FIG. 1

Comparisons of framework regions of light chain of antibody hTNF40 and human group 1 consensus sequences

Hu group 1 consensus : DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 83)

hTNF40 : DIVMTQSQKFMSTSVGDRVSVTC (SEQ ID NO: 84)

Hu Group 1 consensus : WYQQKPGKAPKLLIY (SEQ ID NO: 85)

hTNF40 : WYQQKPGQSPKALIY (SEQ ID NO: 86)

Hu Group 1 consensus : GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 87)

hTNF40 : GVPYRFTGSGSGTDFTLTISTVQSEDLAEYFC (SEQ ID NO: 88)

Hu Group 1 consensus : FGQGTKVEIKR (SEQ ID NO: 89)

hTNF40 : FGAGTKLELKR (SEQ ID NO: 90)

FIG. 3 Sequence of CDRs of hTNF40

H1 DYGMN (SEQ ID NO:1)

H2 WINTYIGEPIYVDDFKG (SEQ ID NO:7)

H2'WINTYIGEPIYADSVKG (SEQ ID NO:2)

H3 GYRSYAMDY (SEQ ID NO:3)

L1 KASQNVGTNVA (SEQ ID NO:4)

L2 SASFLYS (SEQ ID NO:5)

L3 QQYNIYPLT (SEQ ID NO:6)

FIG. 2

Comparisons of framework regions of heavy chain of antibody hTNF40 and human group 1 and group 3 consensus sequences

Hu Group 1 consensus	: QVQLVQSGAEVKKPGASVKVSCKASGYTFT	(SEQ ID NO: 91)
hTNF40	: QIQLVQSGPELKKPGETVKISCKASGYVFT	(SEQ ID NO: 92)
Hu Group 1 consensus	: WVRQAPGQGLEWMG	(SEQ ID NO: 93)
hTNF40	: WVKQAPGKAFKWMG	(SEQ ID NO: 94)
Hu Group 1 consensus	:RVTITRDTSTSTAYMELSSLRSEDTAVYYCAR	(SEQ ID NO: 95)
hTNF40	:RFAFSLETSASTAFLQINNLKNEDTATYFCAR	(SEQ ID NO: 96)
Hu Group 1 consensus	: WGQGTLVTVSS	(SEQ ID NO: 97)
hTNF40	: WGQGTTLTVSS	(SEQ ID NO: 98)
Hu Group 3 consensus	: EVQLVESGGGLVQPGGSLRLSCAASGFTFS	(SEQ ID NO: 106)
hTNF40	: QIQLVQSGPELKKPGETVKISCKASGYVFT	(SEQ ID NO: 92)
Hu Group 3 consensus	: WVRQAPGKGLEWVS	(SEQ ID NO: 107)
hTNF40	: WVKQAPGKAFKWMG	(SEQ ID NO: 94)
Hu Group 3 consensus	:RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	(SEQ ID NO: 108)
hTNF40	:RFAFSLETSASTAFLQINNLKNEDTATYFCAR	(SEQ ID NO: 96)
Hu Group 3 consensus	: WGQGTLVTVSS	(SEQ ID NO: 109)
hTNF40	: WGQGTTLTVSS	(SEQ ID NO: 98)

FIG. 4

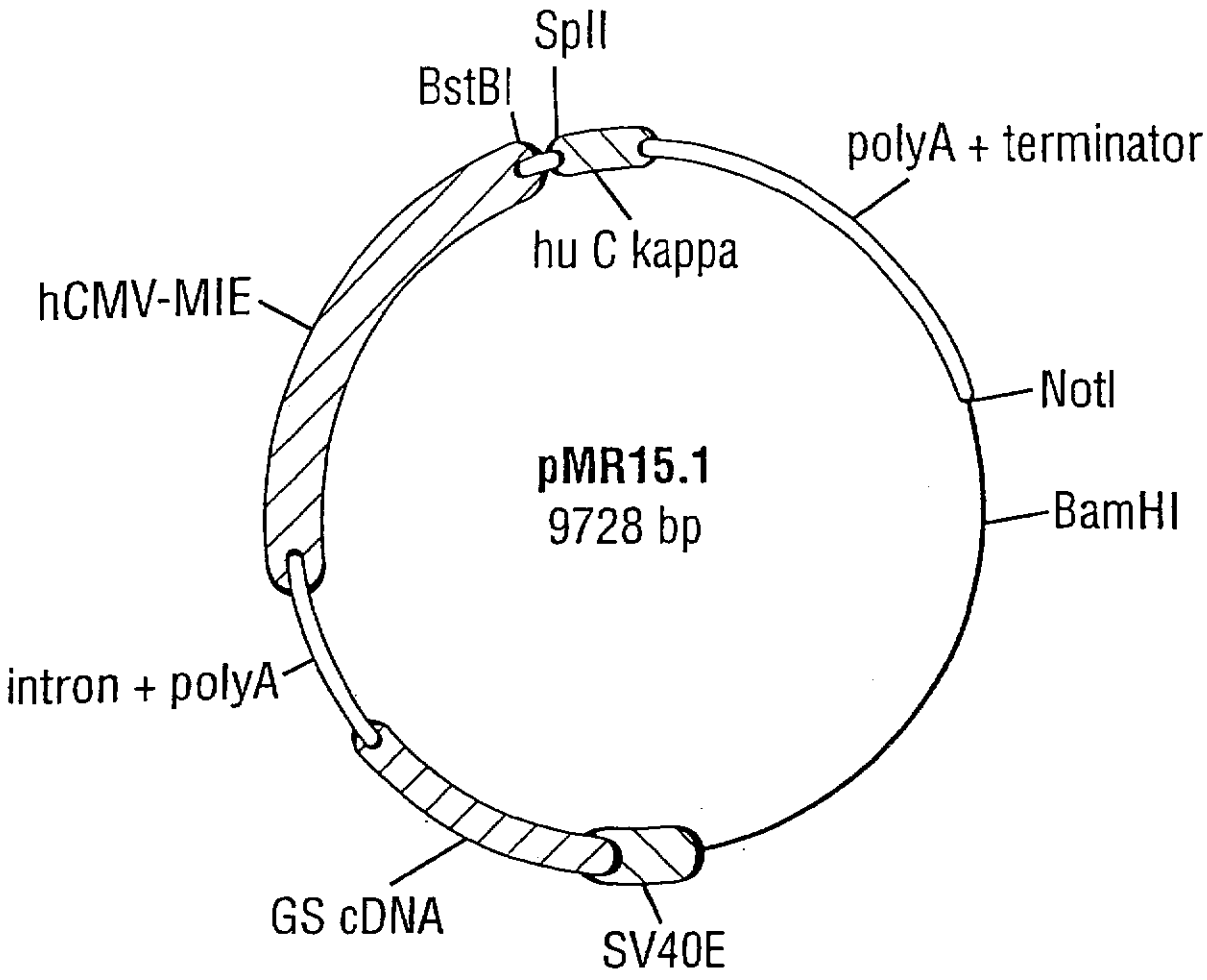

SpII
BstBI
polyA + terminator
hu C kappa
hCMV-MIE
NotI
pMR15.1
9728 bp
BamHI
intron + polyA
GS cDNA
SV40E

FIG. 5

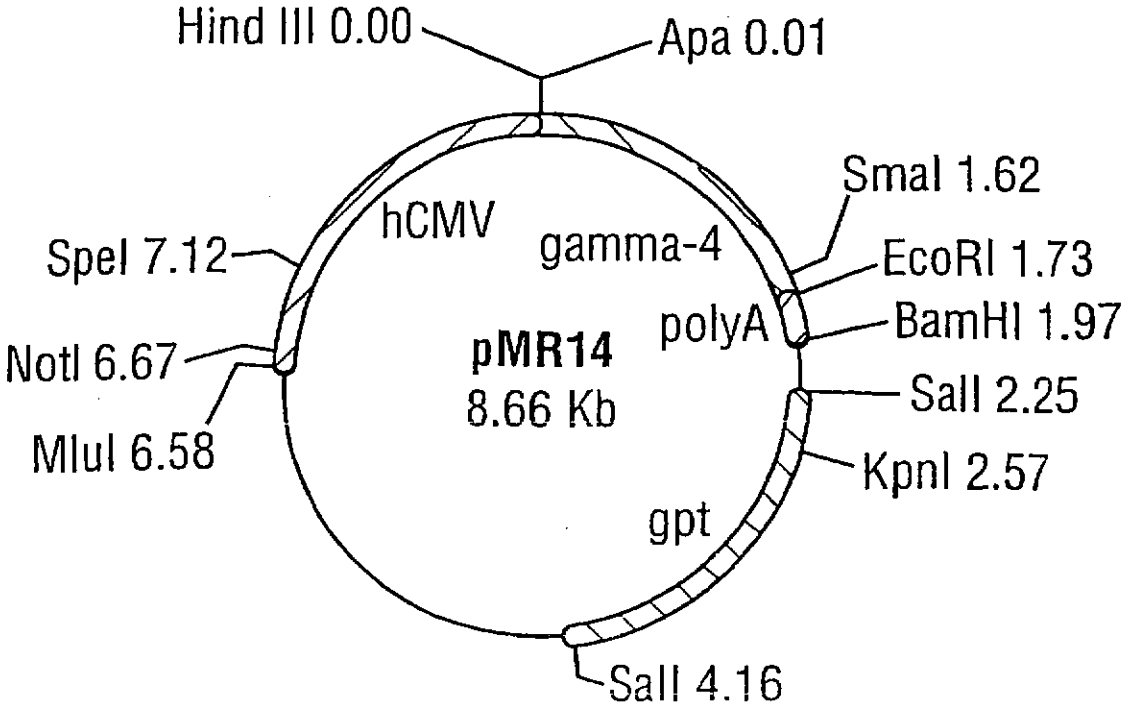

Hind III 0.00
Apa 0.01
SmaI 1.62
hCMV
gamma-4
SpeI 7.12
EcoRI 1.73
polyA
BamHI 1.97
NotI 6.67
pMR14
8.66 Kb
SalI 2.25
MluI 6.58
KpnI 2.57
gpt
SalI 4.16

FIG. 6 Murine VI Sequence of hTNF40 (SEQ ID NO: 99)

```
                10                  20                  30                  40                  50
GAC ATT GTG ATG ACC CAG TCT CAA AAA TTC ATG TCC ACA TCA GTA GGA GAC AGG
CTG TAA CAC TAC TGG GTC AGA GTT TTT AAG TAC AGG TGT AGT CAT CCT CTG TCC
 D   I   V   M   T   Q   S   Q   K   F   M   S   T   S   V   G   D   R>

      60                  70                  80                  90                  100
GTC AGC GTC ACC TGC AAG GCC AGT CAG AAT GTG GGT ACT AAT GTA GCC TGG TAT
CAG TCG CAG TGG ACG TTC CGG TCA GTC TTA CAC CCA TGA TTA CAT CGG ACC ATA
 V   S   V   T   C   K   A   S   Q   N   V   G   T   N   V   A   W   Y>

110                 120                 130                 140                 150                 160
CAA CAG AAA CCA GGA CAA TCT CCT AAA GCA CTG ATT TAC TCG GCA TCC TTC CTA
GTT GTC TTT GGT CCT GTT AGA GGA TTT CGT GAC TAA ATG AGC CGT AGG AAG GAT
 Q   Q   K   P   G   Q   S   P   K   A   L   I   Y   S   A   S   F   L>

        170                 180                 190                 200                 210
TAT AGT GGA GTC CCT TAT CGC TTC ACA GGC AGT GGA TCT GGG ACA GAT TTC ACT
ATA TCA CCT CAG GGA ATA GCG AAG TGT CCG TCA CCT AGA CCC TGT CTA AAG TGA
 Y   S   G   V   P   Y   R   F   T   G   S   G   S   G   T   D   F   T>

   220                 230                 240                 250                 260                 270
CTC ACC ATC AGC ACT GTG CAG TCT GAA GAC TTG GCA GAG TAT TTC TGT CAG CAA
GAG TGG TAG TCG TGA CAC GTC AGA CTT CTG AAC CGT CTC ATA AAG ACA GTC GTT
 L   T   I   S   T   V   Q   S   E   D   L   A   E   Y   F   C   Q   Q>

            280                 290                 300                 310                 320
TAT AAC ATC TAT CCT CTC ACG TTC GGT GCT GGG ACC AAG CTG GAG CTG AAA CGT
ATA TTG TAG ATA GGA GAG TGC AAG CCA CGA CCC TGG TTC GAC CTC GAC TTT GCA
 Y   N   I   Y   P   L   T   F   G   A   G   T   K   L   E   L   K   R>
```


