Amino Acid Sequence of Human IDS

Iduronate-2-sulfatase (IDS)

→ Signal → Mature 42kD

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        10         20         30         40         50
MPPPRTGRGL LWLGLVLSSV CVALGSETQA NSTTDALNVL LIIVDDLRPS
        60         70         80         90        100
LGCYGDKLVR SPNIDQLASH SLLFQNAFAQ QAVCAPSRVS FLTGRRPDTT
       110        120        130        140        150
RLYDFNSYWR VHAGNFSTIP QYFKENGYVT MSVGKVFHPG ISSNHTDDSP
       160        170        180        190        200
YSWSFPPYHP SSEKYENTKT CRGPDGELHA NLLCPVDVLD VPEGTLPDKQ
       210        220        230        240        250
STEQAIQLLE KMKTSASPFF LAVGYHKPHI PFRYPKEFQK LYPLENITLA
       260        270        280        290        300
PDPEVPDGLP PVAYNPWMDI RQREDVQALN ISVPYGPIPV DFQRKIRQSY
       310        320        330        340        350
FASVSYLDTQ VGRLLSALDD LQLANSTIIA FTSDHGWALG EHGEWAKYSN
       360        370        380        390        400
FDVATHVPLI FYVPGRTASL PEAGEKLFPY LDPFDSASQL MEPGRQSMDL
       410        420        430        440        450
VELVSLFPTL AGLAGLQVPP RCPVPSFHVE LCREGKNLLK HFRFRDLEED
   → Mature 14kD
       460        470        480        490        500
PYLPGNPREL IAYSQYPRPS DIPQWNSDKP SLKDIKIMGY SIRTIDYRYT
       510        520        530        540        550
VWVGFNPDEF LANFSDIHAG ELYFVDSDPL QDHNMYNDSQ GGDLFQLLMP
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Italics = signal sequence (*MPPPRTGRGL LWLGLVLSSV CVALG*)

N = N-linked glycosylation sites (GlcNac...)

Boxed = Y-sulfation site (PSSEKYENTKTCRGPD)

Underscore = amino-terminal sequence of 42kD and 14kD peptides (Sleat 2005)

C^{84} = formylglycine modification

N^{280} = M-6-P residue(s)

FIG. 1

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CLUSTAL O(1.2.4) multiple sequence alignment of hIDS to orthologs

SP|P22304|IDS_HUMAN                MPPPRTGRGLLWLGLVLSSVCVALGSETQANSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
TR|K6ZGI9|K6ZGI9_PANTR             MPPPRTGRGLPWLGLVLSSVCVALGSETQANSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
TR|K7BKV4|K7BKV4_PANTR             MPPPRTGRGLPWLGLVLSSVCVALGSETQANSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
TR|H9FTX2|H9FTX2_MACMU             MPTPGSGRGFLWLGLVLSSVCVALGCETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
TR|F7EJG2|F7EJG2_CALJA             MPPPRTSRCLLLLGLVLGSVCVTLGSQAQASSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
TR|U3DTL8|U3DTL8_CALJA             MPPPRPSRCLLLLGLVLGSVCVTLGSQAQASSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
TR|G7NRX7|G7NRX7_MACMU             MPTPGSGRGFLWLGLVLSSVCVALGCETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
TR|G7Q1V9|G7Q1V9_MACFA             MPTPGSGRGFLWLGLVLSSVCVALGCETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
TR|H2PX10|H2PX10_PONAB             MPPPRTGRGLLWLGLVLSSVCVALGSETQADSTTDGLNVLLIIVDDLRPSLGCYGDKLVR 60
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB     MPTPGSGRGFLWLGLVLSSVCVALGSETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
TR|G1RST8|G1RST8_NOMLE             MSPPRTGQGLLWLGVVLSSVCVAXVTSPKPPSFVDALNVLLIIVDDLRPSLGCYGDKLVR 60
UP1000D9F625                       MPTPGSGRGFLWLGLVLSSVCVALGCETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
UP100027 4358B                     MPPPRTGRGLLWLGLVLSSVCVALGSETQANSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
UP100027F6FC5                      MPTPGSGRGFLWLGLVLSSVCVALGCEMQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
UP100027FAE03                      MPPPRTGLCLLLLGLVLGSVCVTLGSQAQANSTTDALNVLLIIVDDLRPSLGCYGDKLVR 60
UP10003ABBF28                      MPTPGSGRGFLWLGLVLSSVCVALGCETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
UP1000533297F                      MPTPASGRGFLWLGLVLSSVCVALGSETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
UP10005F40BD2                      MPTPASGRGFLWLGLVLRSVCVALGSETQANSTTDALNILLIIVDDLRPSLGCYGDKLVR 60
                                   * *  .  :  **:** ****:    .  :  * .*.**:**********************

