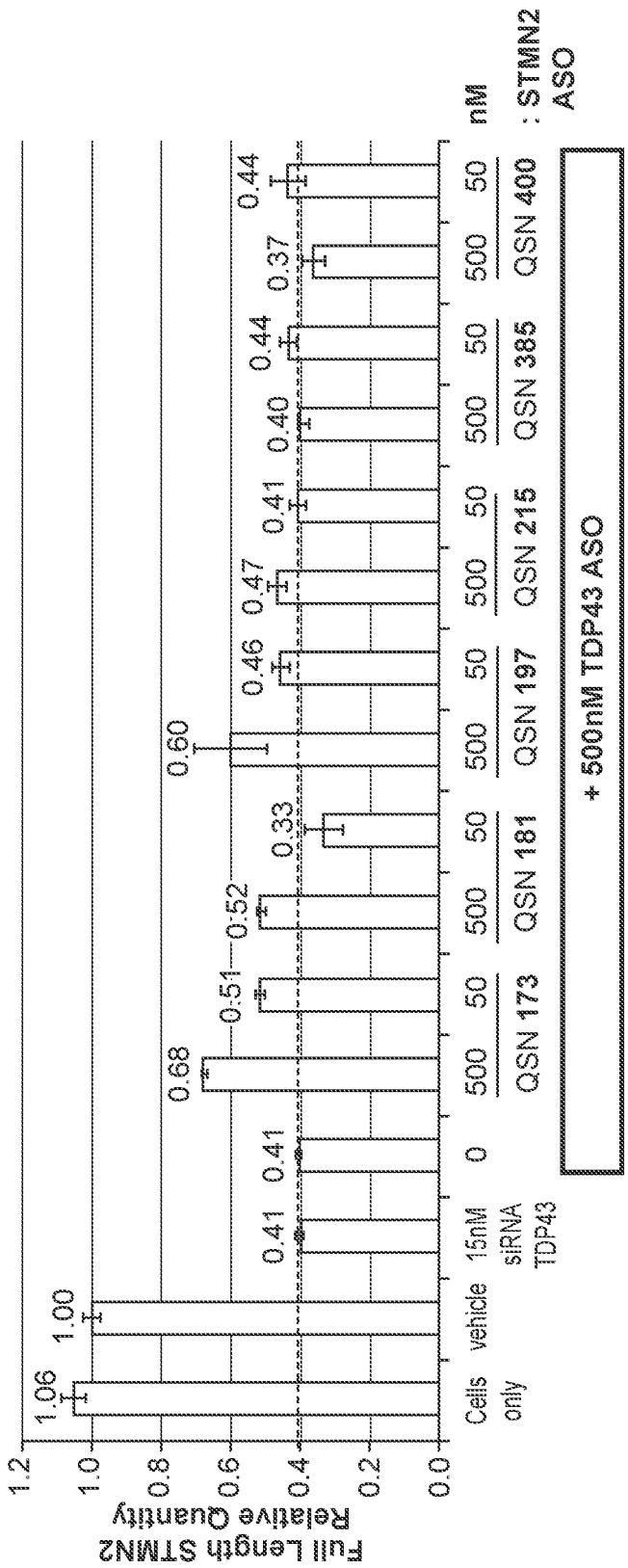

Full Length STMN2
Relative Quantity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.06
1.00
0.41
0.41
0.68
0.51
0.52
0.33
0.60
0.46
0.47
0.41
0.40
0.44
0.37
0.44
Cells only
vehicle
15nM siRNA TDP43
0
500
50
500
50
500
50
500
50
500
50
nM
QSN 173
QSN 181
QSN 197
QSN 215
QSN 385
QSN 400
: STMN2 ASO
+ 500nM TDP43 ASO

FIG. 4

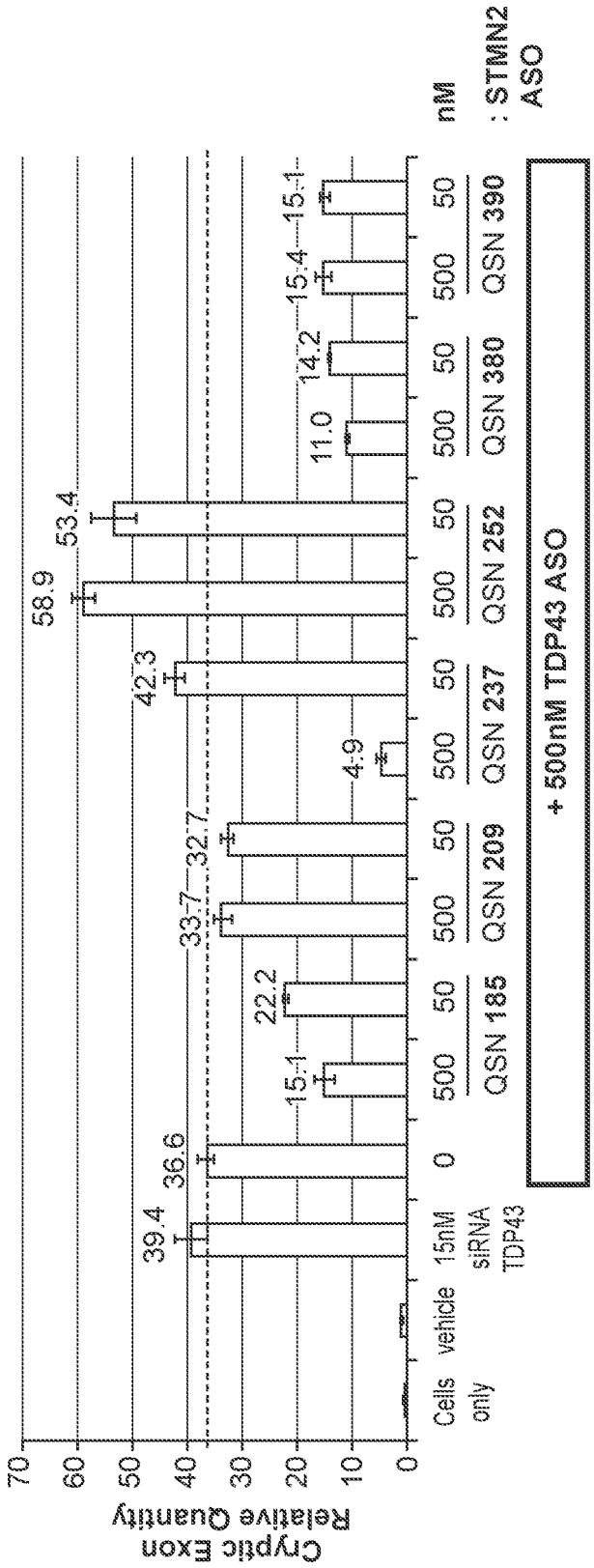

Cryptic Exon Relative Quantity
70
60
50
40
30
20
10
0
Cells only
vehicle
15nM siRNA TDP43
0
500
50
500
50
500
50
500
50
500
50
500
50
nM
QSN 185
QSN 209
QSN 237
QSN 252
QSN 380
QSN 390
: STMN2 ASO
+ 500nM TDP43 ASO
39.4
36.6
15.1
22.2
33.7
32.7
4.9
42.3
58.9
53.4
11.0
14.2
15.4
15.1

FIG. 5A

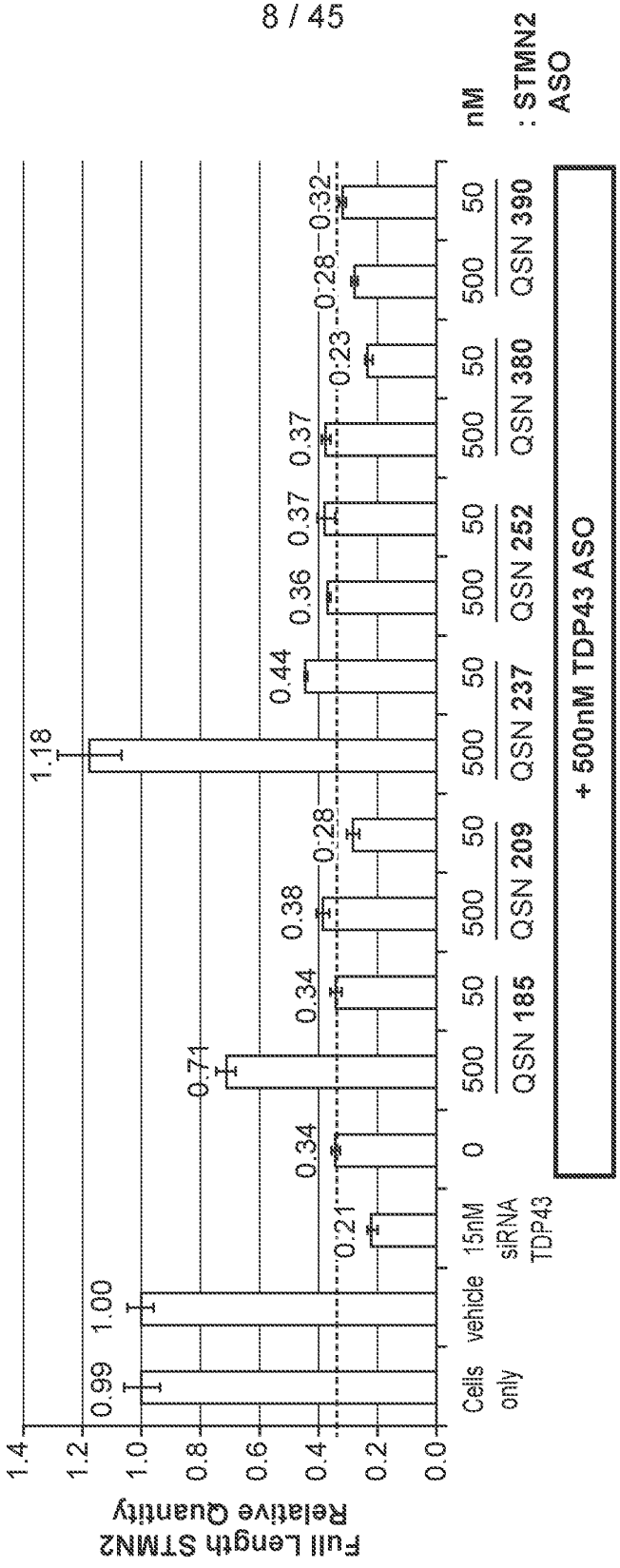

Full Length STMN2
Relative Quantity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.99
1.00
0.21
0.34
0.71
0.34
0.38
0.28
1.18
0.44
0.36
0.37
0.23
0.37
0.28
0.32
Cells only
vehicle
15nM siRNA TDP43
0
500
50
500
50
500
50
500
50
500
50
500
50
nM
QSN 185
QSN 209
QSN 237
QSN 252
QSN 380
QSN 390
: STMN2 ASO
+ 500nM TDP43 ASO

FIG. 5B

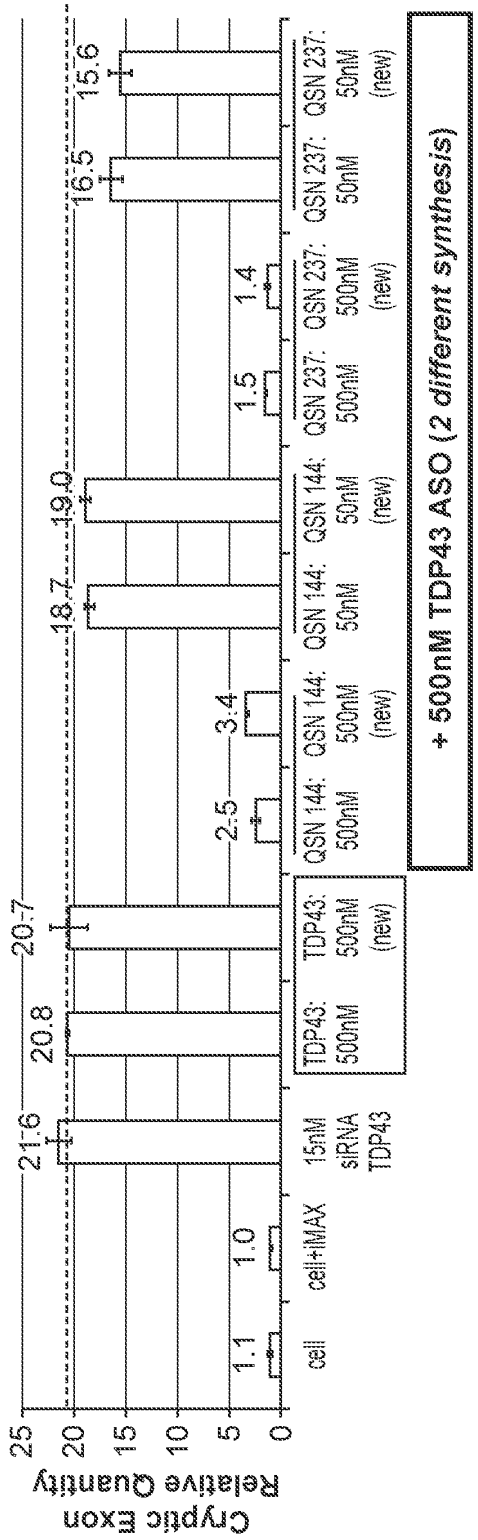

Cryptic Exon Relative Quantity
25
20
15
10
5
0
1.1
1.0
21.6
20.8
20.7
2.5
3.4
18.7
19.0
1.5
1.4
16.5
15.6
cell
cell+iMAX
15nM siRNA TDP43
TDP43: 500nM
TDP43: 500nM (new)
QSN 144: 500nM
QSN 144: 500nM (new)
QSN 144: 50nM
QSN 144: 50nM (new)
QSN 237: 500nM
QSN 237: 500nM (new)
QSN 237: 50nM
QSN 237: 50nM (new)
+ 500nM TDP43 ASO (2 different synthesis)