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FIG. 7 Murine Vh Sequence of hTNF40 (SEQ ID NO: 100)

```
            10                  20                  30                  40                  50
CAG ATC CAG TTG GTG CAG TCT GGA CCT GAG CTG AAG AAG CCT GGA GAG ACA GTC
GTC TAG GTC AAC CAC GTC AGA CCT GGA CTC GAC TTC TTC GGA CCT CTC TGT CAG
 Q   I   Q   L   V   Q   S   G   P   E   L   K   K   P   G   E   T   V>

     60                  70                  80                  90                  100
AAG ATC TCC TGC AAG GCT TCT GGA TAT GTT TTC ACA GAC TAT GGA ATG AAT TGG
TTC TAG AGG ACG TTC CGA AGA CCT ATA CAA AAG TGT CTG ATA CCT TAC TTA ACC
 K   I   S   C   K   A   S   G   Y   V   F   T   D   Y   G   M   N   W>

110                 120                 130                 140                 150                 160
GTG AAG CAG GCT CCA GGA AAG GCT TTC AAG TGG ATG GGC TGG ATA AAC ACC TAC
CAC TTC GTC CGA GGT CCT TTC CGA AAG TTC ACC TAC CCG ACC TAT TTG TGG ATG
 V   K   Q   A   P   G   K   A   F   K   W   M   G   W   I   N   T   Y>

         170                 180                 190                 200                 210
ATT GGA GAG CCA ATA TAT GTT GAT GAC TTC AAG GGA CGA TTT GCC TTC TCT TTG
TAA CCT CTC GGT TAT ATA CAA CTA CTG AAG TTC CCT GCT AAA CGG AAG AGA AAC
 I   G   E   P   I   Y   V   D   D   F   K   G   R   F   A   F   S   L>

   220                 230                 240                 250                 260                 270
GAA ACC TCT GCC AGC ACT GCC TTT TTG CAG ATC AAC AAC CTC AAA AAT GAG GAC
CTT TGG AGA CGG TCG TGA CGG AAA AAC GTC TAG TTG TTG GAG TTT TTA CTC CTG
 E   T   S   A   S   T   A   F   L   Q   I   N   N   L   K   N   E   D>

             280                 290                 300                 310                 320
ACG GCT ACA TAT TTC TGT GCA AGA GGT TAC CGG TCC TAT GCT ATG GAC TAC TGG
TGC CGA TGT ATA AAG ACA CGT TCT CCA ATG GCC AGG ATA CGA TAC CTG ATG ACC
 T   A   T   Y   F   C   A   R   G   Y   R   S   Y   A   M   D   Y   W>

     330                 340                 350
GGT CAA GGA ACC TCA GTC ACC GTC TCT TCA
CCA GTT CCT TGG AGT CAG TGG CAG AGA AGT
 G   Q   G   T   S   V   T   V   S   S>
```


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FIG. 8 Grafted VI Sequence of hTNF40 (SEQ ID NO: 8)

```
          10                  20                  30                  40                  50
GAC ATT CAA ATG ACC CAG AGC CCA TCC AGC CTG AGC GCA TCT GTA GGA GAC CGG
CTG TAA GTT TAC TGG GTC TCG GGT AGG TCG GAC TCG CGT AGA CAT CCT CTG GCC
 D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V   G   D   R>

     60                  70                  80                  90                  100
GTC ACC ATC ACT TGT AAA GCC AGT CAG AAC GTA GGT ACT AAC GTA GCC TGG TAT
CAG TGG TAG TGA ACA TTT CGG TCA GTC TTG CAT CCA TGA TTG CAT CGG ACC ATA
 V   T   I   T   C   K   A   S   Q   N   V   G   T   N   V   A   W   Y>

110                 120                 130                 140                 150                 160
CAG CAA AAA CCA GGT AAA GCC CCA AAA GCC CTC ATC TAC AGT GCC TCT TTC CTC
GTC GTT TTT GGT CCA TTT CGG GGT TTT CGG GAG TAG ATG TCA CGG AGA AAG GAG
 Q   Q   K   P   G   K   A   P   K   A   L   I   Y   S   A   S   F   L>

        170                 180                 190                 200                 210
TAT AGT GGT GTA CCA TAC AGG TTC AGC GGA TCC GGT AGT GGT ACT GAT TTC ACC
ATA TCA CCA CAT GGT ATG TCC AAG TCG CCT AGG CCA TCA CCA TGA CTA AAG TGG
 Y   S   G   V   P   Y   R   F   S   G   S   G   S   G   T   D   F   T>

   220                 230                 240                 250                 260                 270
CTC ACG ATC AGT AGC CTC CAG CCA GAA GAT TTC GCC ACT TAT TAC TGT CAA CAG
GAG TGC TAG TCA TCG GAG GTC GGT CTT CTA AAG CGG TGA ATA ATG ACA GTT GTC
 L   T   I   S   S   L   Q   P   E   D   F   A   T   Y   Y   C   Q   Q>

           280                 290                 300                 310                 320
TAT AAC ATC TAC CCA CTC ACA TTC GGT CAG GGT ACT AAA GTA GAA ATC AAA
ATA TTG TAG ATG GGT GAG TGT AAG CCA GTC CCA TGA TTT CAT CTT TAG TTT
 Y   N   I   Y   P   L   T   F   G   Q   G   T   K   V   E   I   K>
```


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FIG. 9 Grafted VI sequence of hTNF40 (SEQ ID NO: 9)

```
                10                  20                  30                  40                  50
GAC ATT CAA ATG ACC CAG AGC CCA TCC AGC CTG AGC GCA TCT GTA GGA GAC CGG
CTG TAA GTT TAC TGG GTC TCG GGT AGG TCG GAC TCG CGT AGA CAT CCT CTG GCC
 D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V   G   D   R>

      60                  70                  80                  90                  100
GTC ACC ATC ACT TGT AAA GCC AGT CAG AAC GTA GGT ACT AAC GTA GCC TGG TAT
CAG TGG TAG TGA ACA TTT CGG TCA GTC TTG CAT CCA TGA TTG CAT CGG ACC ATA
 V   T   I   T   C   K   A   S   Q   N   V   G   T   N   V   A   W   Y>

110                 120                 130                 140                 150                 160
CAG CAA AAA CCA GGT AAA GCC CCA AAA CTC CTC ATC TAC AGT GCC TCT TTC CTC
GTC GTT TTT GGT CCA TTT CGG GGT TTT GAG GAG TAG ATG TCA CGG AGA AAG GAG
 Q   Q   K   P   G   K   A   P   K   L   L   I   Y   S   A   S   F   L>

        170                 180                 190                 200                 210
TAT AGT GGT GTA CCA TAC AGG TTC AGC GGA TCC GGT AGT GGT ACT GAT TTC ACC
ATA TCA CCA CAT GGT ATG TCC AAG TCG CCT AGG CCA TCA CCA TGA CTA AAG TGG
 Y   S   G   V   P   Y   R   F   S   G   S   G   S   G   T   D   F   T>

   220                 230                 240                 250                 260                 270
CTC ACG ATC AGT AGC CTC CAG CCA GAA GAT TTC GCC ACT TAT TAC TGT CAA CAG
GAG TGC TAG TCA TCG GAG GTC GGT CTT CTA AAG CGG TGA ATA ATG ACA GTT GTC
 L   T   I   S   S   L   Q   P   E   D   F   A   T   Y   Y   C   Q   Q>

            280                 290                 300                 310                 320
TAT AAC ATC TAC CCA CTC ACA TTC GGT CAG GGT ACT AAA GTA GAA ATC AAA
ATA TTG TAG ATG GGT GAG TGT AAG CCA GTC CCA TGA TTT CAT CTT TAG TTT
 Y   N   I   Y   P   L   T   F   G   Q   G   T   K   V   E   I   K>
```


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FIG. 10 Grafted Vh sequence of hTNF40 (SEQ ID NO: 10)

```
      10                  20                  30                  40                  50
CAG GTG CAG CTG GTC CAG TCA GGA GCA GAG GTT AAG AAG CCT GGT GCT TCC GTC
GTC CAC GTC GAC CAG GTC AGT CCT CGT CTC CAA TTC TTC GGA CCA CGA AGG CAG
 Q   V   Q   L   V   Q   S   G   A   E   V   K   K   P   G   A   S   V>

      60                  70                  80                  90                  100
AAA GTT TCG TGT AAG GCC TCA GGC TAC GTG TTC ACA GAC TAT GGT ATG AAT TGG
TTT CAA AGC ACA TTC CGG AGT CCG ATG CAC AAG TGT CTG ATA CCA TAC TTA ACC
 K   V   S   C   K   A   S   G   Y   V   F   T   D   Y   G   M   N   W>

110                 120                 130                 140                 150                 160
GTC AGA CAG GCC CCG GGA CAA GGC CTG GAA TGG ATG GGT TGG ATT AAT ACT TAC
CAG TCT GTC CGG GGC CCT GTT CCG GAC CTT ACC TAC CCA ACC TAA TTA TGA ATG
 V   R   Q   A   P   G   Q   G   L   E   W   M   G   W   I   N   T   Y>

        170                 180                 190                 200                 210
ATT GGA GAG CCT ATT TAT GCT CAA AAG TTC CAG GGC AGA GTC ACG TTC ACT CTA
TAA CCT CTC GGA TAA ATA CGA GTT TTC AAG GTC CCG TCT CAG TGC AAG TGA GAT
 I   G   E   P   I   Y   A   Q   K   F   Q   G   R   V   T   F   T   L>

  220                 230                 240                 250                 260                 270
GAC ACC TCC ACA AGC ACT GCA TAC ATG GAG CTG TCA TCT CTG AGA TCC GAG GAC
CTG TGG AGG TGT TCG TGA CGT ATG TAC CTC GAC AGT AGA GAC TCT AGG CTC CTG
 D   T   S   T   S   T   A   Y   M   E   L   S   S   L   R   S   E   D>

          280                 290                 300                 310                 320
ACC GCA GTG TAC TAT TGT GCT AGA GGA TAC AGA TCT TAT GCC ATG GAC TAC TGG
TGG CGT CAC ATG ATA ACA CGA TCT CCT ATG TCT AGA ATA CGG TAC CTG ATG ACC
 T   A   V   Y   Y   C   A   R   G   Y   R   S   Y   A   M   D   Y   W>

    330                 340                 350
GGC CAG GGT ACC CTA GTC ACA GTC TCC TCA
CCG GTC CCA TGG GAT CAG TGT CAG AGG AGT
 G   Q   G   T   L   V   T   V   S   S>
```

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FIG. 11 Grafted Vh Sequence of hTNF40.4 (SEQ ID NO: 11)

```
           10          20          30          40          50
GAG GTT CAG CTG GTC GAG TCA GGA GGC GGT CTC GTG CAG CCT GGC GGA TCA CTG
CTC CAA GTC GAC CAG CTC AGT CCT CCG CCA GAG CAC GTC GGA CCG CCT AGT GAC
 E   V   Q   L   V   E   S   G   G   G   L   V   Q   P   G   G   S   L>

     60          70          80          90          100
AGA TTG TCC TGT GCT GCA TCT GGT TAC GTC TTC ACA GAC TAT GGA ATG AAT TGG
TCT AAC AGG ACA CGA CGT AGA CCA ATG CAG AAG TGT CTG ATA CCT TAC TTA ACC
 R   L   S   C   A   A   S   G   Y   V   F   T   D   Y   G   M   N   W>

110         120         130         140         150         160
GTT AGA CAG GCC CCG GGA AAG GGC CTG GAA TGG ATG GGT TGG ATT AAT ACT TAC
CAA TCT GTC CGG GGC CCT TTC CCG GAC CTT ACC TAC CCA ACC TAA TTA TGA ATG
 V   R   Q   A   P   G   K   G   L   E   W   M   G   W   I   N   T   Y>

       170         180         190         200         210
ATT GGA GAG CCT ATT TAT GCT GAC AGC GTC AAG GGC AGA TTC ACG TTC TCT CTA
TAA CCT CTC GGA TAA ATA CGA CTG TCG CAG TTC CCG TCT AAG TGC AAG AGA GAT
 I   G   E   P   I   Y   A   D   S   V   K   G   R   F   T   F   S   L>

  220         230         240         250         260         270
GAC ACA TCC AAG TCA ACA GCA TAC CTC CAA ATG AAT AGC CTG AGA GCA GAG GAC
CTG TGT AGG TTC AGT TGT CGT ATG GAG GTT TAC TTA TCG GAC TCT CGT CTC CTG
 D   T   S   K   S   T   A   Y   L   Q   M   N   S   L   R   A   E   D>

          280         290         300         310         320
ACC GCA GTG TAC TAT TGT GCT AGA GGA TAC AGA TCT TAT GCC ATG GAC TAC TGG
TGG CGT CAC ATG ATA ACA CGA TCT CCT ATG TCT AGA ATA CGG TAC CTG ATG ACC
 T   A   V   Y   Y   C   A   R   G   Y   R   S   Y   A   M   D   Y   W>

    330         340         350
GGC CAG GGT ACC CTA GTC ACA GTC TCC TCA
CCG GTC CCA TGG GAT CAG TGT CAG AGG AGT
 G   Q   G   T   L   V   T   V   S   S>
```