FIG. 6A

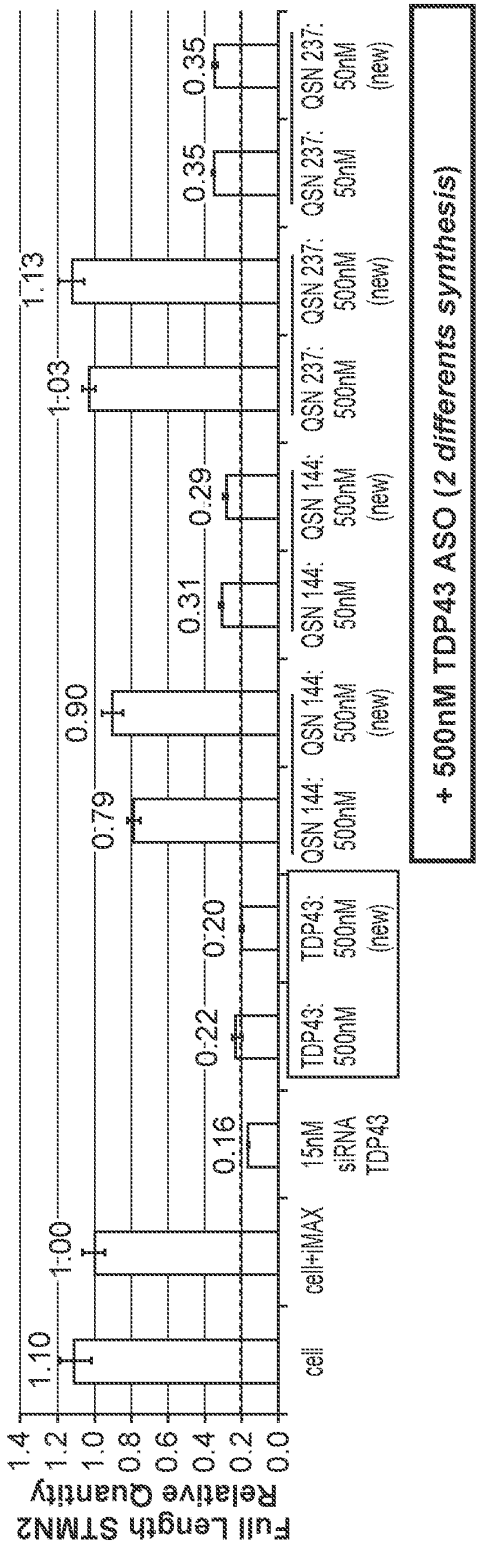

Full Length STMN2 Relative Quantity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.10
1.00
0.16
0.22
0.20
0.79
0.90
0.31
0.29
1.03
1.13
0.35
0.35
cell
cell+iMAX
15nM siRNA TDP43
TDP43: 500nM
TDP43: 500nM (new)
QSN 144: 500nM
QSN 144: 500nM (new)
QSN 144: 50nM
QSN 144: 50nM (new)
QSN 237: 500nM
QSN 237: 500nM (new)
QSN 237: 50nM
QSN 237: 50nM (new)
+ 500nM TDP43 ASO (2 differents synthesis)

FIG. 6B

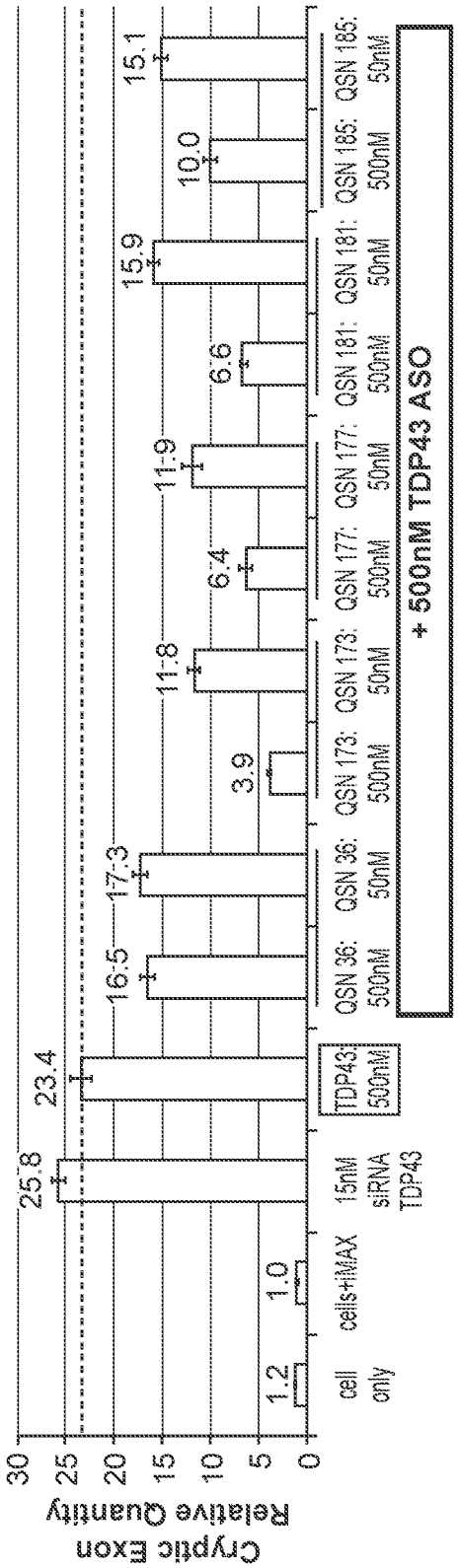

Cryptic Exon
Relative Quantity
30
25
20
15
10
5
0
1.2
1.0
25.8
23.4
16.5
17.3
3.9
11.8
6.4
11.9
6.6
15.9
10.0
15.1
cell only
cells+iMAX
15nM siRNA TDP43
TDP43 500nM
QSN 36: 500nM
QSN 36: 50nM
QSN 173: 500nM
QSN 173: 50nM
QSN 177: 500nM
QSN 177: 50nM
QSN 181: 500nM
QSN 181: 50nM
QSN 185: 500nM
QSN 185: 50nM
+ 500nM TDP43 ASO

FIG. 7A

Full Length STMN2
Relative Quantity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.10
1.01
0.35
0.42
0.61
0.59
0.92
0.70
0.55
0.52
0.79
0.52
0.73
0.58
cell only
cells+iMAX
15nM siRNA TDP43
TDP43 500nM
QSN 36: 500nM
QSN 36: 50nM
QSN 173: 500nM
QSN 173: 50nM
QSN 177: 500nM
QSN 177: 50nM
QSN 181: 500nM
QSN 181: 50nM
QSN 185: 500nM
QSN 185: 50nM
+ 500nM TDP43 ASO

FIG. 7B

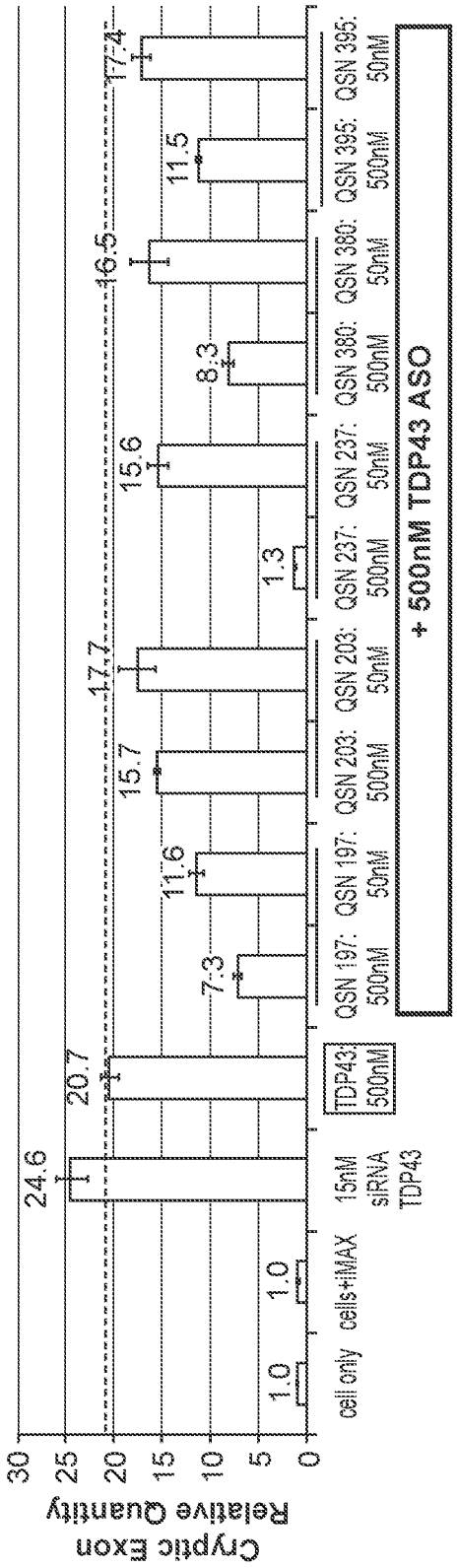

Cryptic Exon Relative Quantity
30
25
20
15
10
5
0
24.6
20.7
17.7
15.7
16.5
17.4
15.6
11.6
11.5
8.3
7.3
1.3
1.0
1.0
cell only
cells+iMAX
15nM siRNA TDP43
TDP43 500nM
QSN 197: 500nM
QSN 197: 50nM
QSN 203: 500nM
QSN 203: 50nM
QSN 237: 500nM
QSN 237: 50nM
QSN 380: 500nM
QSN 380: 50nM
QSN 395: 500nM
QSN 395: 50nM
+ 500nM TDP43 ASO

FIG. 8A

Full Length STMN2 Relative Quantity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1.09
1.01
0.93
0.76
0.70
0.60
0.58
0.49
0.46
0.41
0.40
0.38
0.31
0.25
cell only
cells+iMAX
15nM siRNA TDP43
TDP43 500nM
QSN 197: 500nM
QSN 197: 50nM
QSN 203: 500nM
QSN 203: 50nM
QSN 237: 500nM
QSN 237: 50nM
QSN 380: 500nM
QSN 380: 50nM
QSN 395: 500nM
QSN 395: 50nM
+ 500nM TDP43 ASO

FIG. 8B

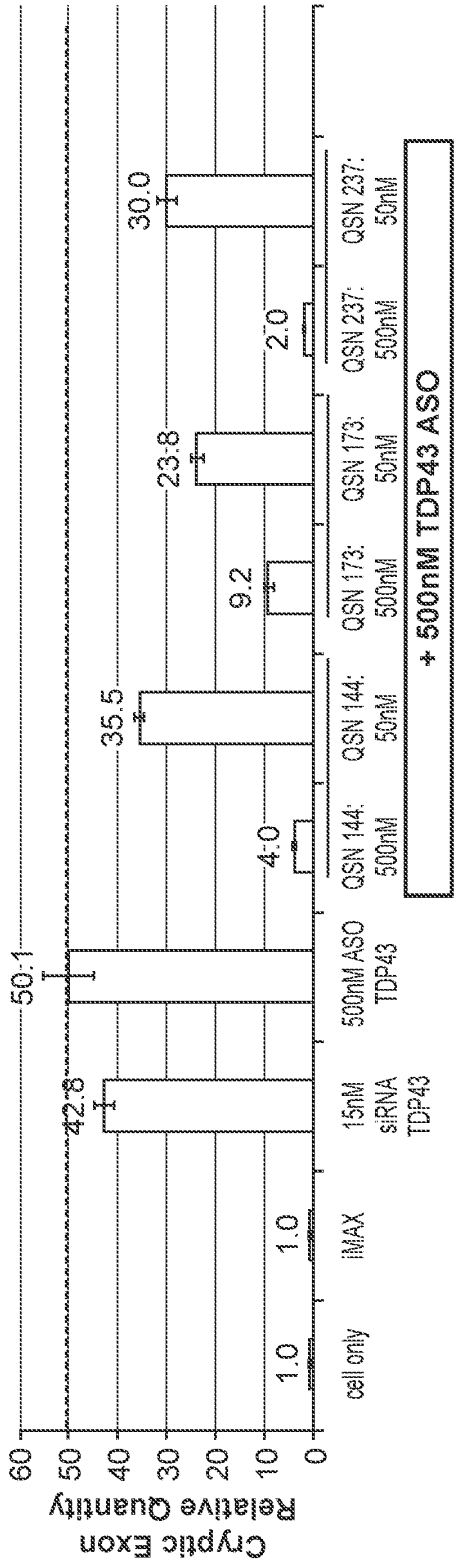

Cryptic Exon Relative Quantity
60
50
40
30
20
10
0
50.1
42.8
35.5
30.0
23.8
9.2
4.0
2.0
1.0
1.0
1.0
cell only
iMAX
15nM siRNA TDP43
500nM ASO TDP43
QSN 144: 500nM
QSN 144: 50nM
QSN 173: 500nM
QSN 173: 50nM
QSN 237: 500nM
QSN 237: 50nM
+ 500nM TDP43 ASO

FIG. 9A

Full Length STMN2 Relative Quantity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
TDP43
STMN2 FL
1.14
0.88
1.02
1.01
0.16
0.17
0.25
0.37
0.87
0.50
0.47
0.20
0.86
0.35
0.55
0.20
0.90
0.23
0.42
0.19
cell only
iMAX
15nM siRNA TDP43
500nM TDP43 ASO
QSN 144: 500nM
QSN 144: 50nM
QSN 173: 500nM
QSN 173: 50nM
QSN 237: 500nM
QSN 237: 50nM
+ 500nM TDP43 ASO