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FIG. 12

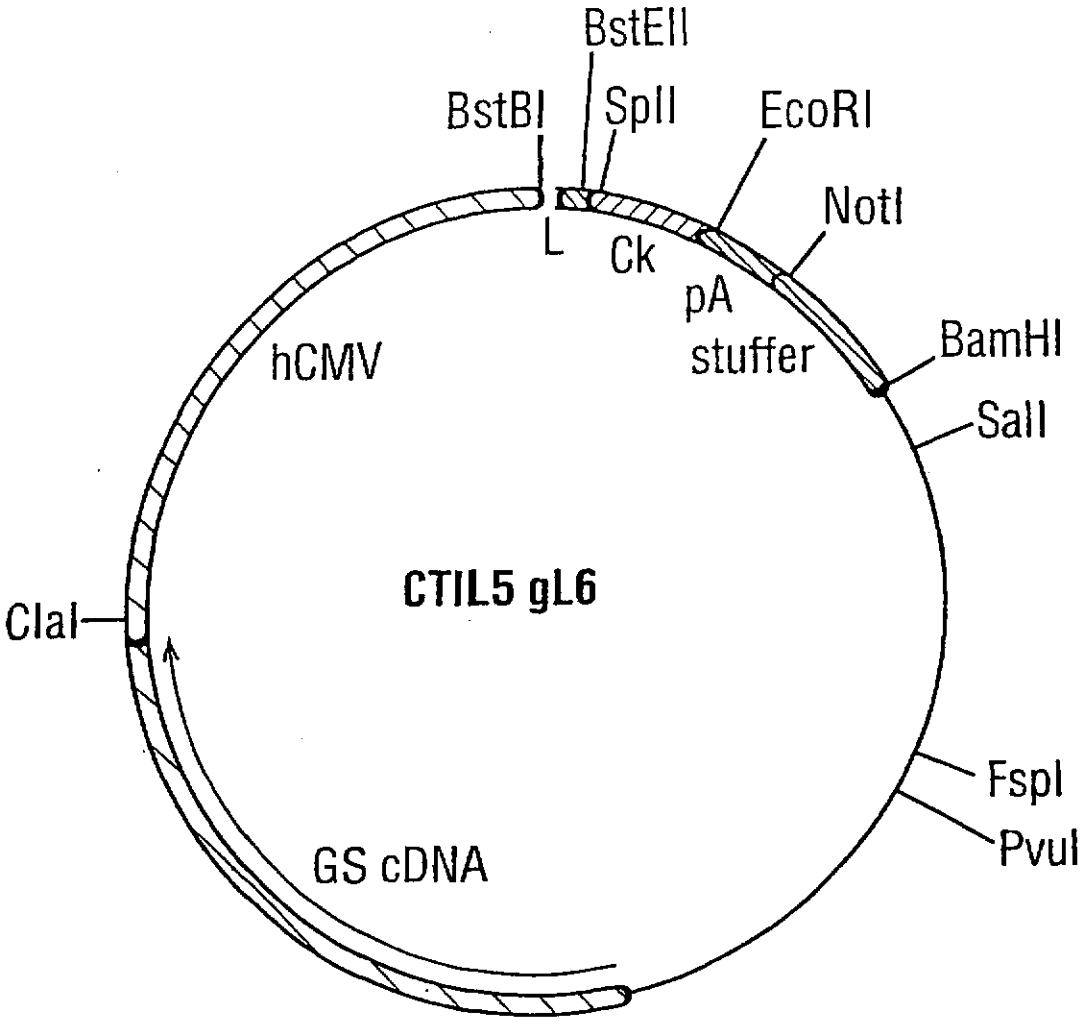

BstEII
BstBI
SpII
EcoRI
NotI
L
Ck
pA
stuffer
BamHI
SalI
hCMV
CTIL5 gL6
ClaI
FspI
PvuI
GS cDNA

FIG. 13

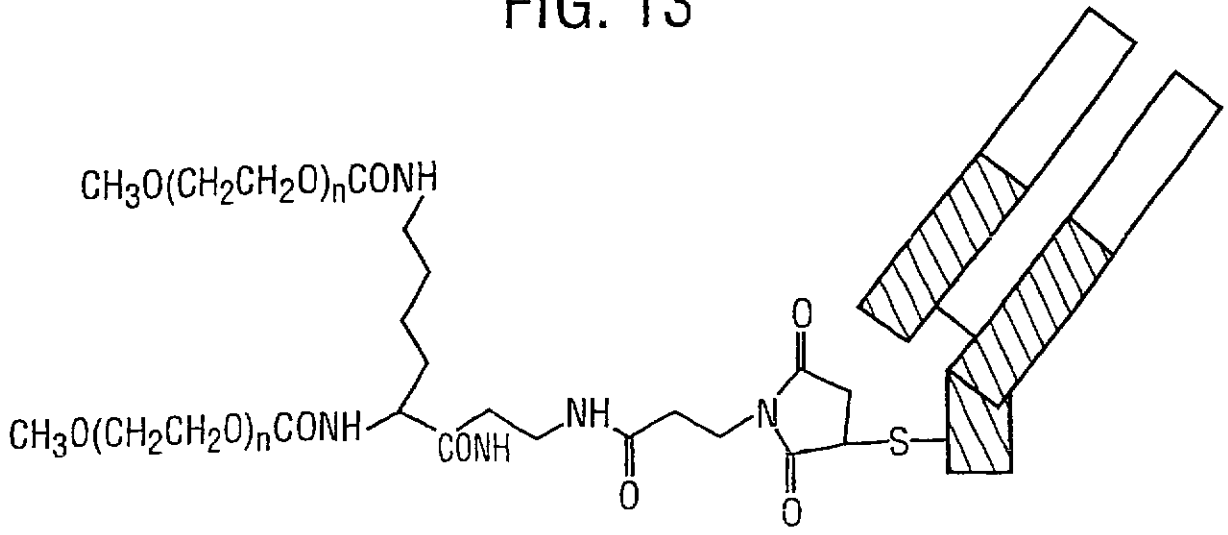

CH3O(CH2CH2O)nCONH
CH3O(CH2CH2O)nCONH
CONH
NH
O
O
N
O
S

FIG. 14

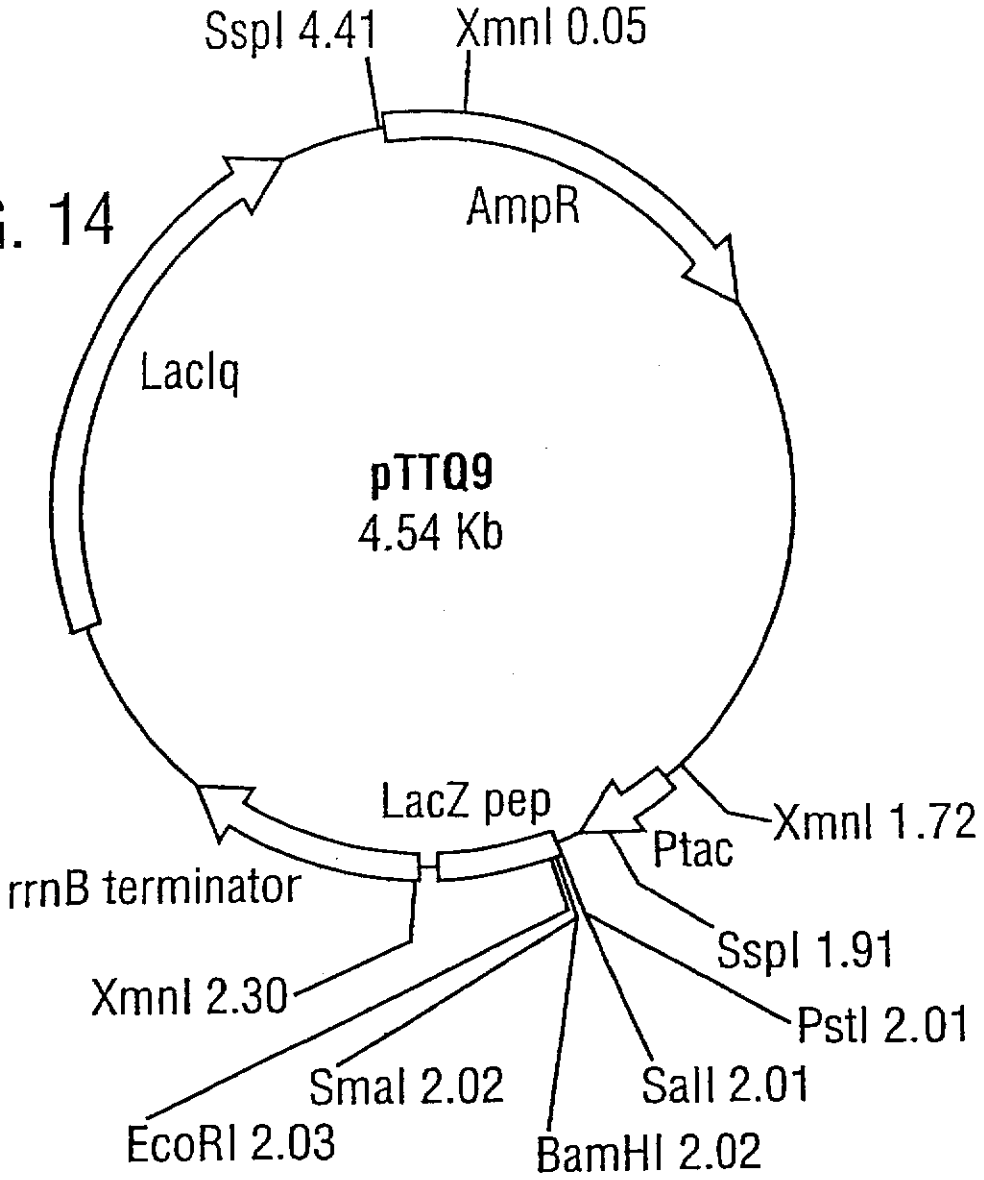

SspI 4.41
XmnI 0.05
AmpR
LacIq
pTTQ9
4.54 Kb
LacZ pep
Ptac
XmnI 1.72
rrnB terminator
SspI 1.91
XmnI 2.30
PstI 2.01
SmaI 2.02
SalI 2.01
EcoRI 2.03
BamHI 2.02