FIG. 9B

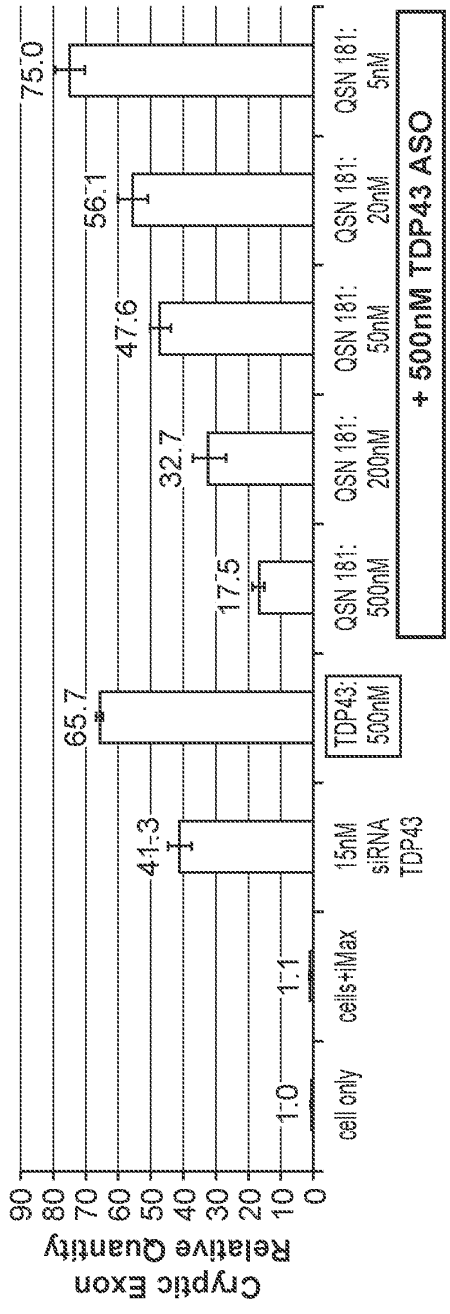


FIG. 10A

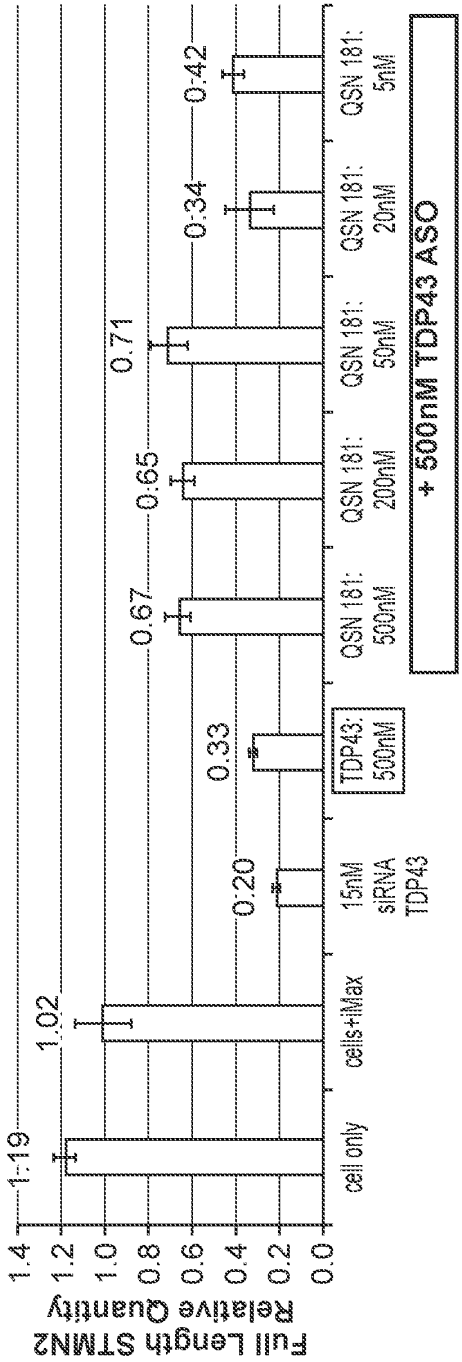


FIG. 10B

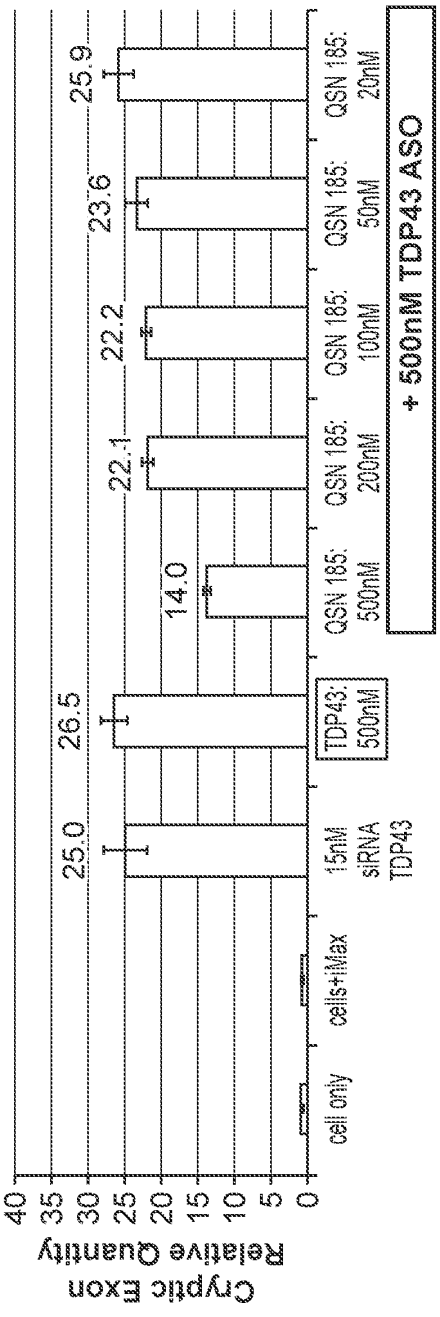


FIG. 11A

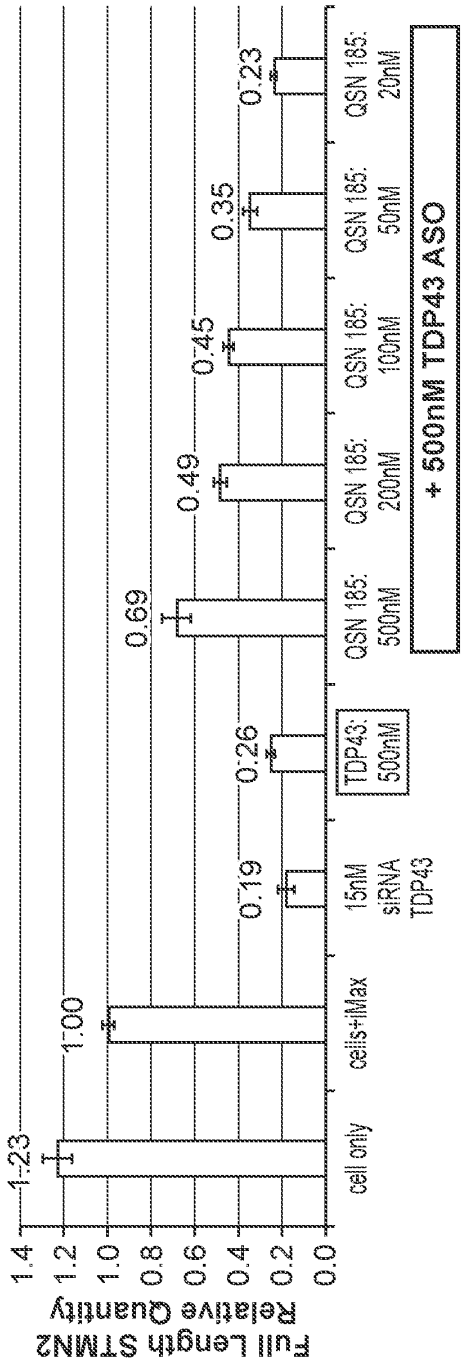


FIG. 11B

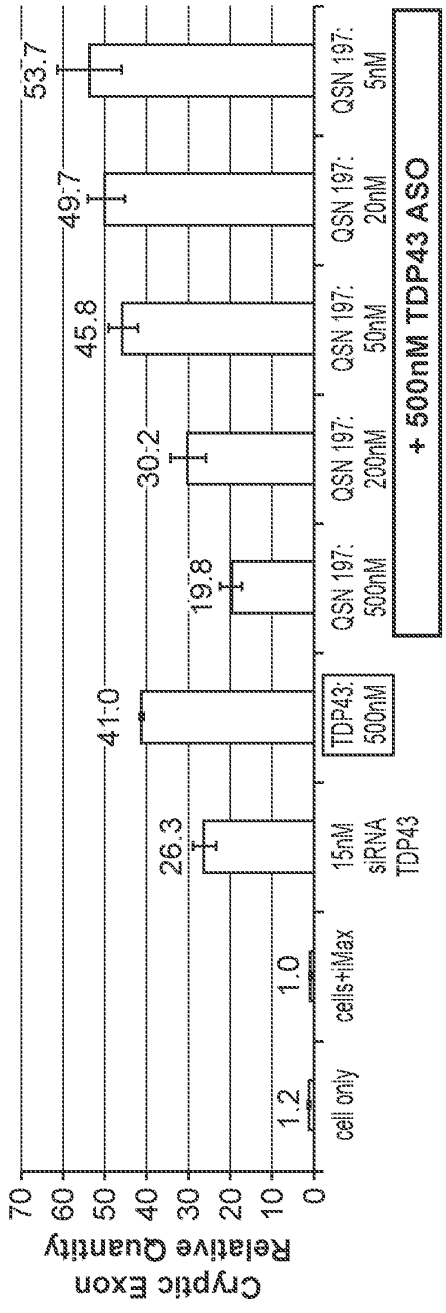


FIG. 12A

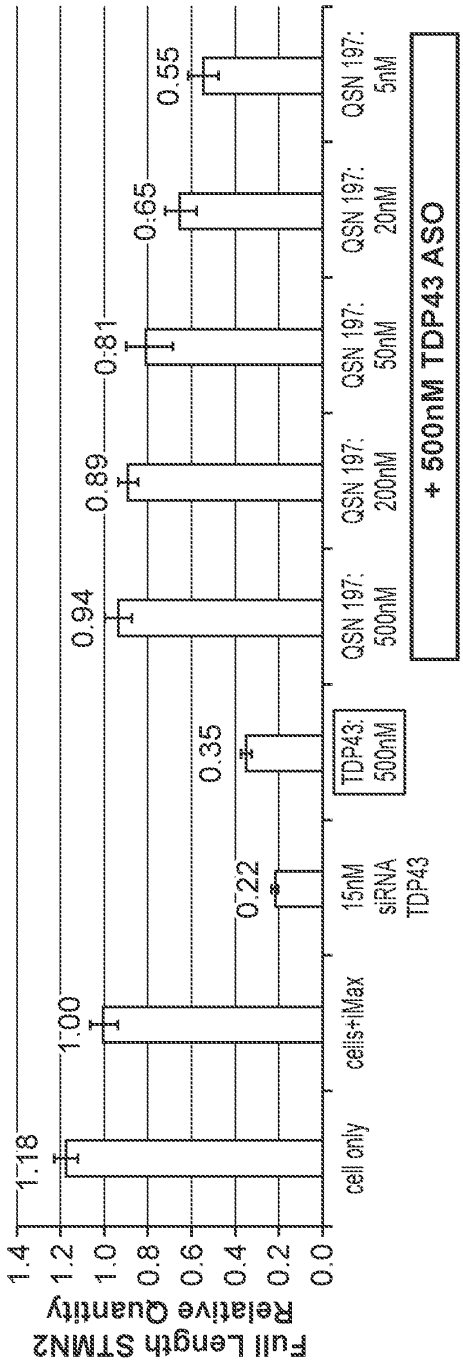


FIG. 12B

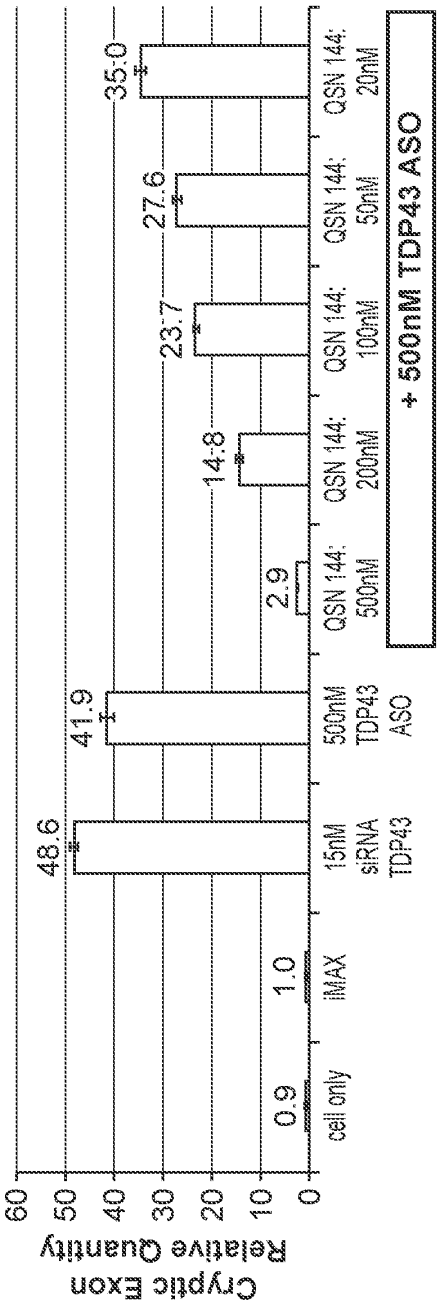


FIG. 13A

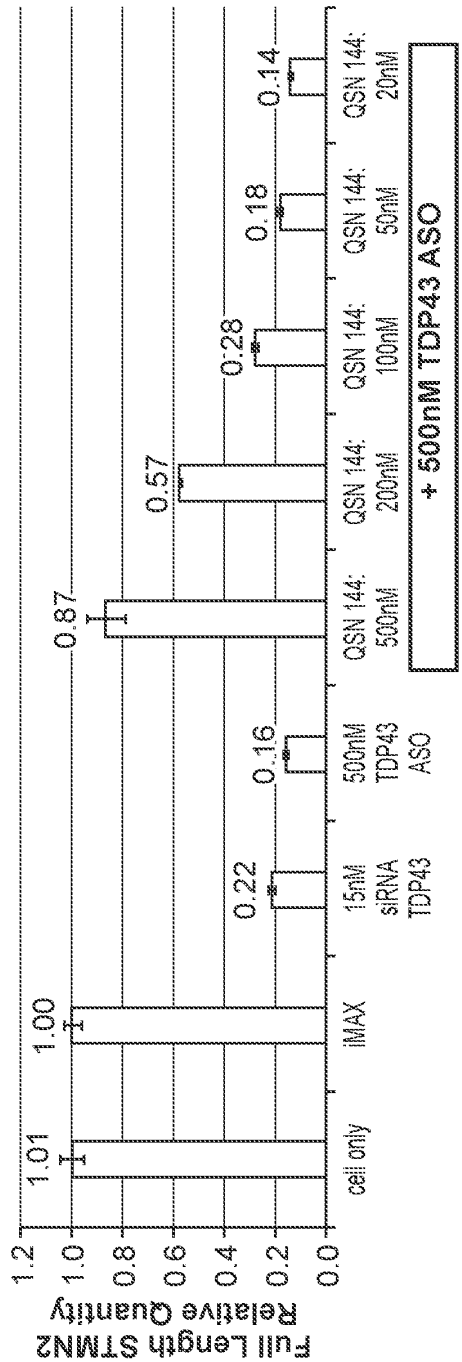


FIG. 13B

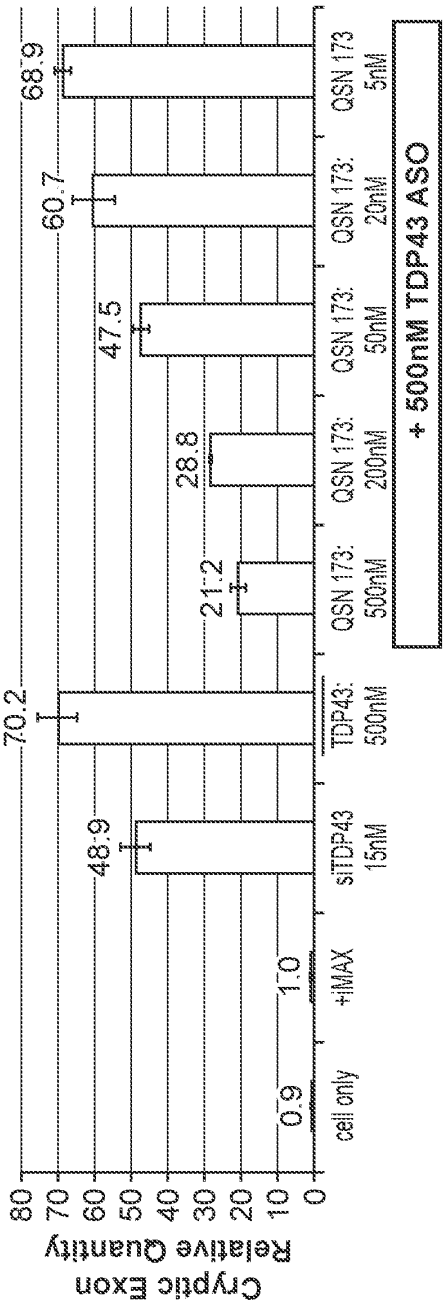


FIG. 14A

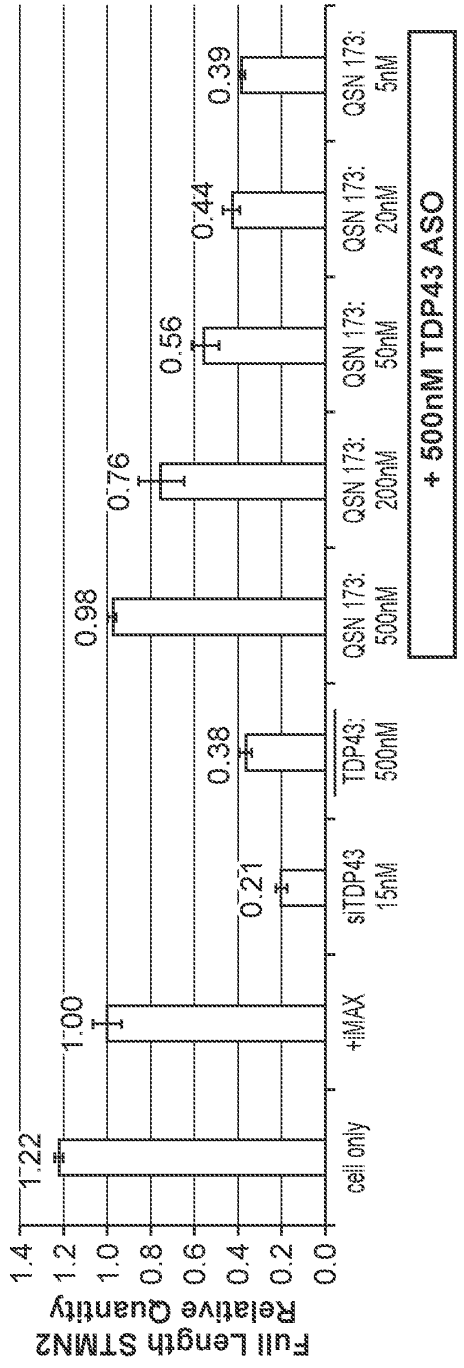


FIG. 14B

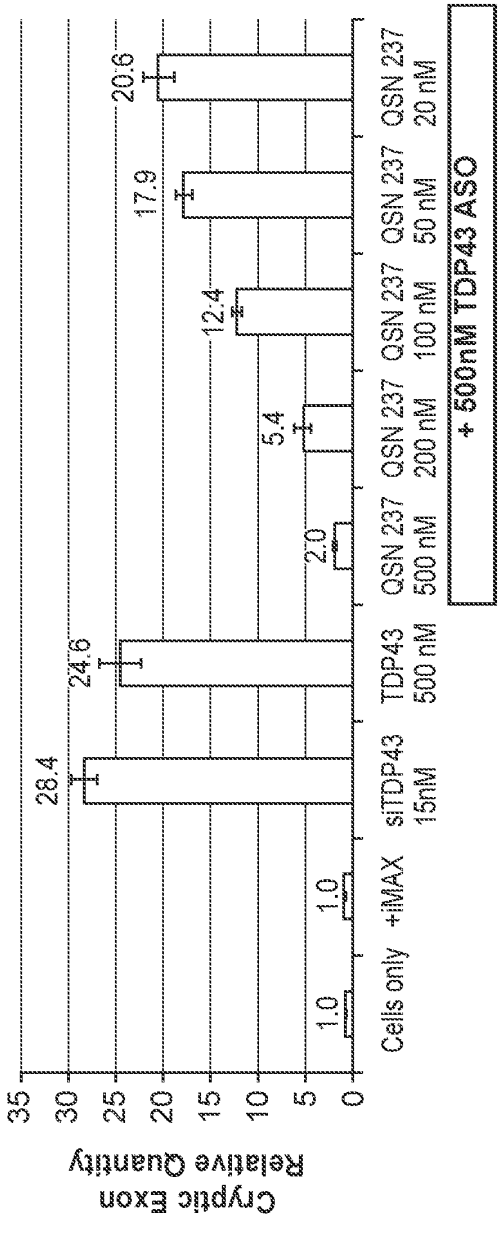


FIG. 15A

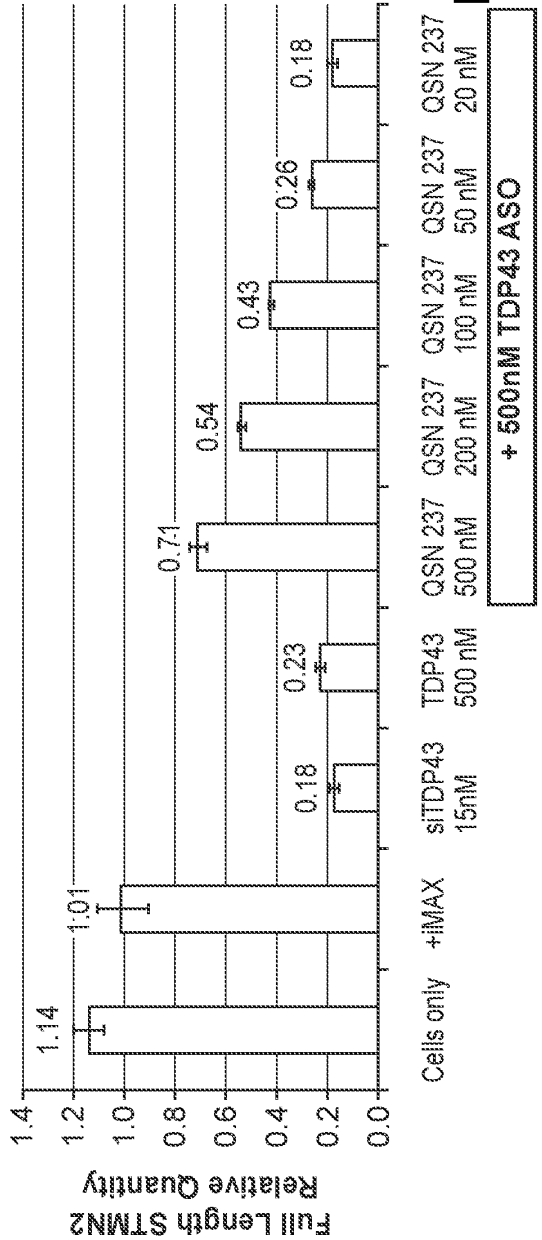


FIG. 15B

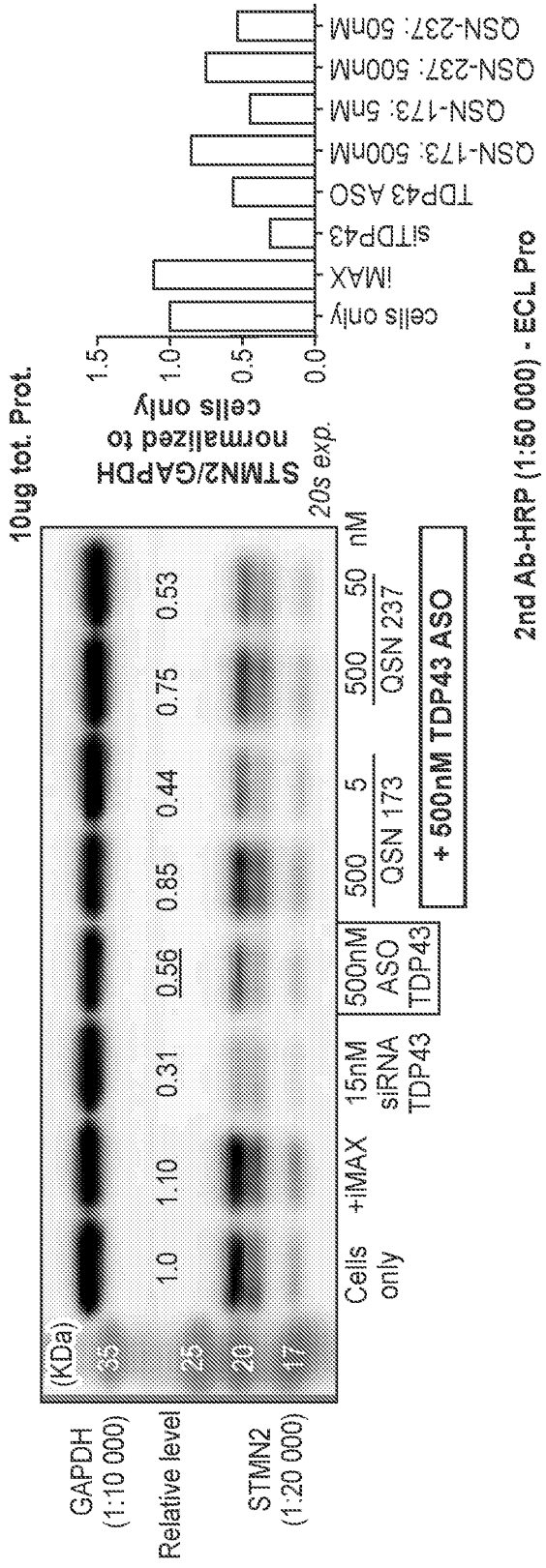

10ug tot. Prot.
2nd Ab-HRP (1:50 000) - ECL Pro
STMN2/GAPDH normalized to cells only
20s exp.
1.5
1.0
0.5
0.0
cells only
iMAX
siTDP43
TDP43 ASO
QSN-173: 500nM
QSN-173: 5nM
QSN-237: 500nM
QSN-237: 50nM
(KDa)
55
25
20
17
GAPDH (1:10 000)
STMN2 (1:20 000)
Relative level
1.0 1.10 0.31 0.56 0.85 0.44 0.75 0.53
Cells only
+iMAX
15nM siRNA TDP43
500nM ASO TDP43
500 5 500 50 nM
QSN 173 QSN 237
+ 500nM TDP43 ASO