FIG. 16

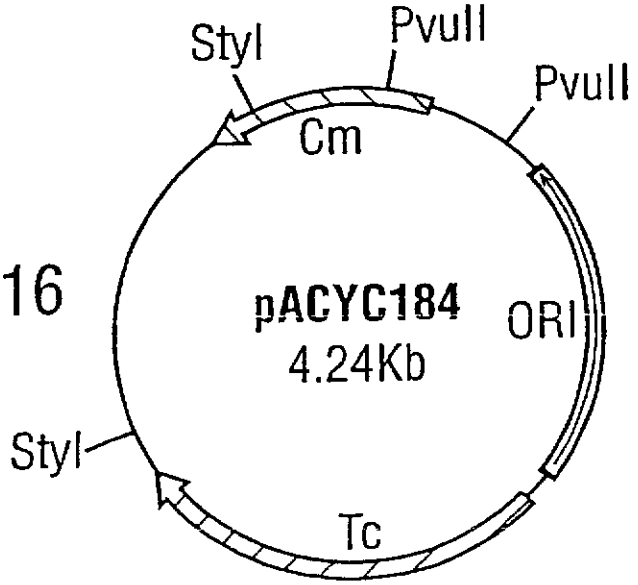
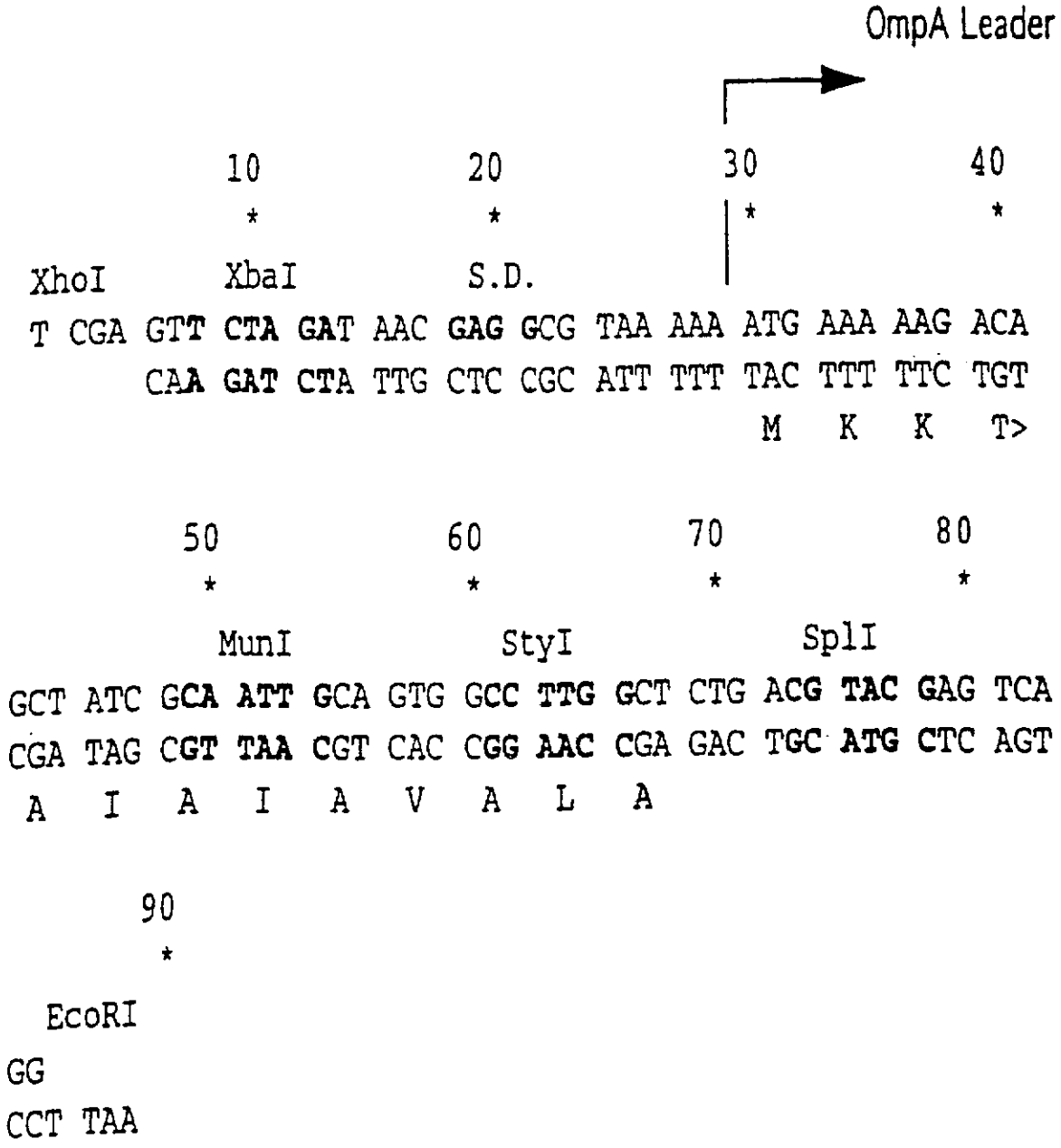

StyI
PvuII
PvuII
Cm
pACYC184
4.24Kb
ORI
StyI
Tc

FIG. 15

Sequence of OmpA Oligonucleotide Adapter (SEQ ID NO: 101)



- Internal restriction sites are shown in bold
- The 5' XhoI cohesive end ligates into the Vector SalI site, blocking it
- S.D. represents the OmpA Shine Dalgarno sequence

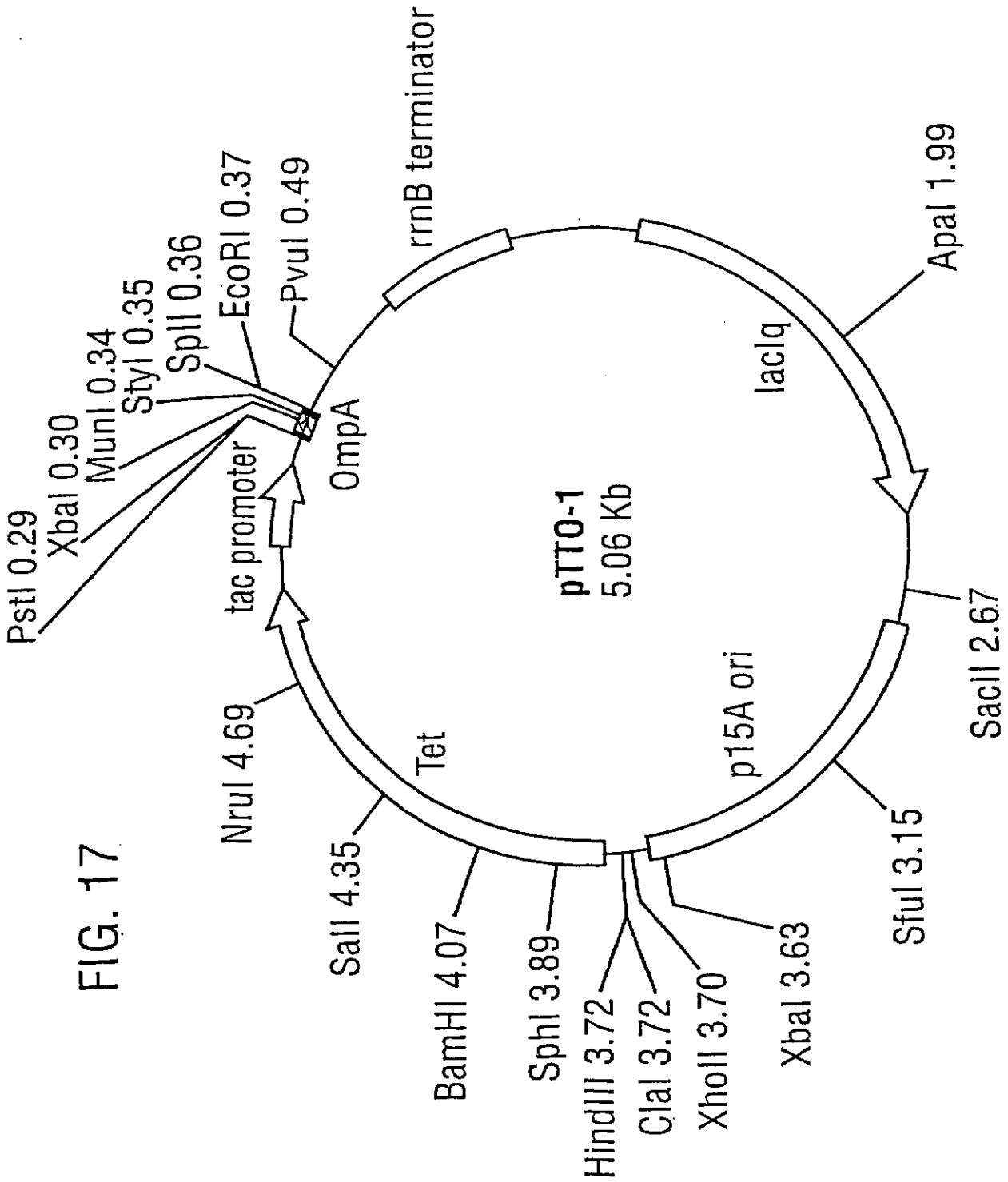

pTTO-1
5.06 Kb
rrnB terminator
ApaI 1.99
SacII 2.67
SfuI 3.15
XbaI 3.63
XhoII 3.70
ClaI 3.72
HindIII 3.72
SphI 3.89
BamHI 4.07
SalI 4.35
NruI 4.69
PstI 0.29
XbaI 0.30
MunI 0.34
StyI 0.35
SpII 0.36
EcoRI 0.37
PvuI 0.49
tac promoter
OmpA
lacIq
p15A ori
Tet

FIG. 17

FIG. 18

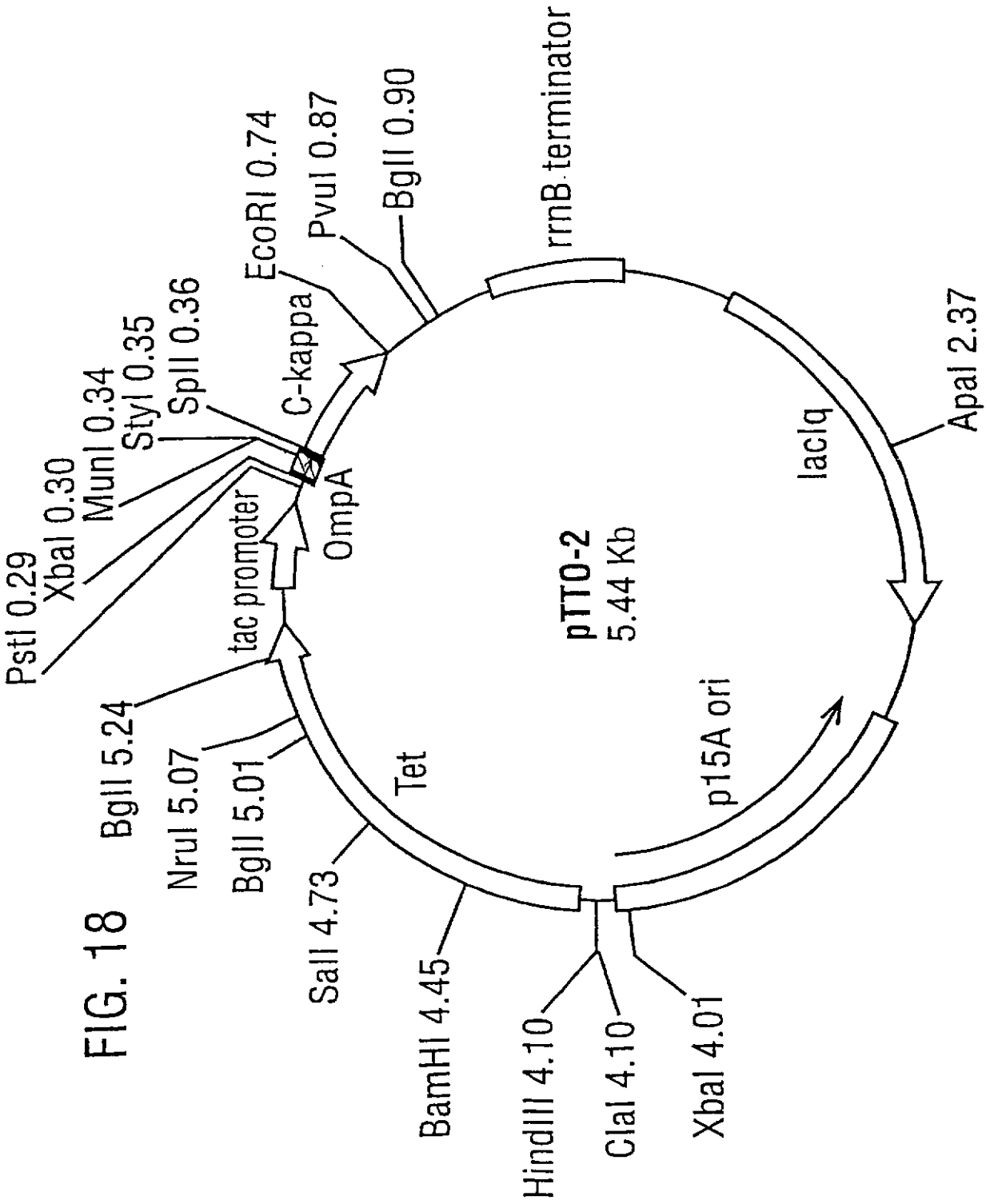

pTTO-2
5.44 Kb
rrnB terminator
EcoRI 0.74
PvuI 0.87
BglI 0.90
C-kappa
SpII 0.36
StyI 0.35
MunI 0.34
XbaI 0.30
PstI 0.29
tac promoter
OmpA
BglI 5.24
NruI 5.07
BglI 5.01
Tet
SalI 4.73
BamHI 4.45
HindIII 4.10
ClaI 4.10
XbaI 4.01
p15A ori
lacIq
ApaI 2.37