FIG. 16

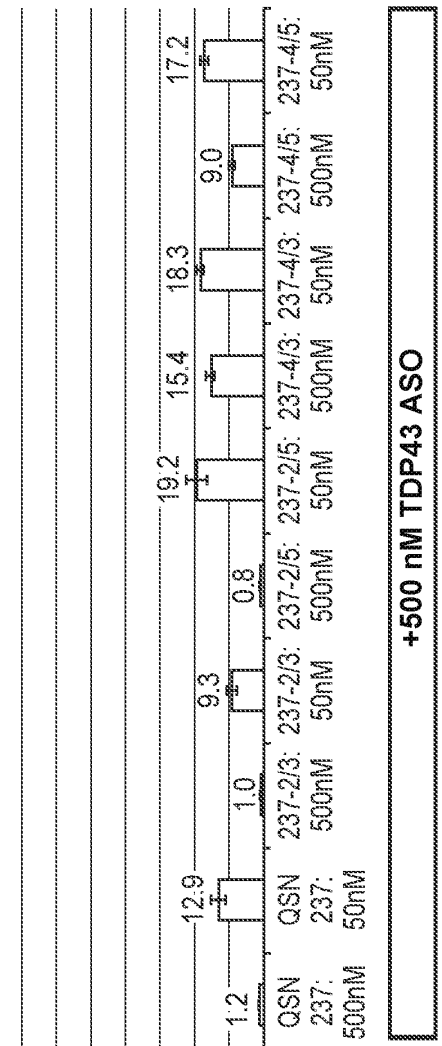


FIG. 17A

FIG. 17B

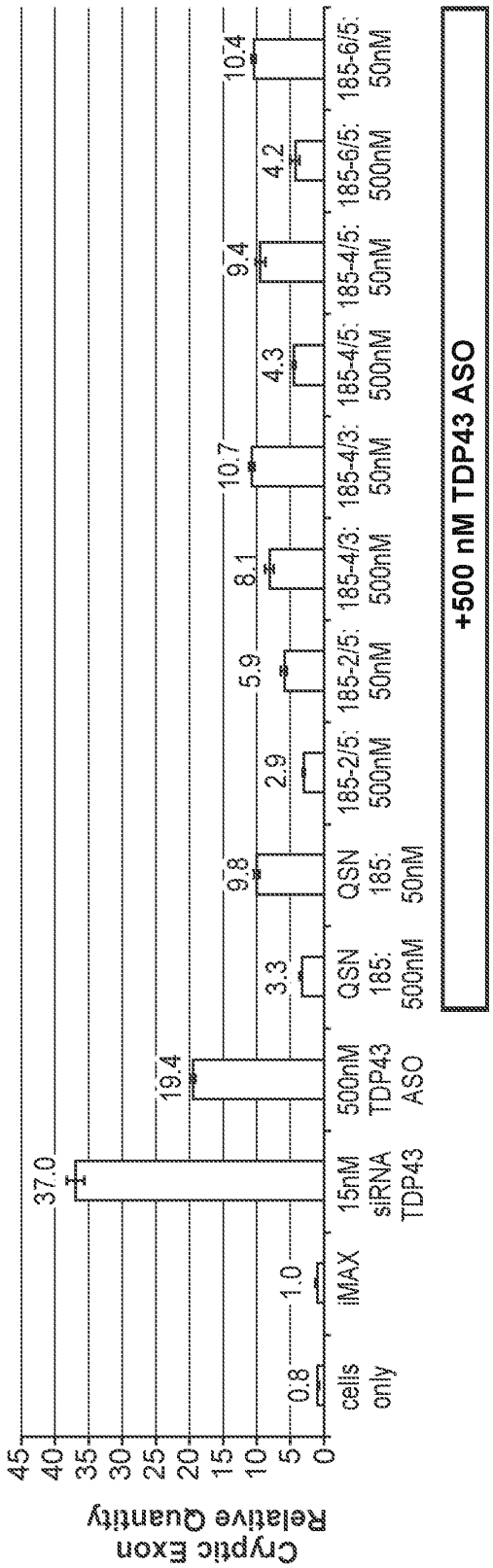


FIG. 18A

FIG. 18B

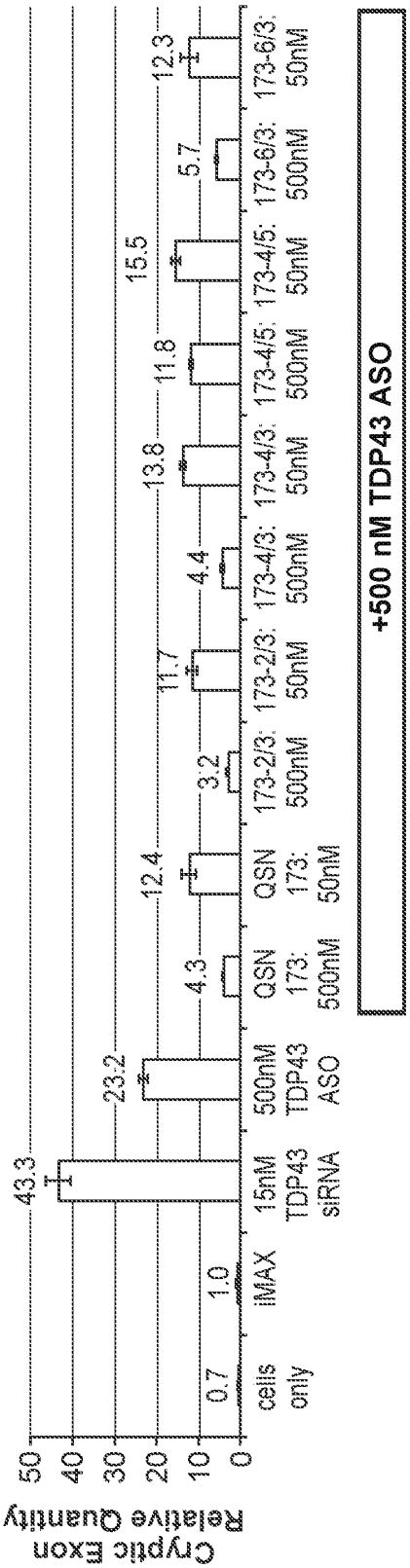


FIG. 19A

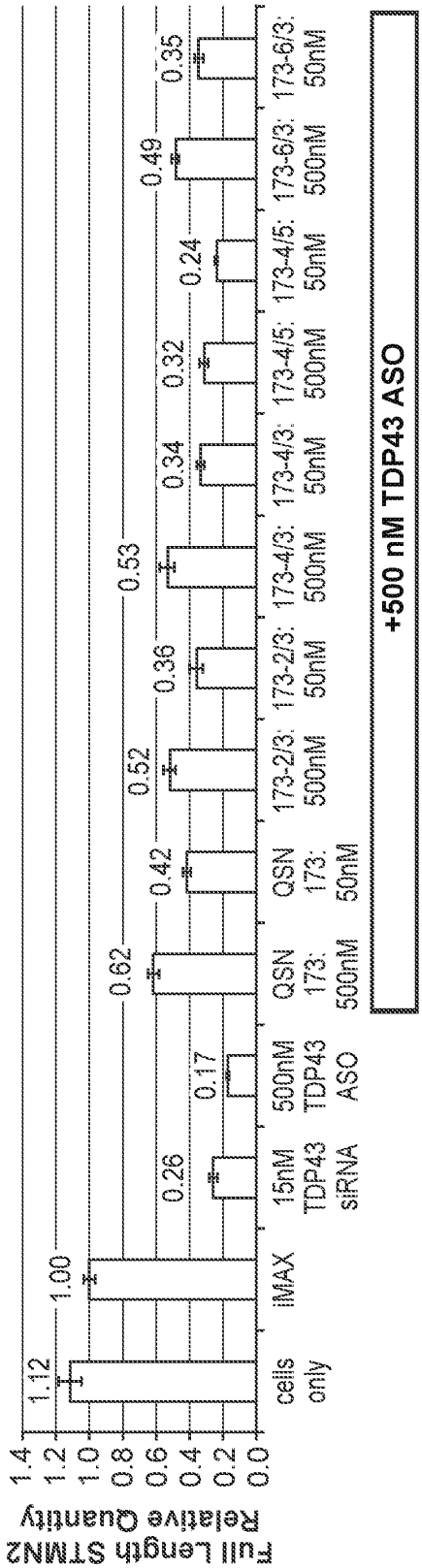


FIG. 19B

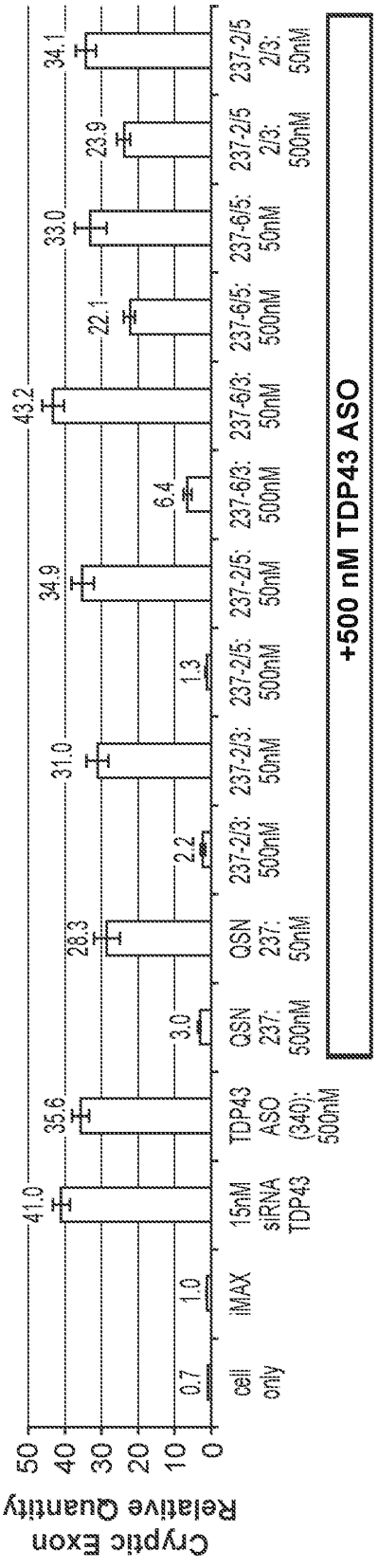


FIG. 20A

FIG. 20B

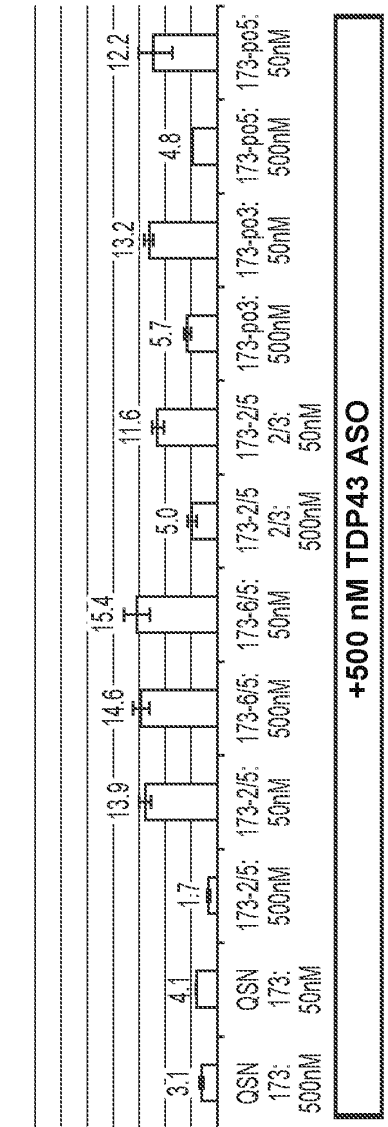


FIG. 21A

FIG. 21B

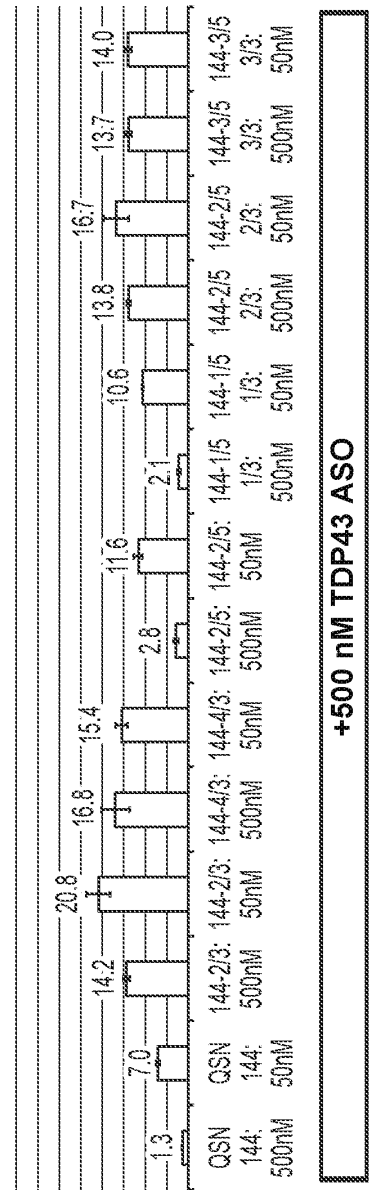


FIG. 22A

FIG. 22B

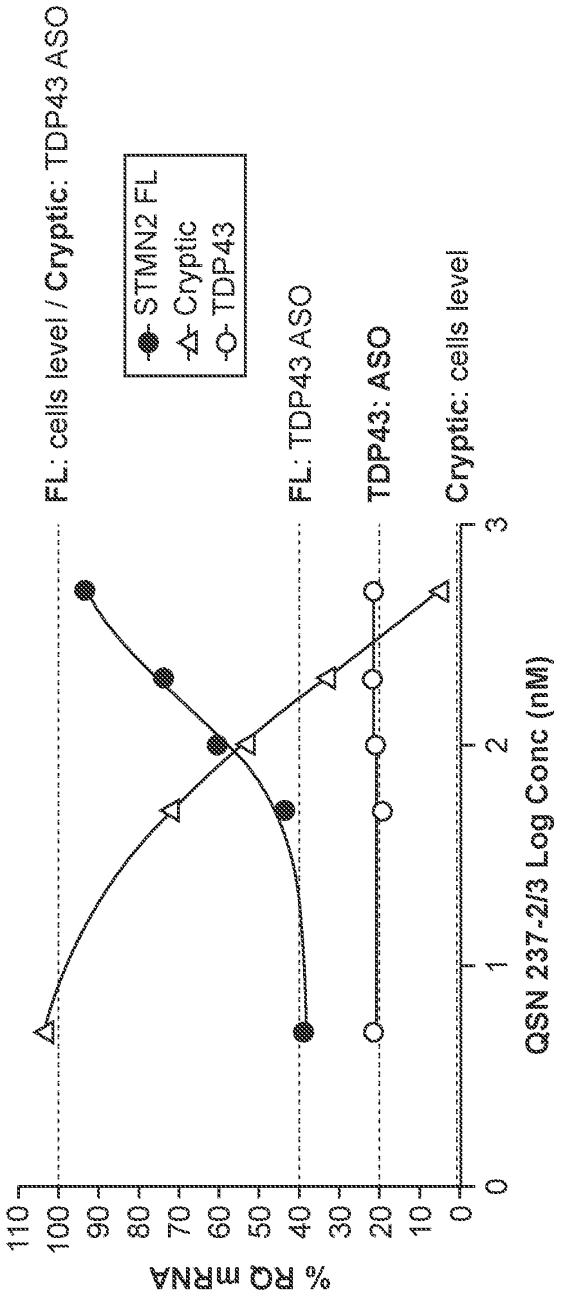

FL: cells level / Cryptic: TDP43 ASO
STMN2 FL
Cryptic
TDP43
FL: TDP43 ASO
TDP43: ASO
Cryptic: cells level
% RQ mRNA
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
QSN 237-2/3 Log Conc (nM)

FIG. 23

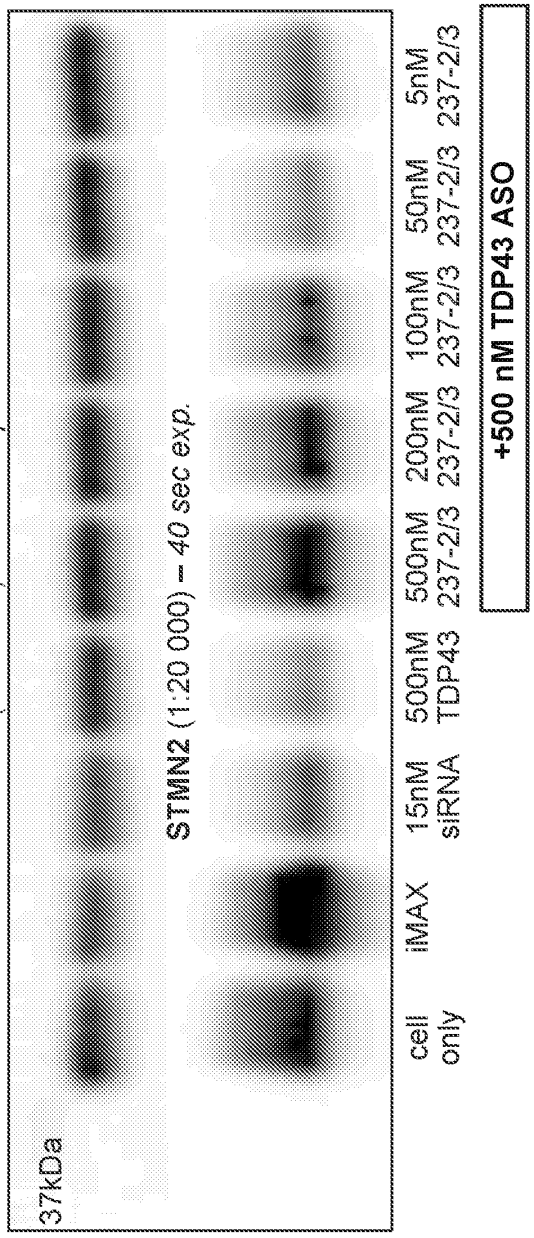

GAPDH (1:10 000) – 3 sec exp.
37kDa
STMN2 (1:20 000) – 40 sec exp.
cell only
iMAX
15nM siRNA
500nM TDP43
500nM 237-2/3
200nM 237-2/3
100nM 237-2/3
50nM 237-2/3
5nM 237-2/3
+500 nM TDP43 ASO

FIG. 24A

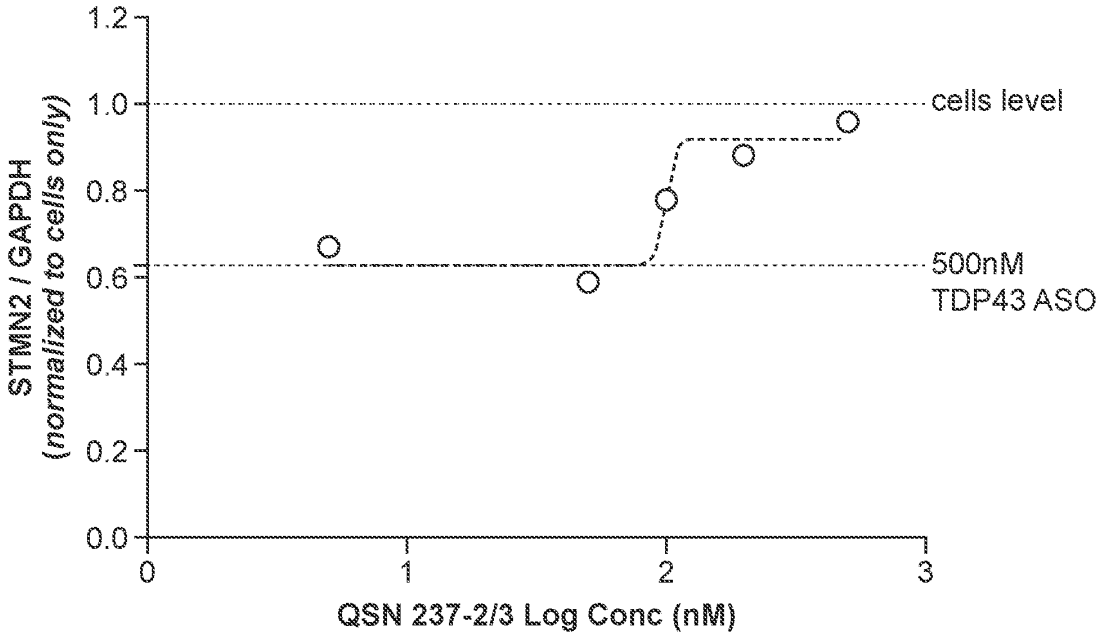

1.2
1.0
0.8
0.6
0.4
0.2
0.0
STMN2 / GAPDH
(normalized to cells only)
cells level
500nM
TDP43 ASO
0
1
2
3
QSN 237-2/3 Log Conc (nM)