FIG. 19

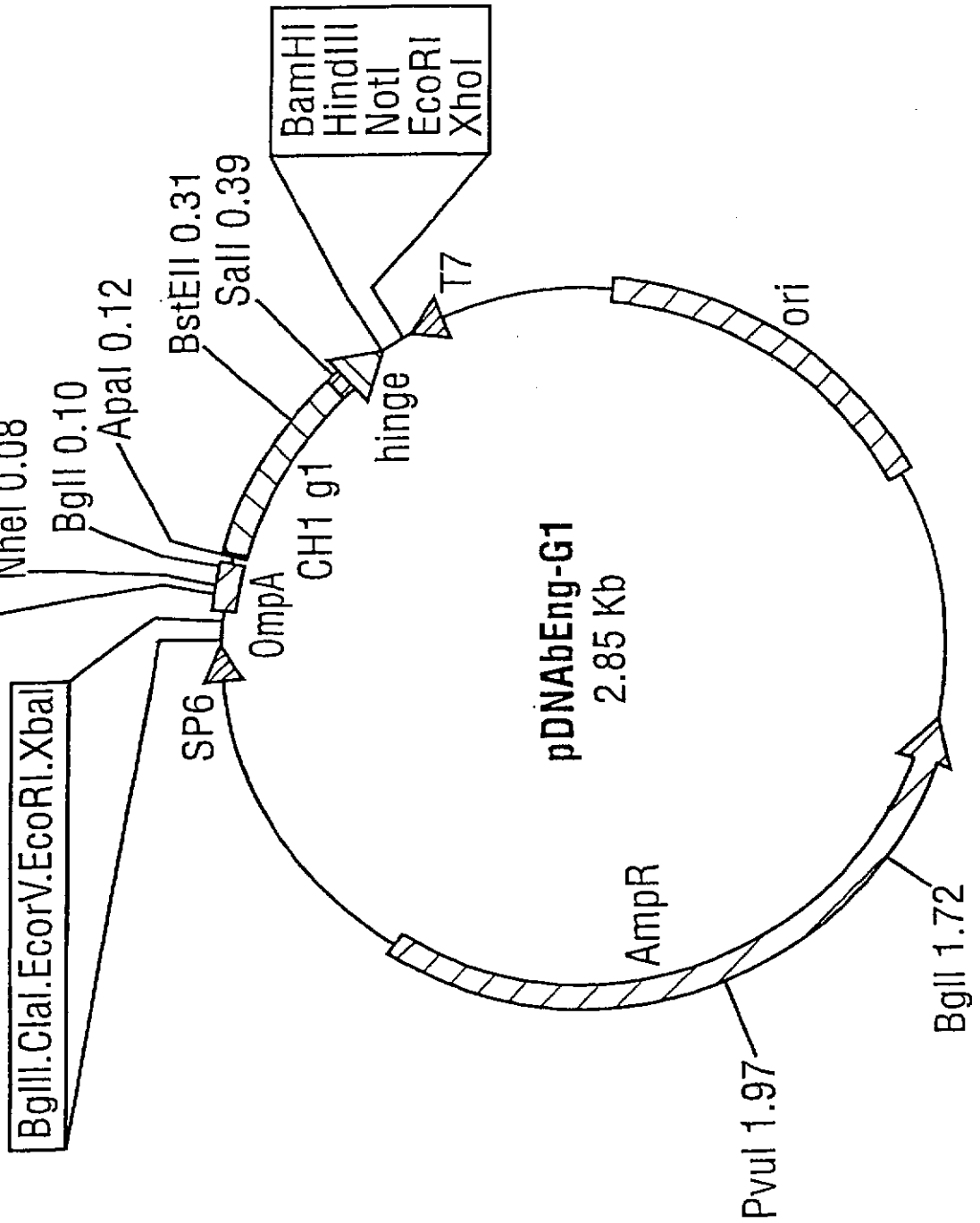

BamHI
HindIII
NotI
EcoRI
XhoI
BstEII 0.31
SalI 0.39
ApaI 0.12
BglI 0.10
NheI 0.08
MunI 0.07
BglII.ClaI.EcorV.EcoRI.XbaI
SP6
OmpA
CH1 g1
hinge
T7
ori
pDNAbEng-G1
2.85 Kb
AmpR
PvuI 1.97
BglI 1.72

FIG. 20 OLIGONUCLEOTIDE CASSETTES ENCODING DIFFERENT INTERGENIC SEQUENCES FOR E. Coli Fab' EXPRESSION

IGS CASSETTE-1; Intergenic space = -1

G,AGC,TCA,CCA,GTA,ACA,AAA,AGT,TTT,AAT,AGA,GGA,GAG,TGT,TAATG,AAG,AAG,ACT,GCT,ATA,GCA,ATT,G (SEQ ID No: 102)

S S P V T K S F N R G E C * M K K T A I A I

End of c-Kappa sequence -> *Start of OmpA sequence ->*

IGS CASSETTE-2; Intergenic space = +1

G,AGC,TCA,CCA,GTA,ACA,AAA,AGT,TTT,AAT,AGA,GGG,GAG,TGT,TAA AATG,AAG,AAG,ACT,GCT,ATA,GCA,ATT,G (SEQ ID No: 103)

S S P V T K S F N R G E C * M K K T A I A I

IGS CASSETTE-3; Intergenic space = +13

G,AGC,TCA,CCA,GTA,ACA,AAA,AGC,TTT,AAT,AGA,GGA,GAG,TGT,TGA GGAGGAAAAAAAAATG,AAG,AAA,ACT,GCT,ATA,GCA,ATT,G (SEQ ID No: 104)

S S P V T K S F N R G E C * M K K T A I A I

IGS CASSETTE-4; Intergenic space = +13

G,AGC,TCA,CCA,GTA,ACA,AAA,AGT,TTT,AAT,AGA,GGA,GAG,TGT,TGA CGAGGATTATATAATG,AAG,AAA,ACT,GCT,ATA,GCA,ATT,G (SEQ ID No: 105)

S S P V T K S F N R G E C * M K K T A I A I

2 DEC 2004

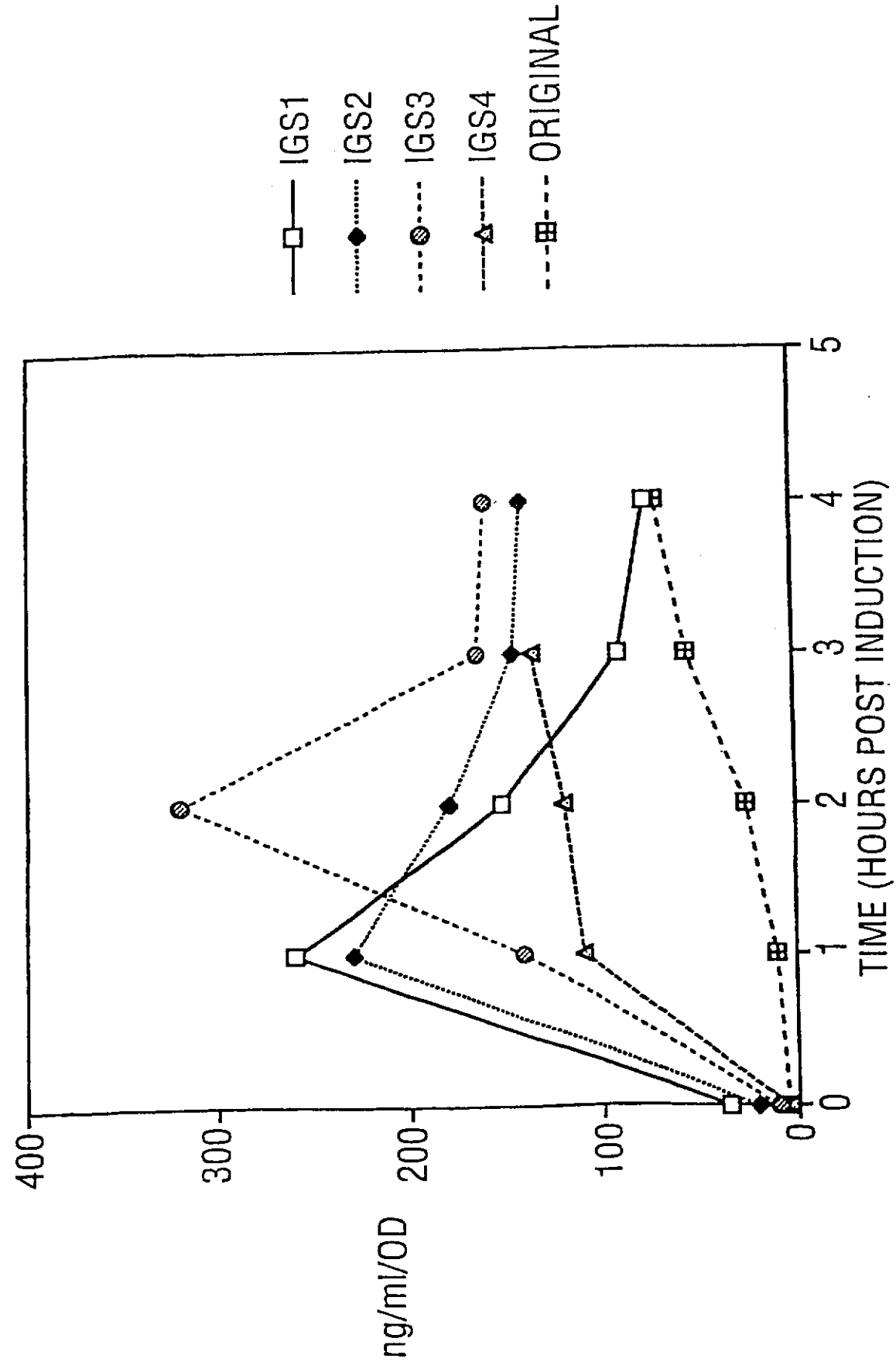


FIG. 21 Periplasmic Fab' accumulation - IGS variants

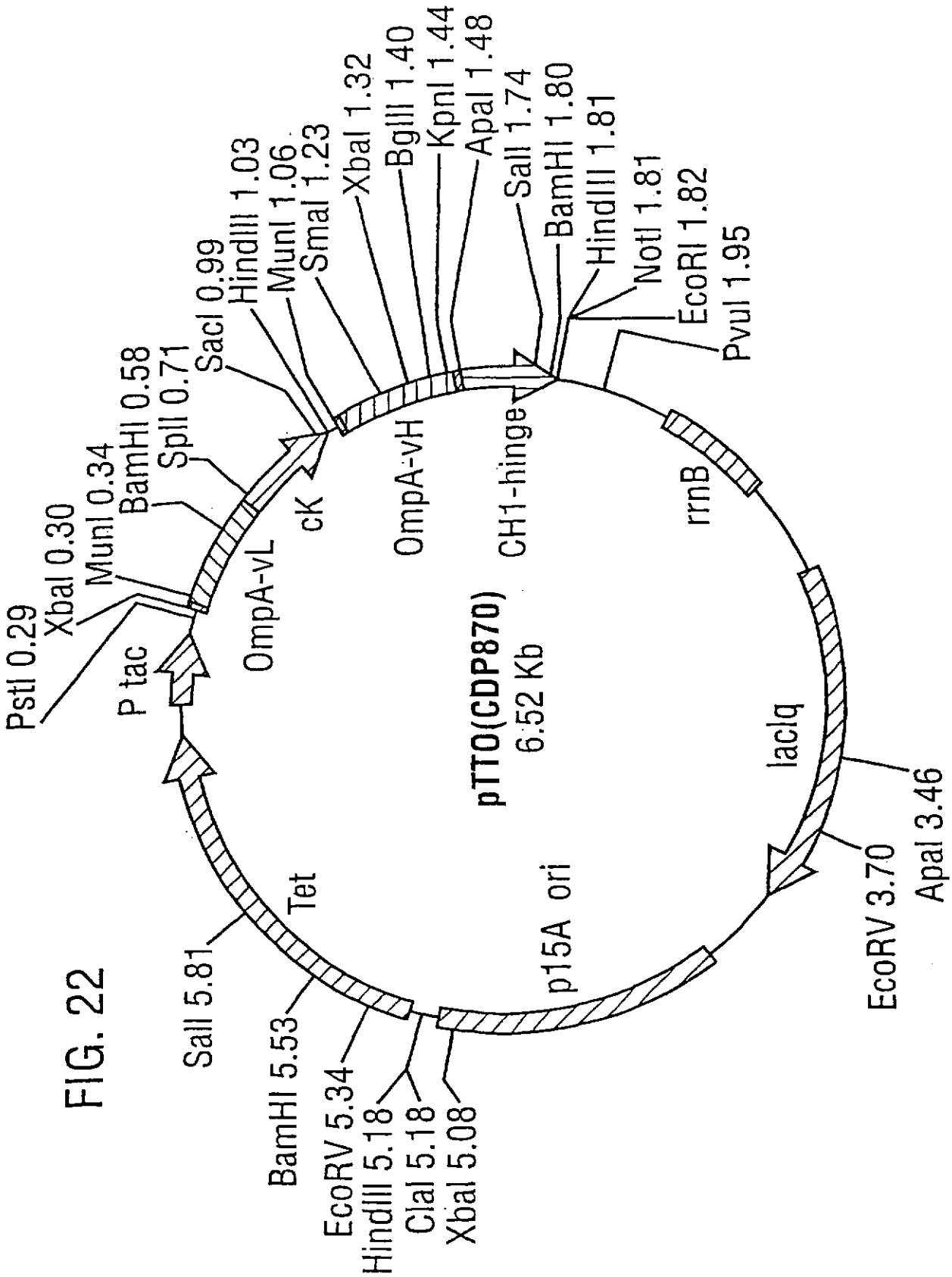

pTTO(CDP870)
6.52 Kb
PstI 0.29
XbaI 0.30
MunI 0.34
BamHI 0.58
SpII 0.71
P tac
OmpA-vL
cK
SacI 0.99
HindIII 1.03
MunI 1.06
SmaI 1.23
XbaI 1.32
BglII 1.40
KpnI 1.44
ApaI 1.48
OmpA-vH
SalI 1.74
CH1-hinge
BamHI 1.80
HindIII 1.81
NotI 1.81
EcoRI 1.82
PvuI 1.95
rrnB
laclq
ApaI 3.46
EcoRV 3.70
p15A ori
Tet
SalI 5.81
BamHI 5.53
EcoRV 5.34
HindIII 5.18
ClaI 5.18
XbaI 5.08

FIG. 22

FIG. 23

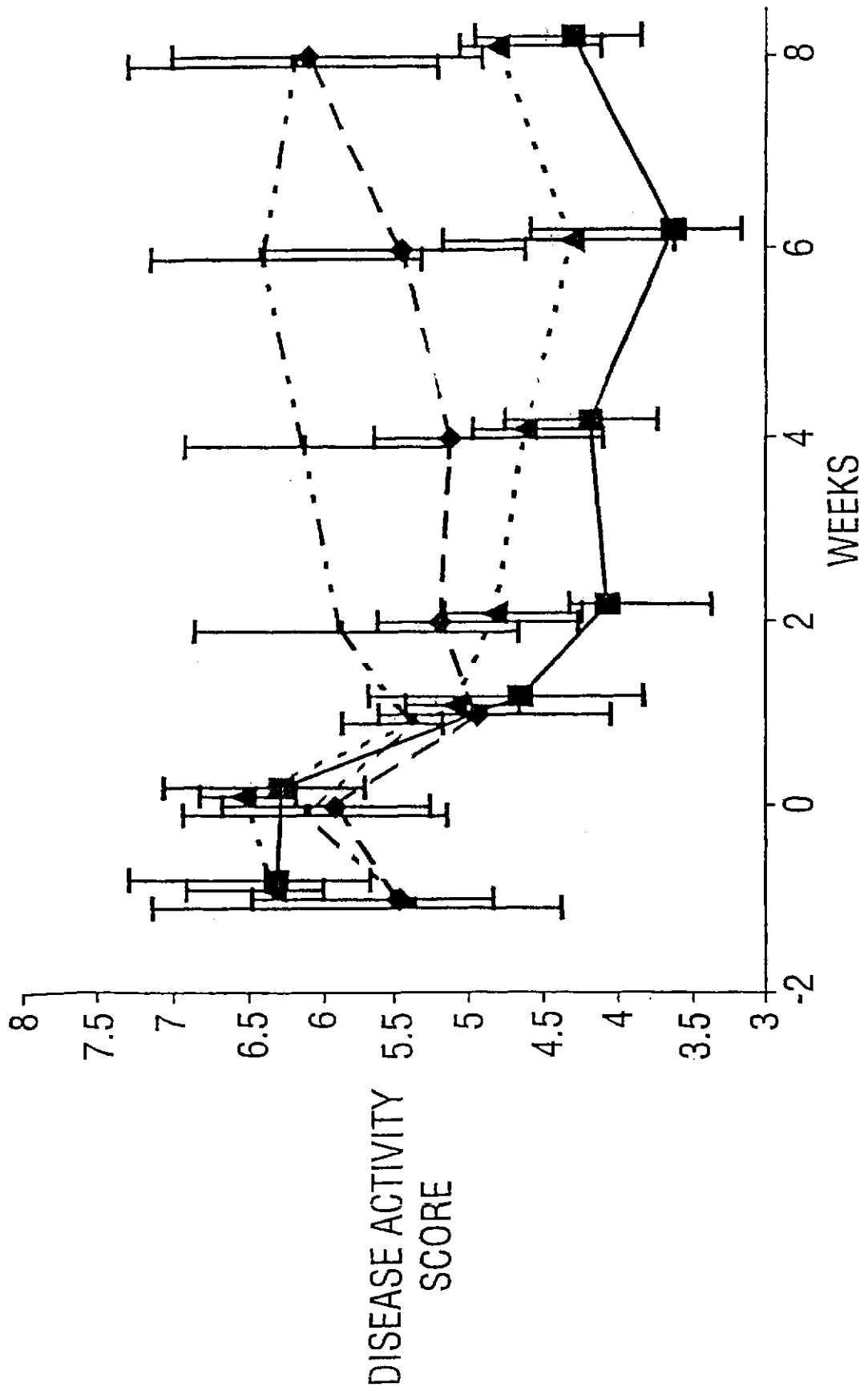


FIG. 24

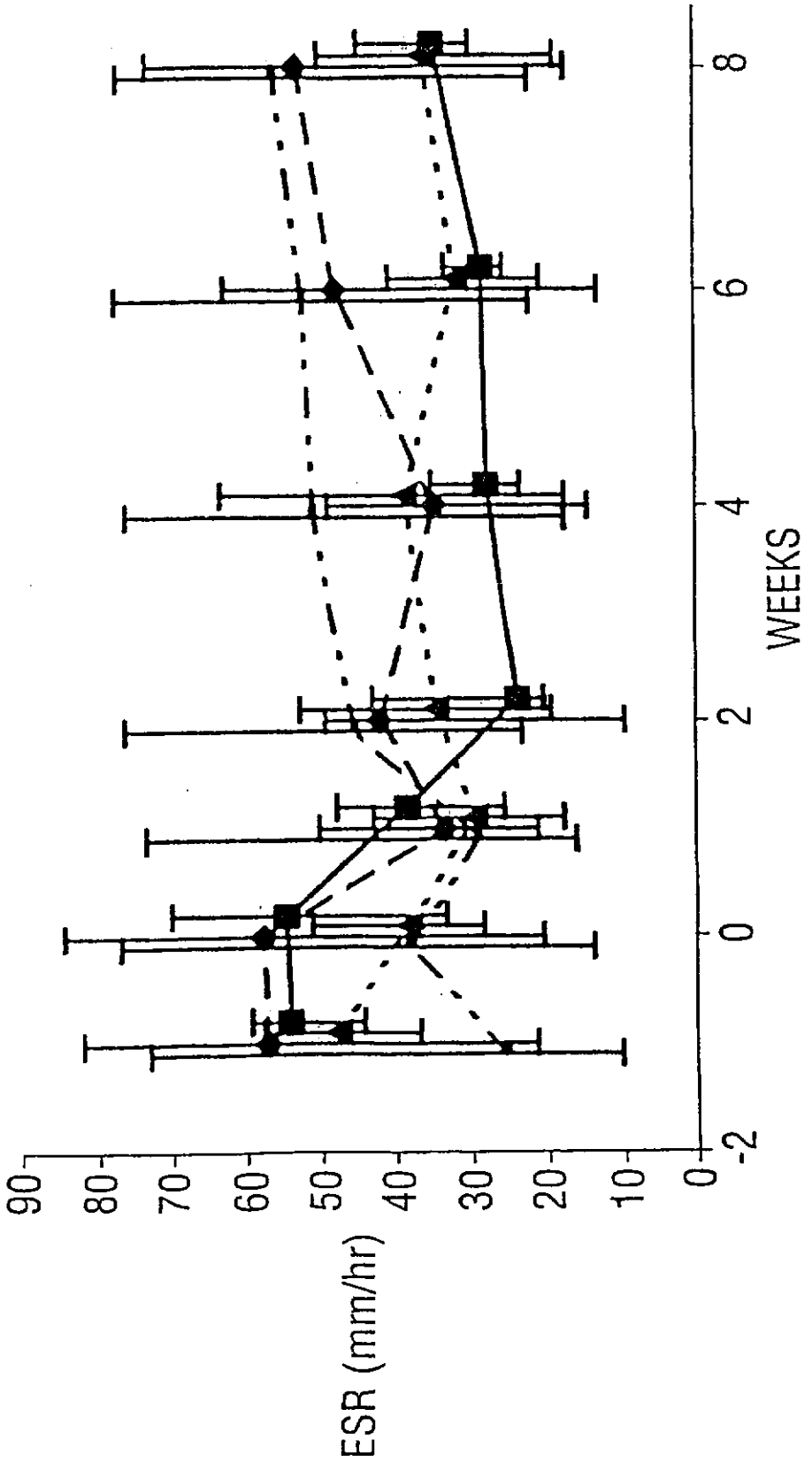


FIG. 24(contd.)

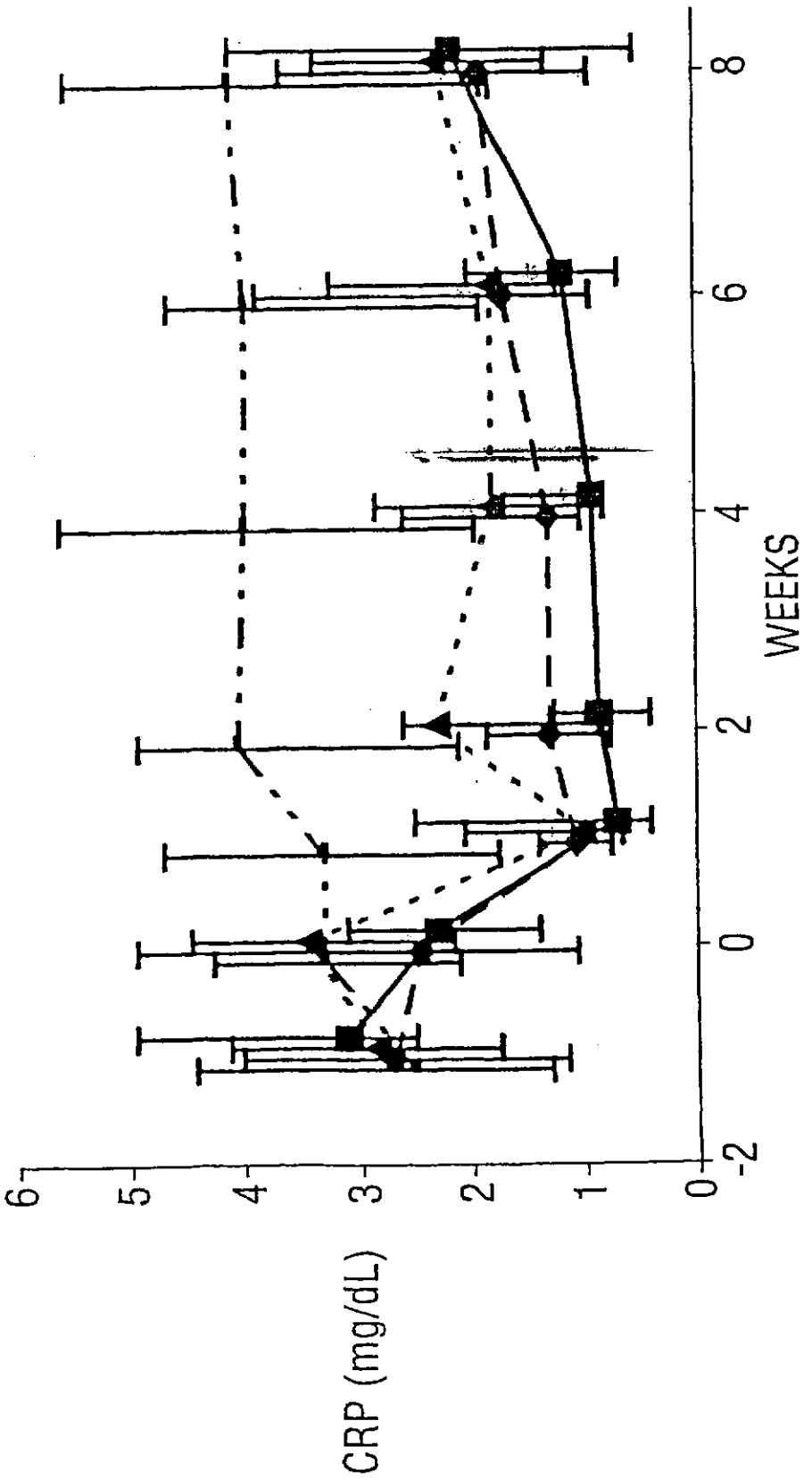


FIG. 24(contd.)