FIG. 24B

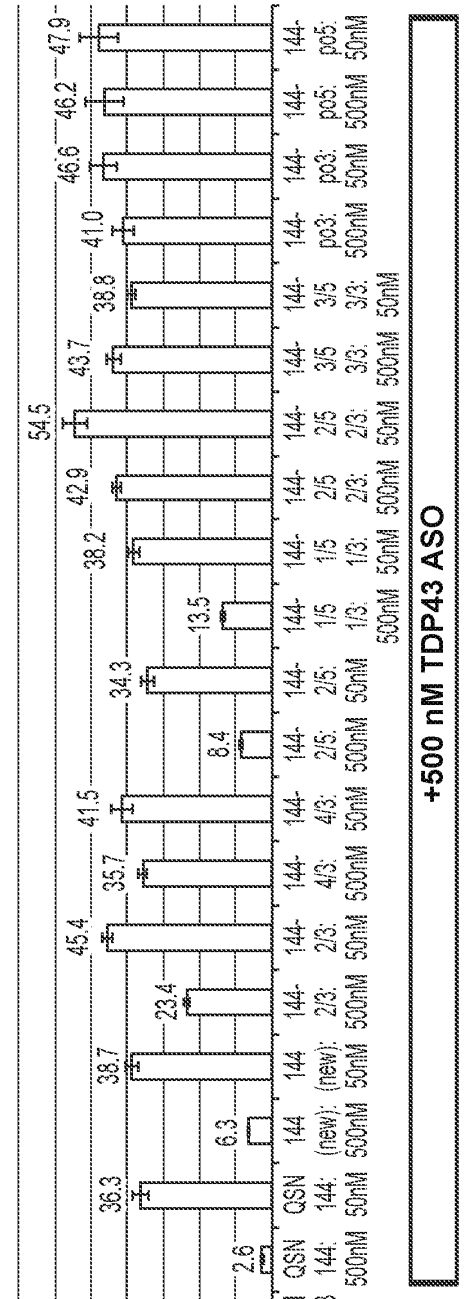


FIG. 25A

FIG. 25B

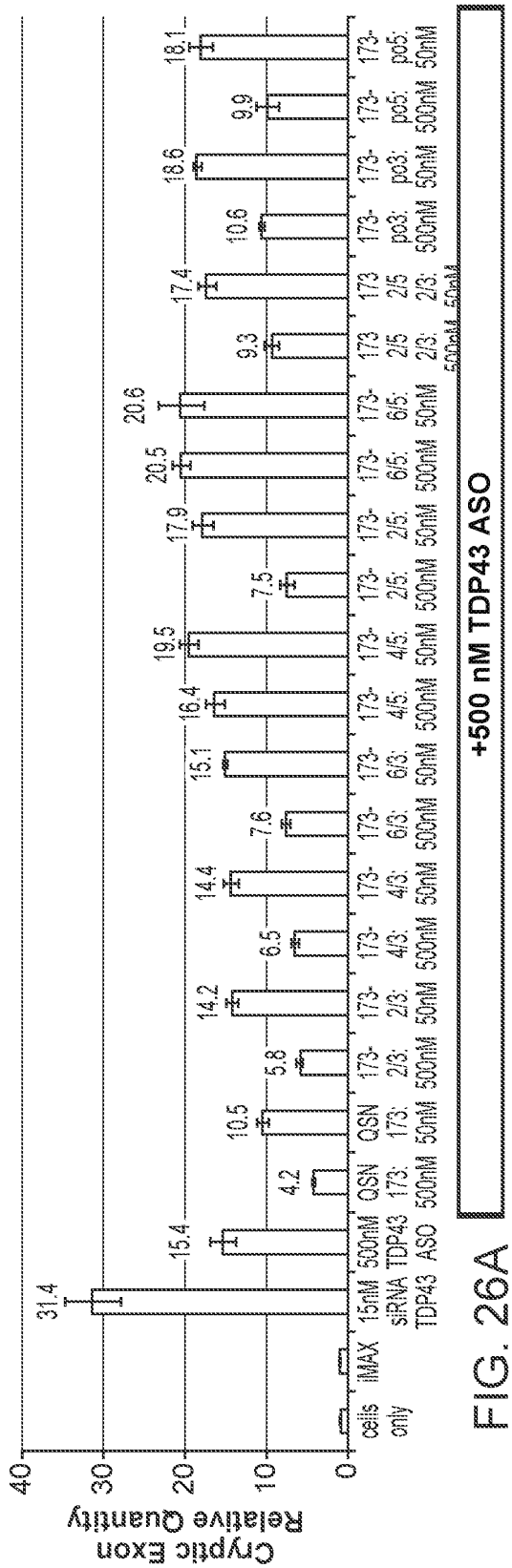


FIG. 26A

FIG. 26B

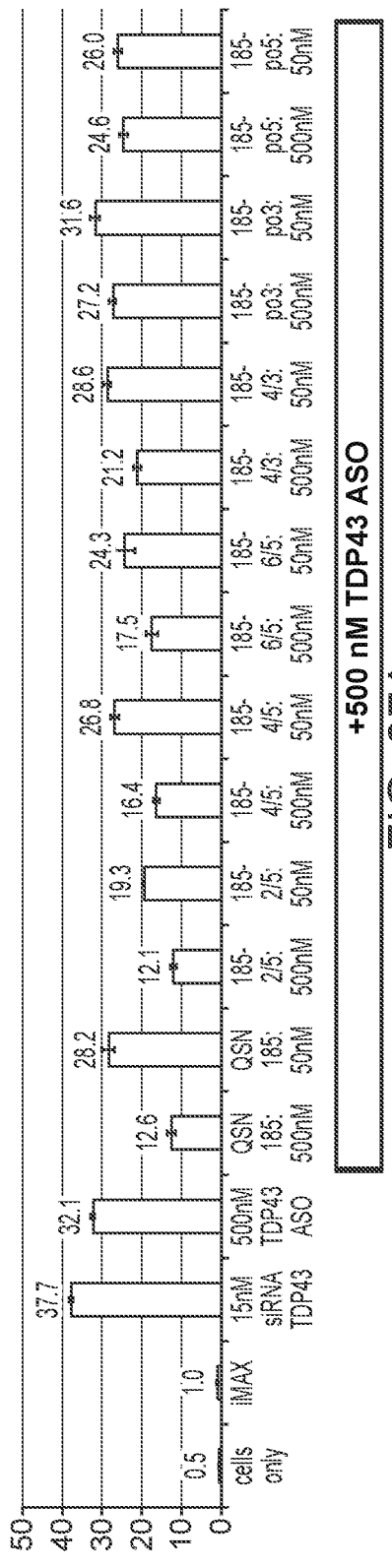


FIG. 27A

FIG. 27B

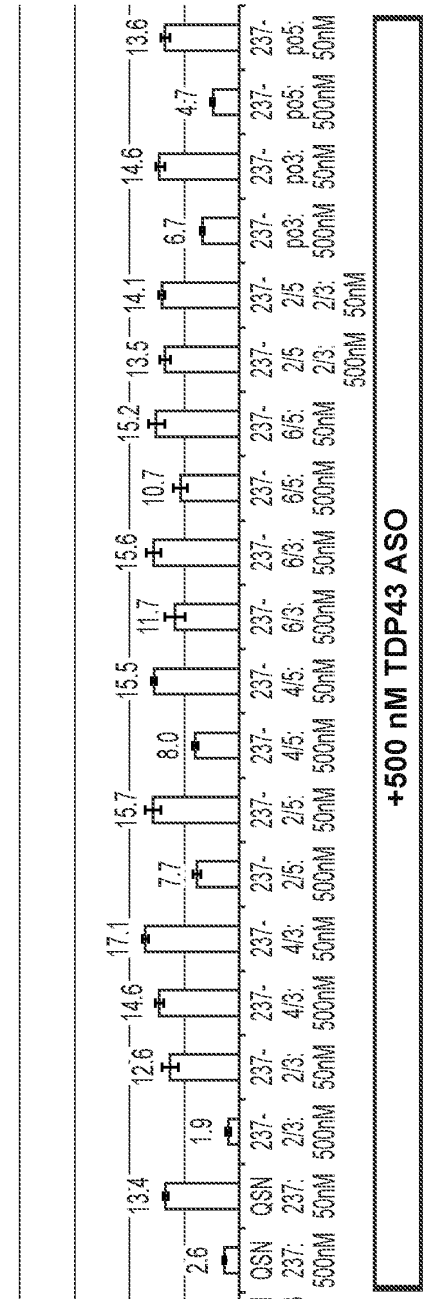


FIG. 28A

FIG. 28B

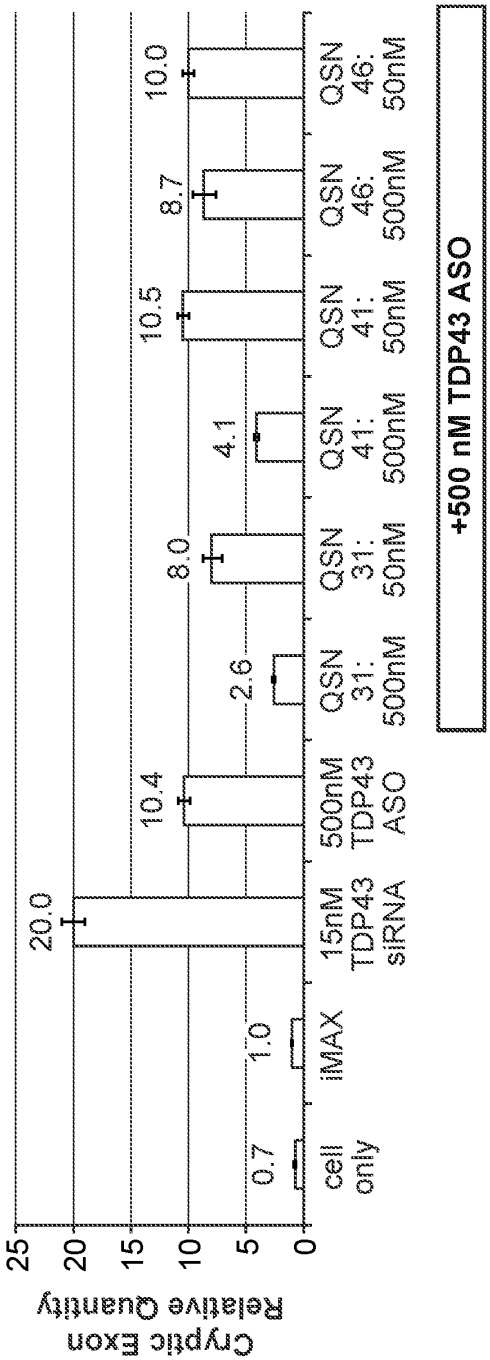


FIG. 29A

FIG. 29B

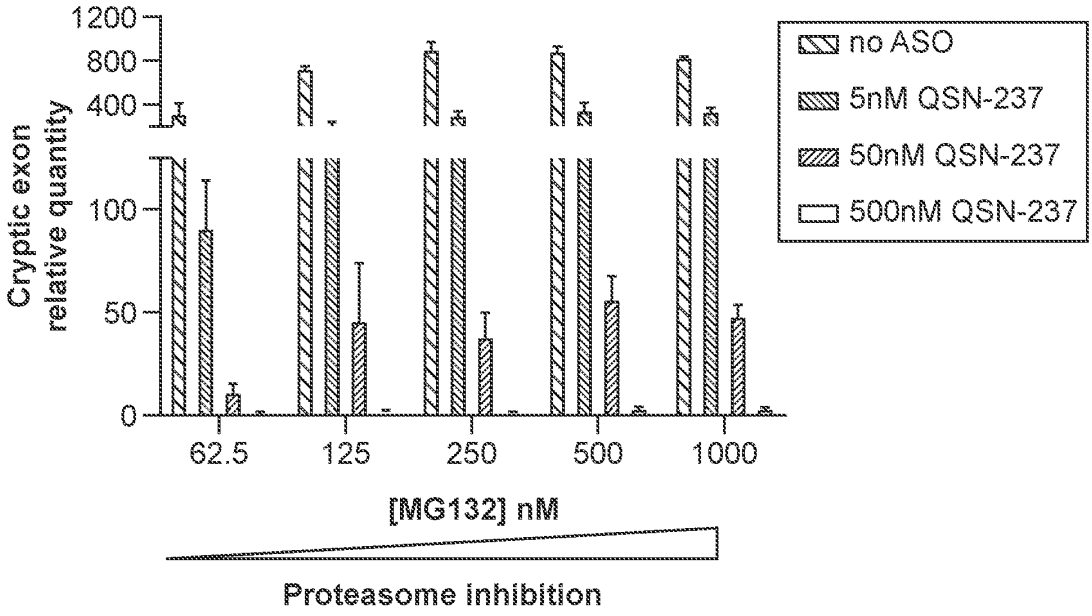

1200
800
400
100
50
0
Cryptic exon
relative quantity
62.5
125
250
500
1000
[MG132] nM
Proteasome inhibition
no ASO
5nM QSN-237
50nM QSN-237
500nM QSN-237