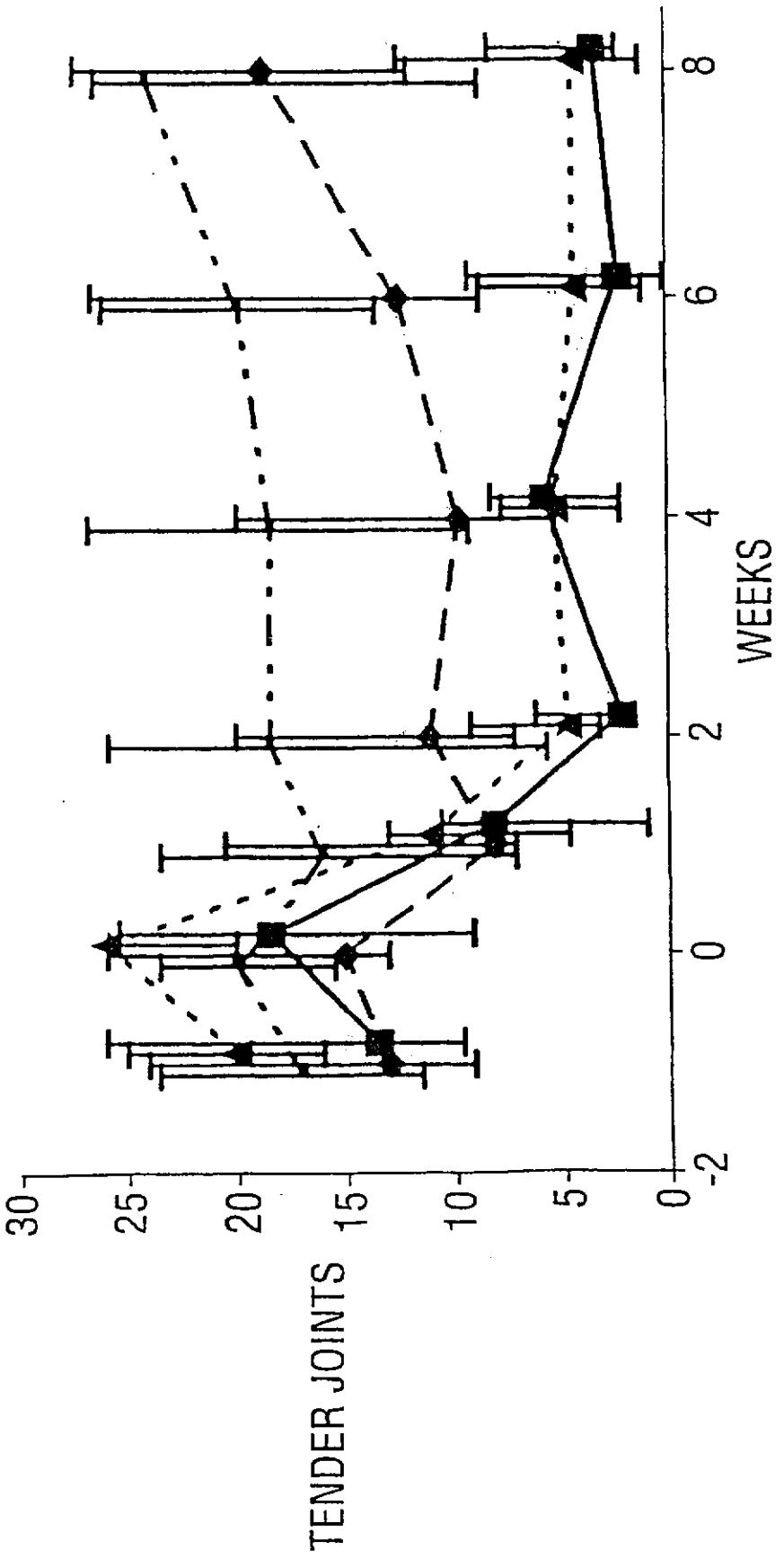
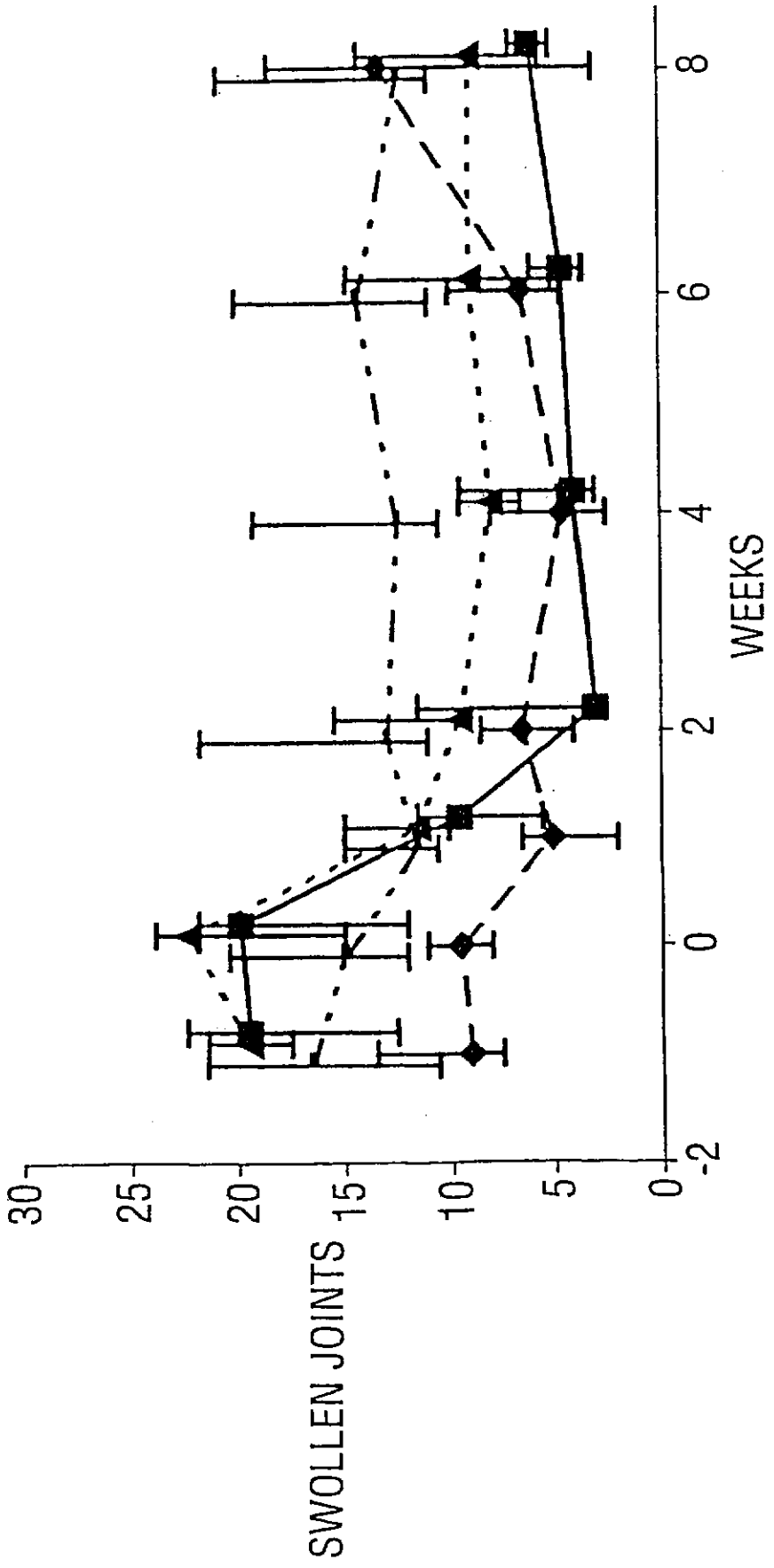


FIG. 24(contd.)



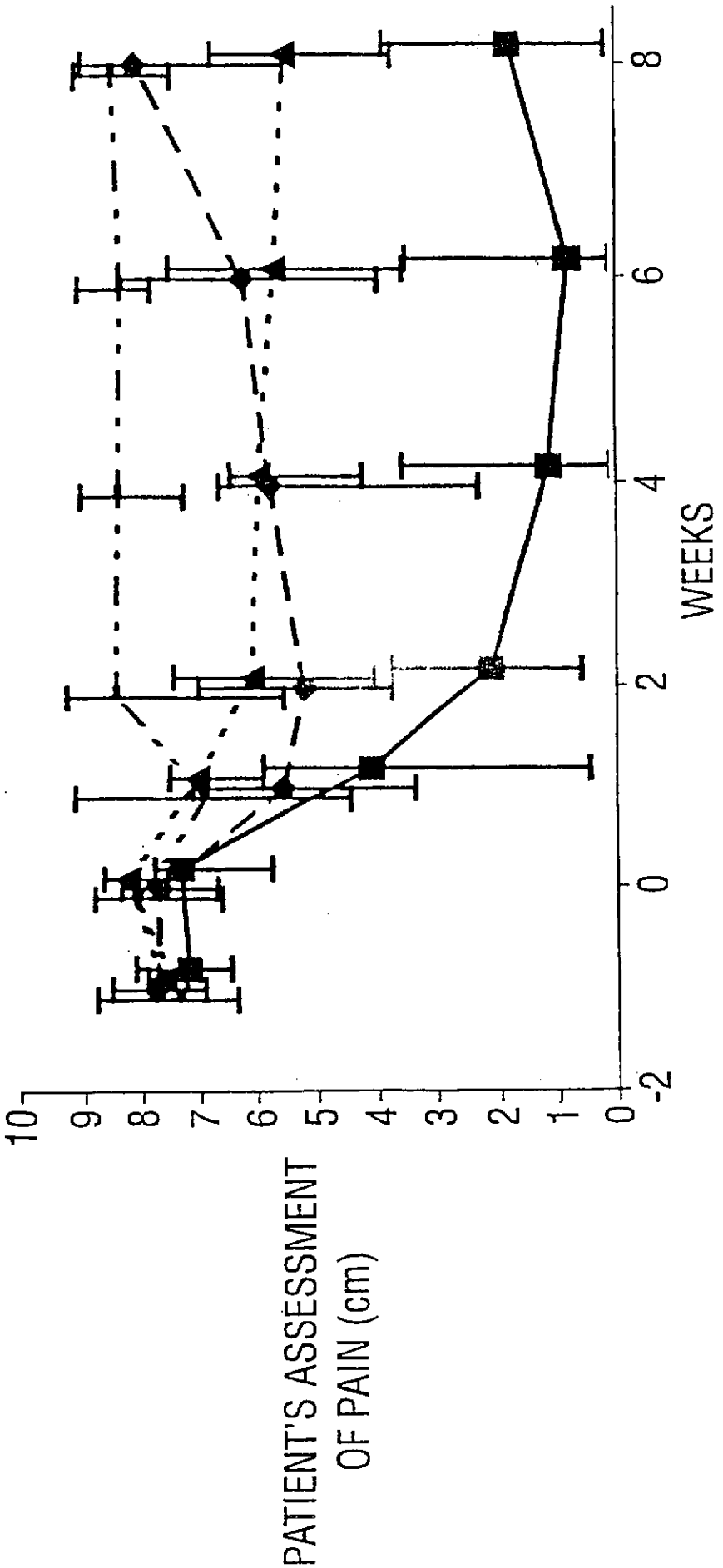


FIG. 24(contd.)