FIG. 30

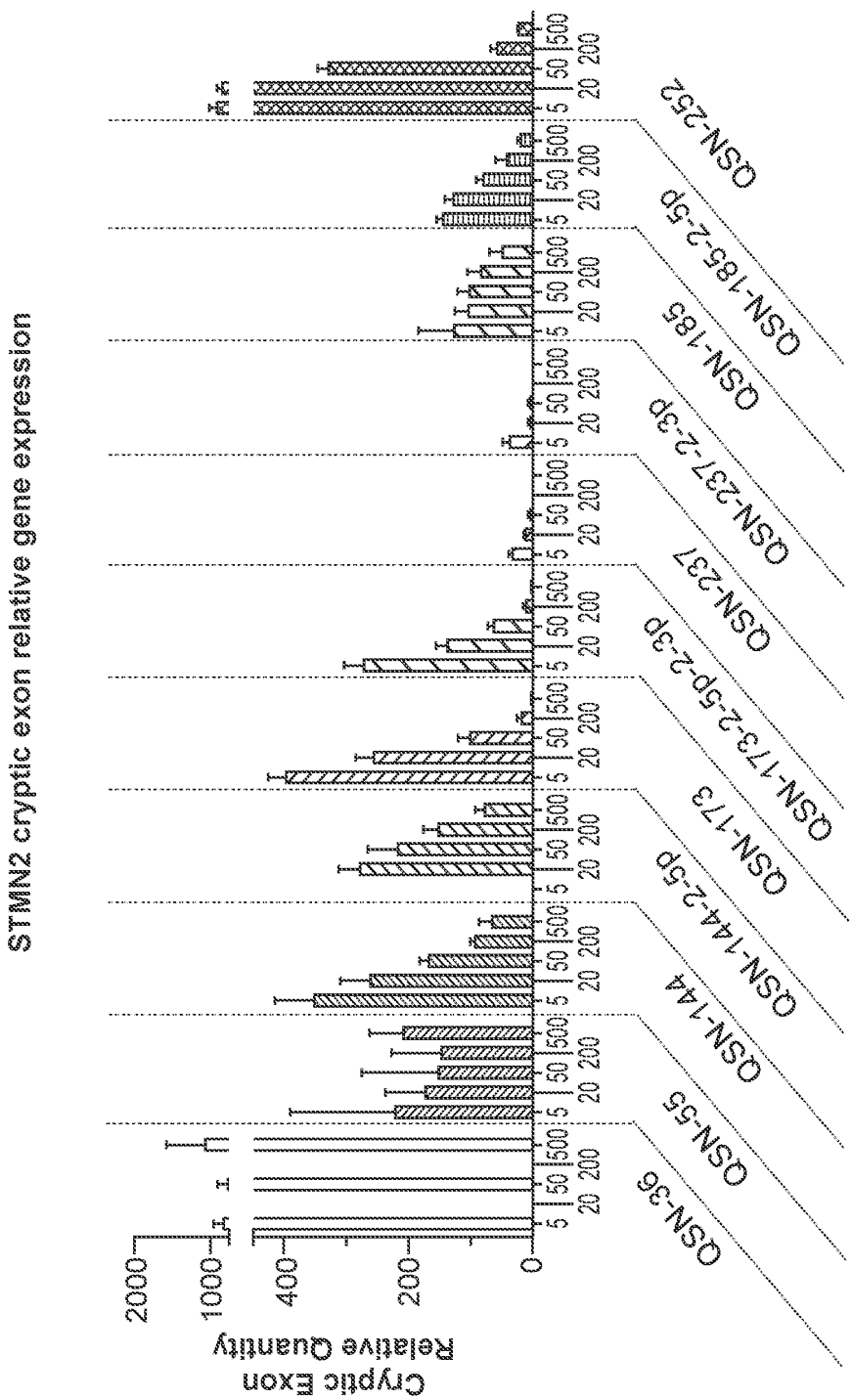

STMN2 cryptic exon relative gene expression
Cryptic Exon Relative Quantity
2000
1000
400
200
0
5
50
500
20
200
GSN-36
GSN-55
GSN-144
GSN-144-2-5p
GSN-173
GSN-173-2-5p-2-3p
GSN-237
GSN-237-2-3p
GSN-185
GSN-185-2-5p
GSN-252

FIG. 31A

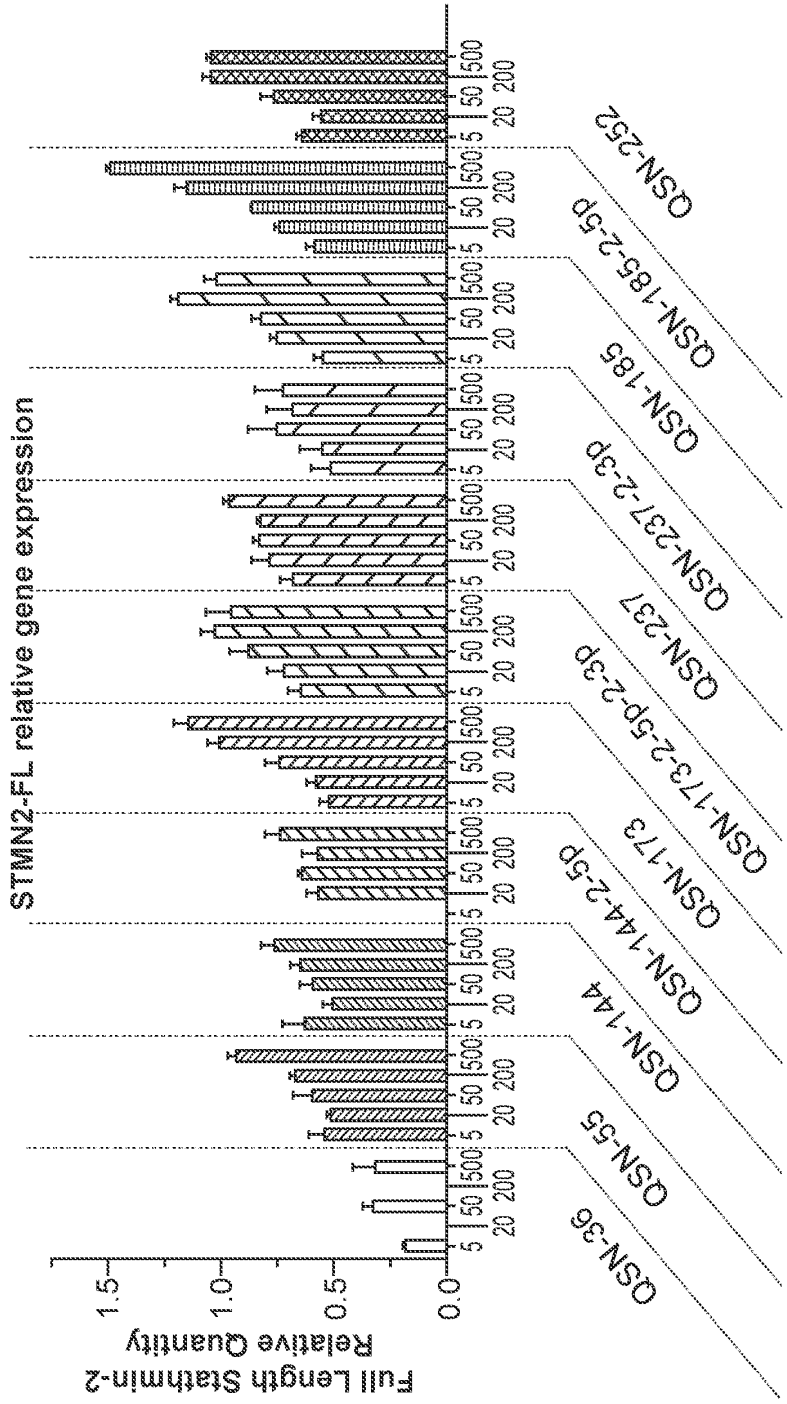

STMN2-FL relative gene expression
Full Length Stathmin-2
Relative Quantity
0.0
0.5
1.0
1.5
5
50
500
5
50
500
20
200
OSN-36
OSN-55
OSN-144
OSN-144-2-5p
OSN-173
OSN-173-2-5p-2-3p
OSN-237
OSN-237-2-3p
OSN-185
OSN-185-2-5p
OSN-252

FIG. 31B

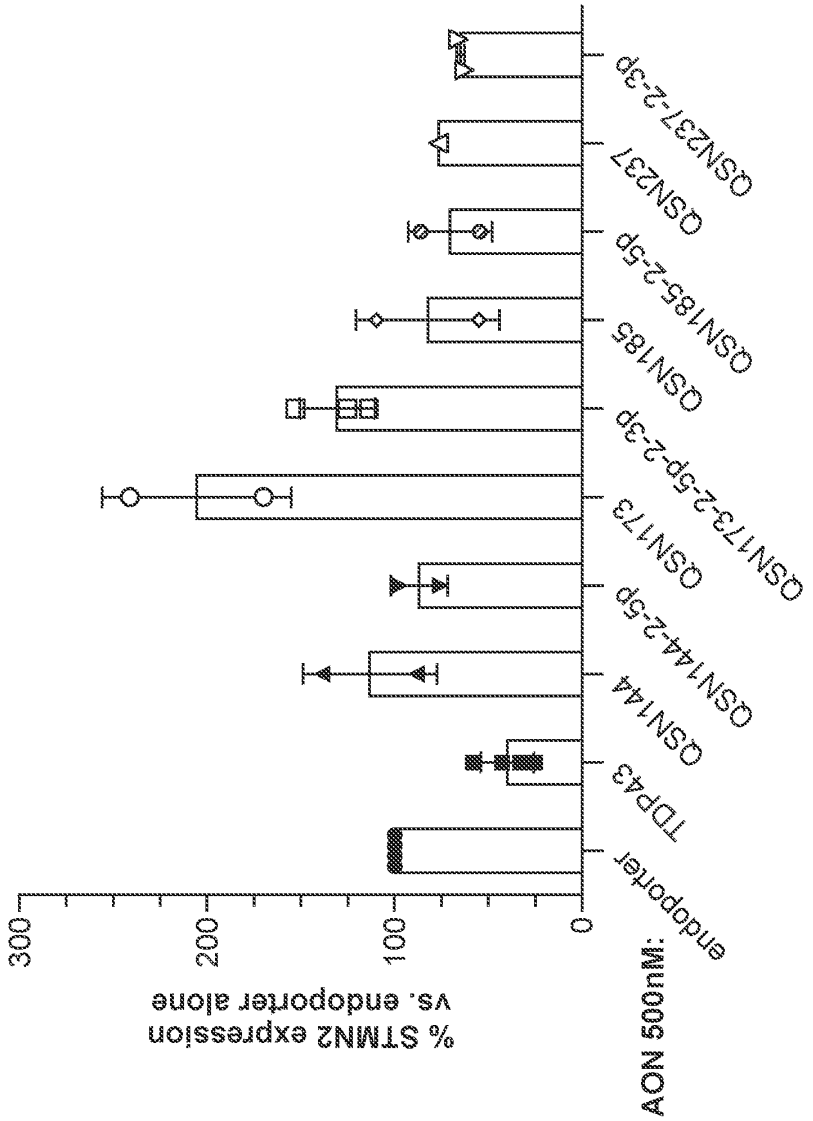

% STMN2 expression
vs. endoporter alone
300
200
100
0
AON 500nM:
endoporter
TDP43
QSN144
QSN144-2-5p
QSN173
QSN173-2-5p-2-3p
QSN185
QSN185-2-5p
QSN237
QSN237-2-3p

FIG. 32

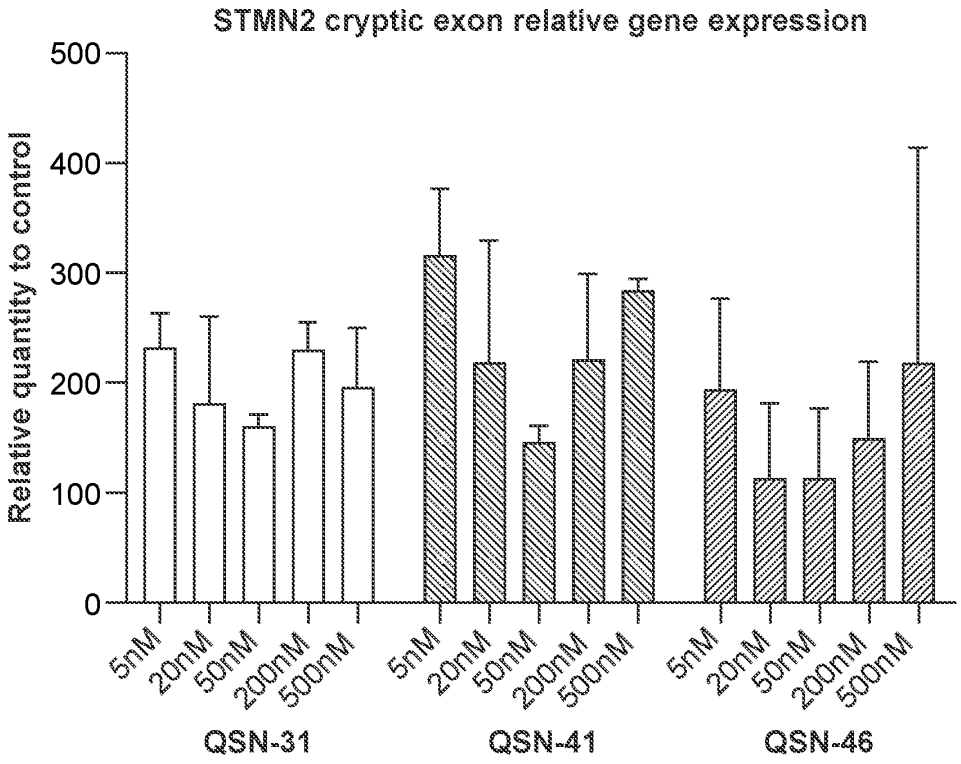

STMN2 cryptic exon relative gene expression
Relative quantity to control
500
400
300
200
100
0
5nM
20nM
50nM
200nM
500nM
QSN-31
QSN-41
QSN-46

FIG. 33A

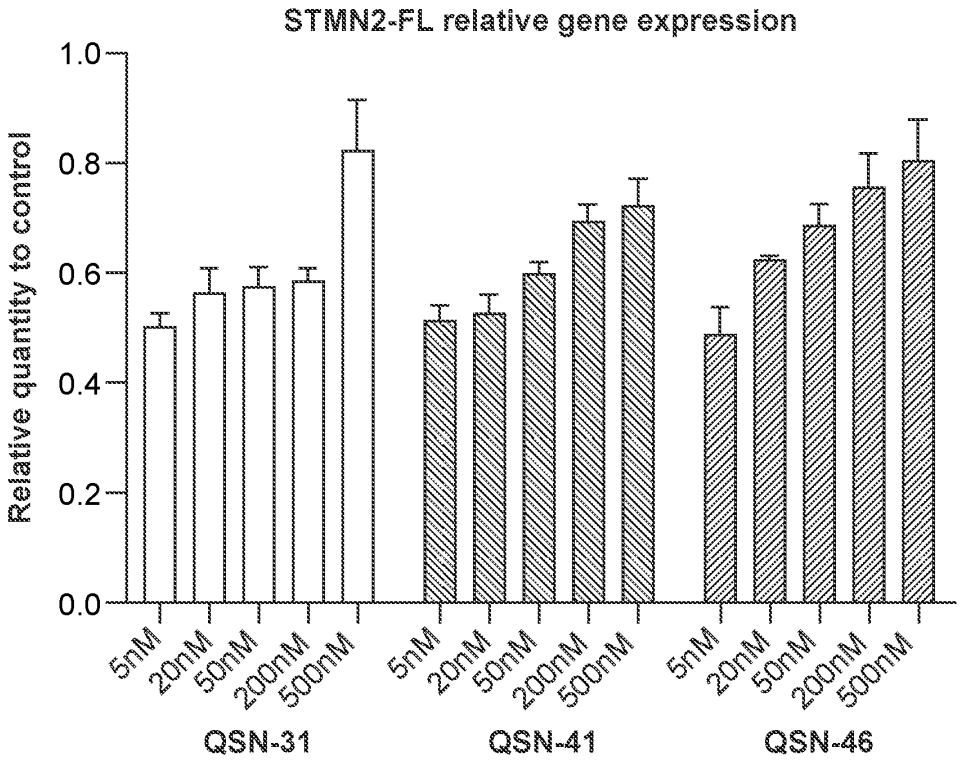

STMN2-FL relative gene expression
Relative quantity to control
1.0
0.8
0.6
0.4
0.2
0.0
5nM
20nM
50nM
200nM
500nM
QSN-31
QSN-41
QSN-46

FIG. 33B

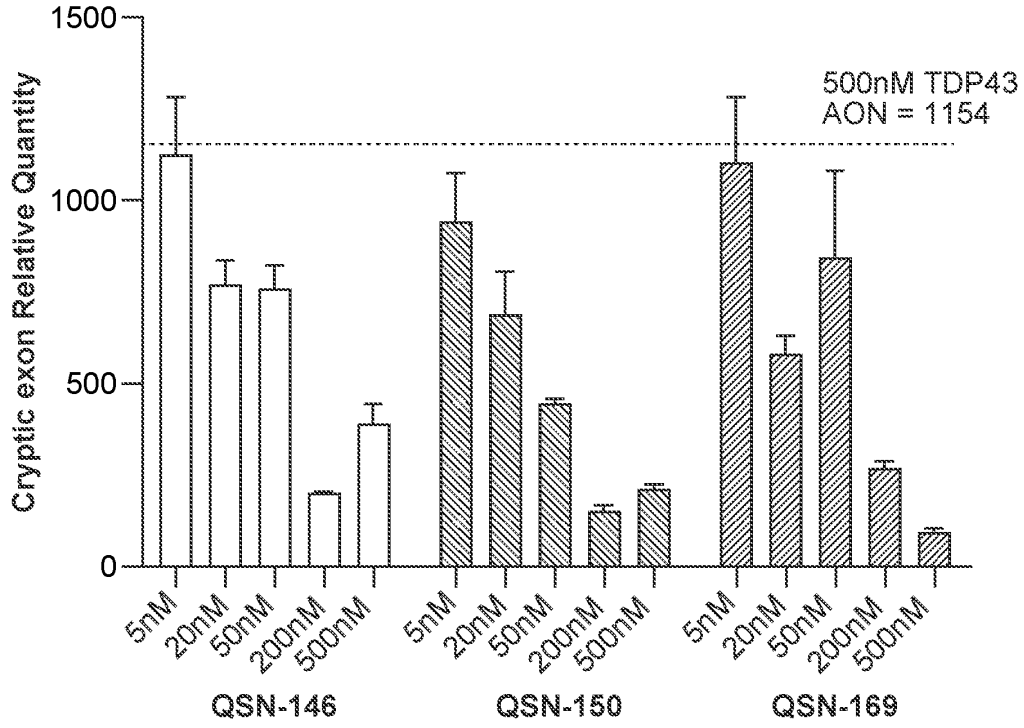

1500
1000
500
0
Cryptic exon Relative Quantity
500nM TDP43
AON = 1154
5nM
20nM
50nM
200nM
500nM
QSN-146
QSN-150
QSN-169

FIG. 34A

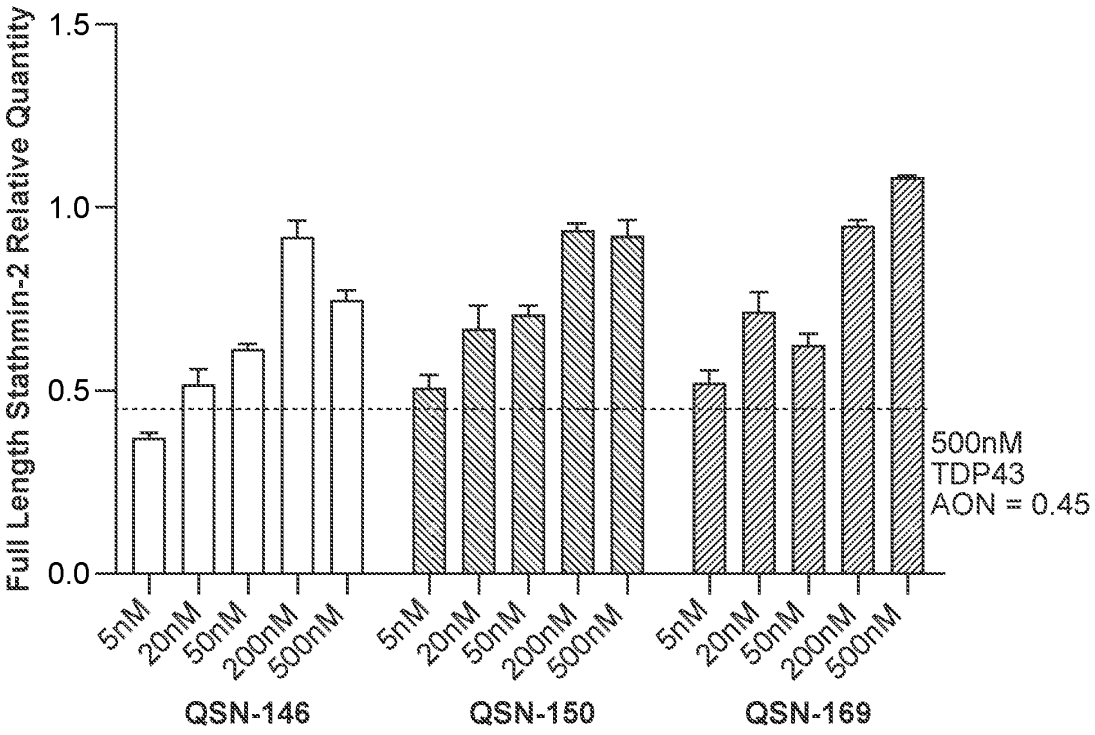

Full Length Stathmin-2 Relative Quantity
1.5
1.0
0.5
0.0
500nM
TDP43
AON = 0.45
5nM
20nM
50nM
200nM
500nM
QSN-146
QSN-150
QSN-169

FIG. 34B

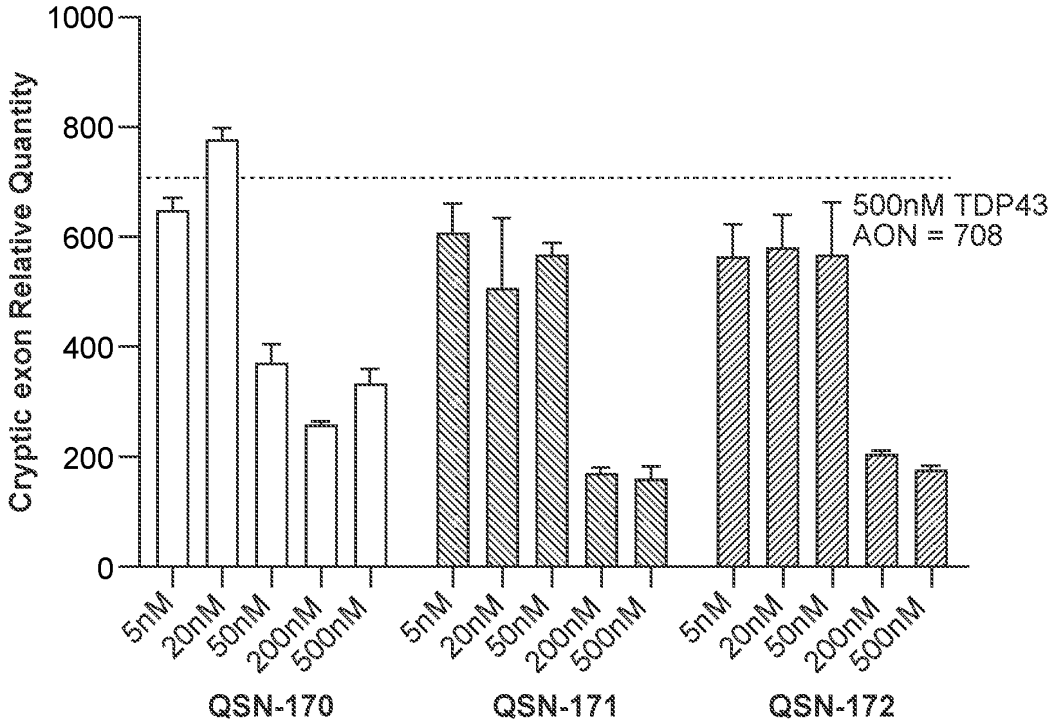

Cryptic exon Relative Quantity
1000
800
600
400
200
0
500nM TDP43
AON = 708
5nM
20nM
50nM
200nM
500nM
QSN-170
QSN-171
QSN-172

FIG. 34C

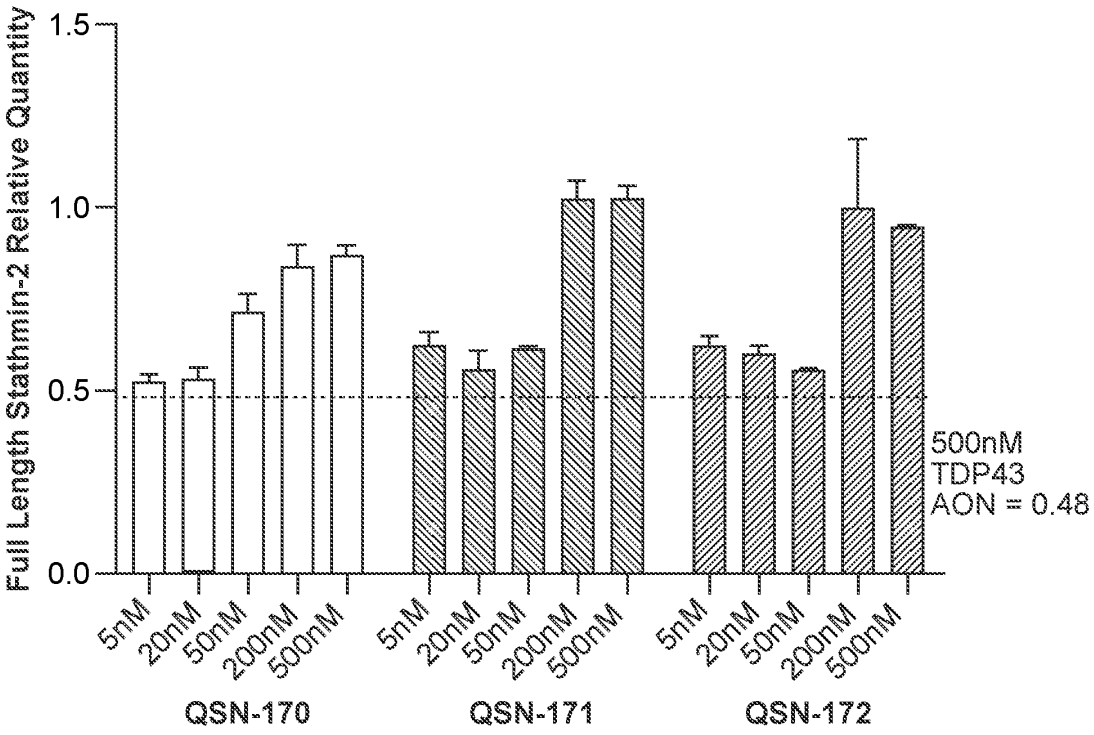

Full Length Stathmin-2 Relative Quantity
1.5
1.0
0.5
0.0
500nM
TDP43
AON = 0.48
5nM
20nM
50nM
200nM
500nM
QSN-170
QSN-171
QSN-172

FIG. 34D

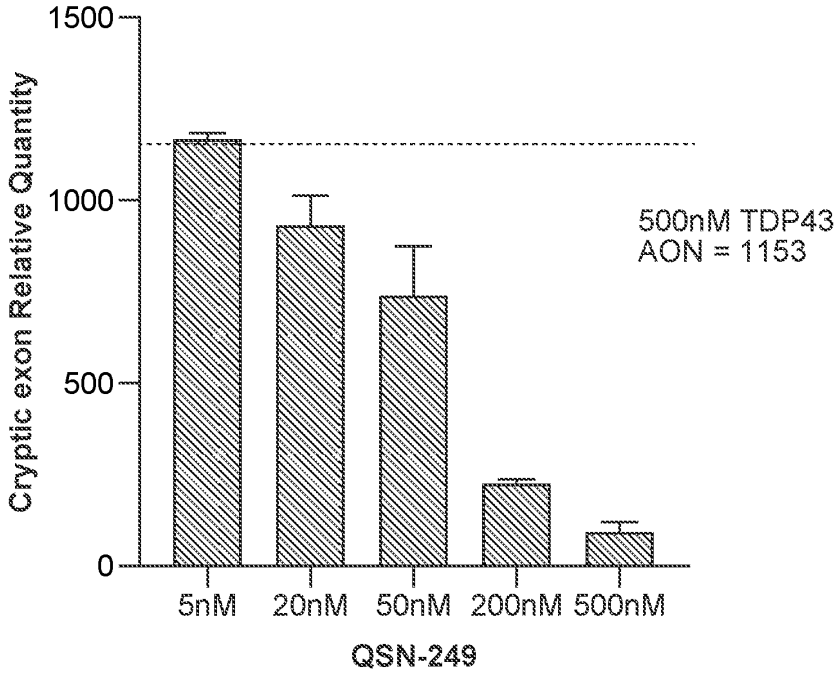

1500
1000
500
0
Cryptic exon Relative Quantity
500nM TDP43
AON = 1153
5nM
20nM
50nM
200nM
500nM
QSN-249

FIG. 34E

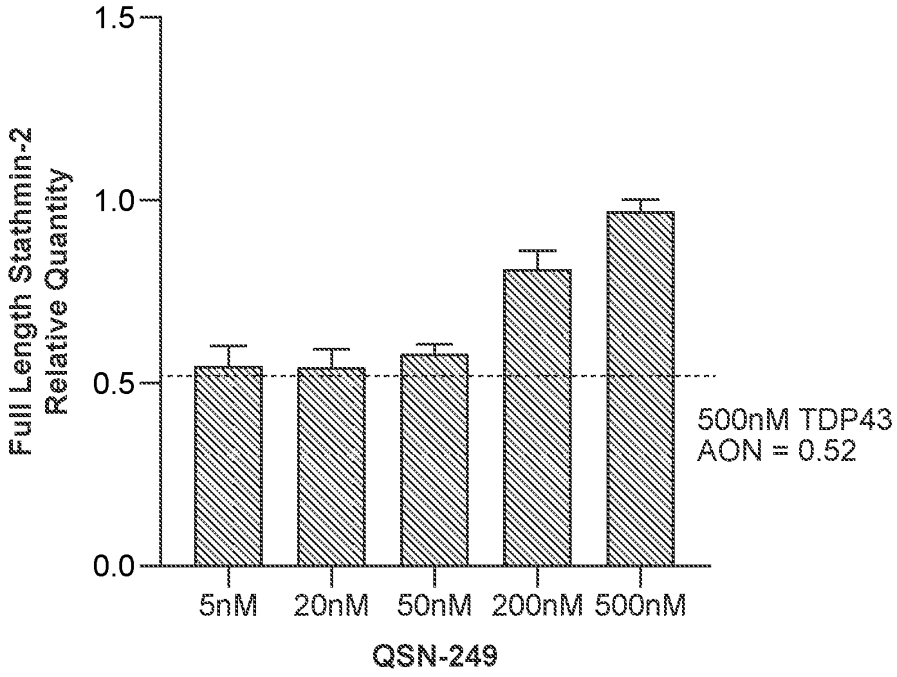

1.5
1.0
0.5
0.0
Full Length Stathmin-2
Relative Quantity
500nM TDP43
AON = 0.52
5nM
20nM
50nM
200nM
500nM
QSN-249

FIG. 34F