FIG. 24(contd.)

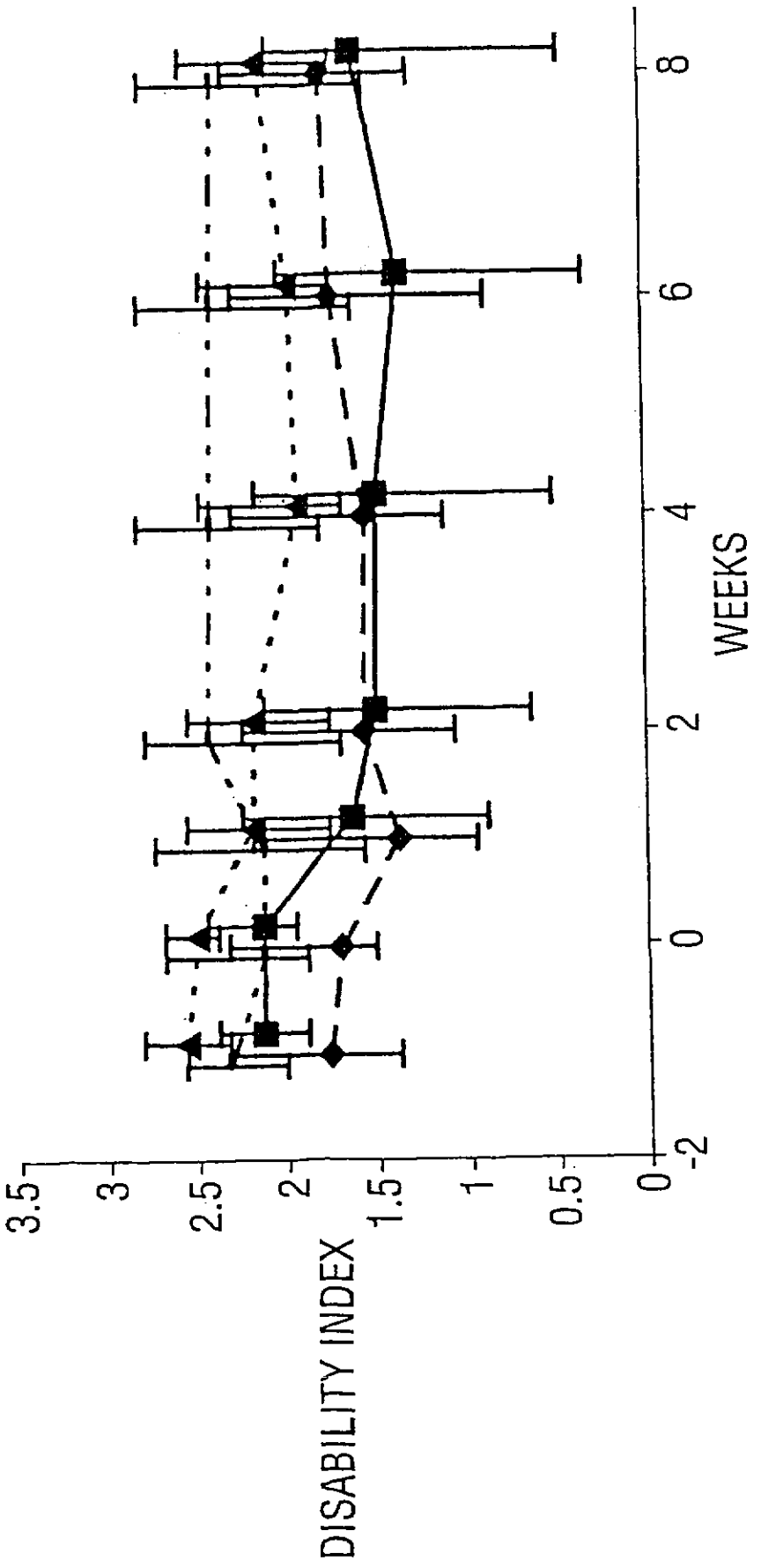


FIG. 24(contd.)

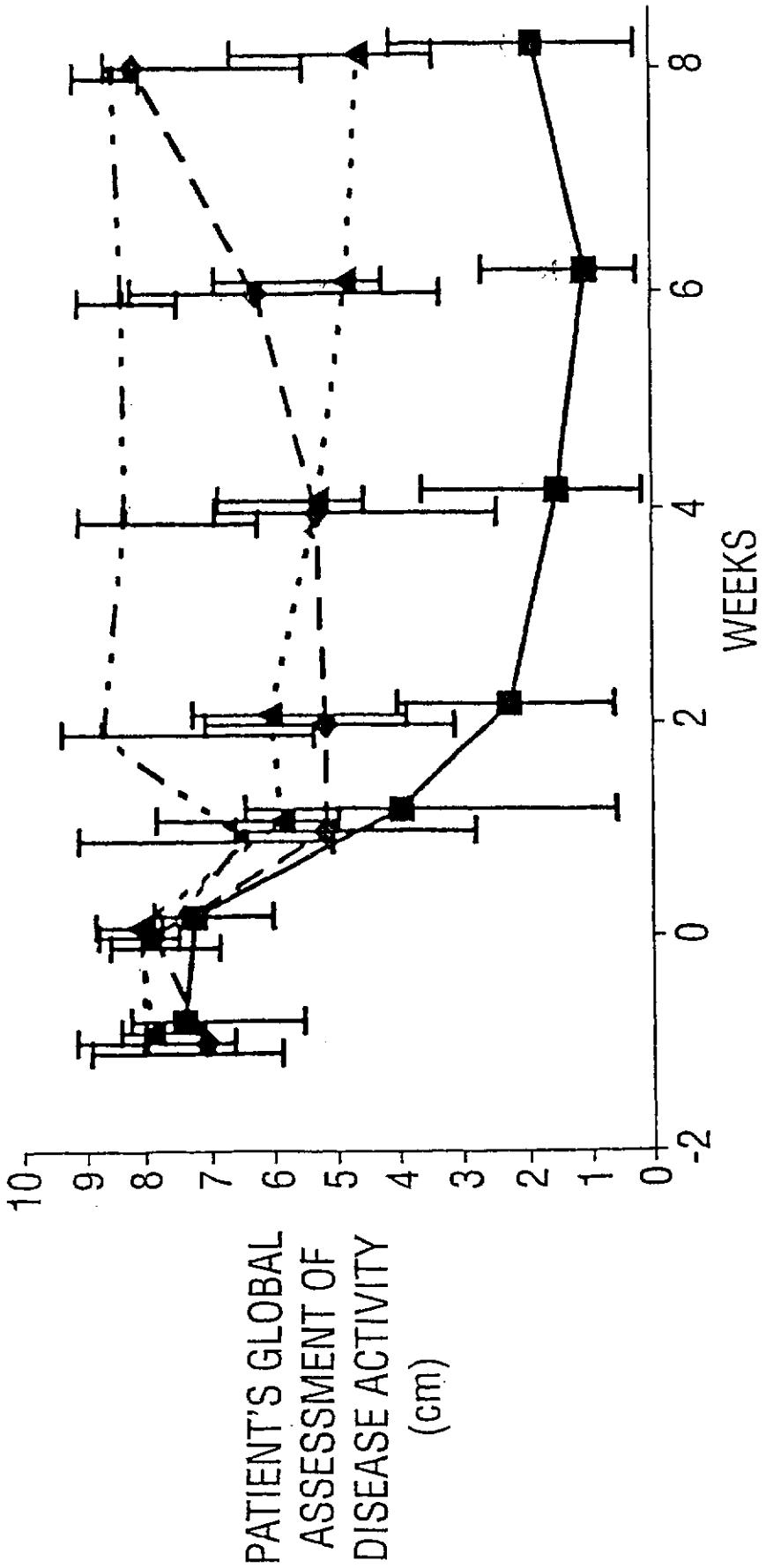
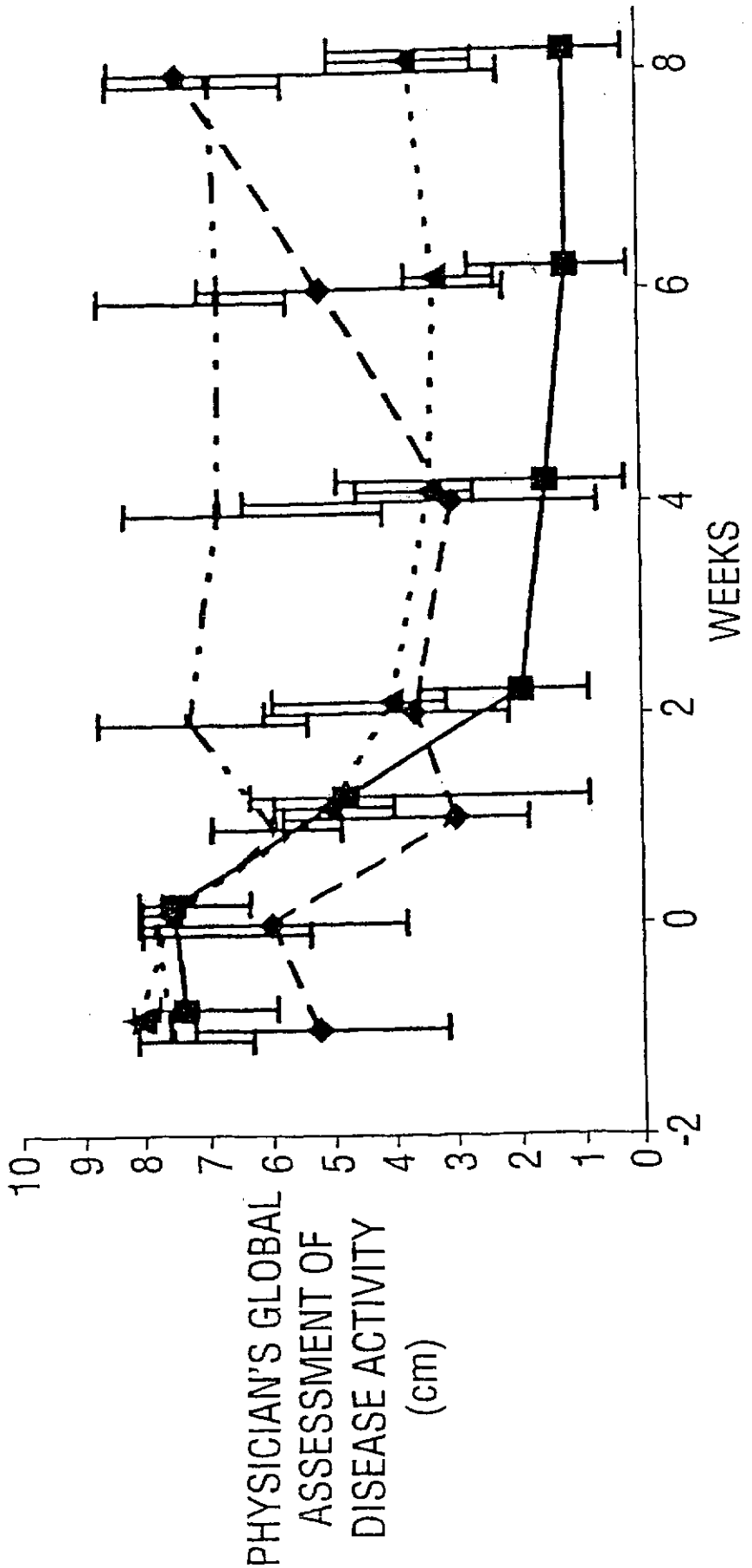

PATIENT'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (cm)
10
9
8
7
6
5
4
3
2
1
0
-2
0
2
4
6
8
WEEKS

FIG. 24(contd.)


PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (cm)
10
9
8
7
6
5
4
3
2
1
0
-2
0
2
4
6
8
WEEKS