SP|P22304|IDS_HUMAN                SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|K6ZGI9|K6ZGI9_PANTR             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDPTRLYDFNSYWRVHAGNFSTIP 120
TR|K7BKV4|K7BKV4_PANTR             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|H9FTX2|H9FTX2_MACMU             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|F7EJG2|F7EJG2_CALJA             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|U3DTL8|U3DTL8_CALJA             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|G7NRX7|G7NRX7_MACMU             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|G7Q1V9|G7Q1V9_MACFA             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
TR|H2PX10|H2PX10_PONAB             SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
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FIG. 2

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TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB  SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLHNFNSYWRVHAGNFSTIP 120
TR|G1RST8|G1RST8_NOMLE          SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLIGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI0000D9F625                   SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI000274358B                   SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI00027F6FC5                   SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI00027FAE03                   SPNIDQLASHSLLFQNAFVQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI0003ABBF28                   SPNIDQLASHSLLFQNAFAQEAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI000533297F                   SPNIDQLASHSLLFQNAFAQQAVCAPSRVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
UPI0005F40BD2                   SPNIDQLASHSLLFQNAFAQQAVCTPSHVSFLTGRRPDTTRLYDFNSYWRVHAGNFSTIP 120
                                ************************.*:***:**:********** ***::*********************

SP|P22304|IDS_HUMAN             QYFKENGYVTMSVGKVFHPGISSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|K6ZGI9|K6ZGI9_PANTR          QYFKENGYVTMSVGKVFHPGISSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|K7BKV4|K7BKV4_PANTR          QYFKENGYVTMSVGKVFHPGISSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|H9FTX2|H9FTX2_MACMU          QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|F7EJG2|F7EJG2_CALJA          QYFKDNGYVTMSVGKVFHPGISSNHSDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|U3DTL8|U3DTL8_CALJA          QYFKDNGYVTMSVGKVFHPGISSNHSDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|G7NRX7|G7NRX7_MACMU          QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|G7Q1V9|G7Q1V9_MACFA          QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|H2PX10|H2PX10_PONAB          QYFKENGYVTMSVGKVFHPGISSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB  QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
TR|G1RST8|G1RST8_NOMLE          QYFKENGYVTMSVGKVFHPGISSNHTDDSPYSWSFPPYHPSSXXXXXKTCRGPDGELHA 180
UPI0000D9F625                   QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
UPI000274358B                   QYFKENGYVTMSVGKVFHPGISSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
UPI00027F6FC5                   QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
UPI00027FAE03                   QYFKDNGYVTMSVGKVFHPGISSNHSDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
UPI0003ABBF28                   QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
UPI000533297F                   QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
UPI0005F40BD2                   QYFKENGYVTMSVGKVFHPGITSNHTDDSPYSWSFPPYHPSSEKYENTKTCRGPDGELHA 180
                                ****:**********************:***:**********************  ************
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FIG. 2 continued

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SP|P22304|IDS_HUMAN                NLLCPVDVLDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|K6ZGI9|K6ZGI9_PANTR             NLLCPVDVLDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|K7BKV4|K7BKV4_PANTR             NLLCPVDVLDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|H9FTX2|H9FTX2_MACMU             NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|F7EJG2|F7EJG2_CALJA             NLLCPVDVVDVPEGTLPDKQSTEEAIRLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|U3DTL8|U3DTL8_CALJA             NLLCPVDVVDVPEGTLPDKQSTEEAIRLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|G7NRX7|G7NRX7_MACMU             NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|G7Q1V9|G7Q1V9_MACFA             NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|H2PX10|H2PX10_PONAB             NLIAKKMCWMFPRAPCCDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB     NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
TR|G1RST8|G1RST8_NOMLE             NLLCPVDLVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI0000D9F625                      NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI000274358B                      NLLCPVDLVDVPEGTLPDKQSTEQAIRLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI00027F6FC5                      NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI00027FAE03                      NLLCPVDVVDVPEGTLPDKQSTEEAIRLLKKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI0003ABBF28                      NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI000533297F                      NLLCPVDVVDVPEGTLPDKQSTEQAVQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
UPI0005F40BD2                      NLLCPVDVVDVPEGTLPDKQSTEQAIQLLEKMKTSASPFFLAVGYHKPHIPFRYPKEFQK 240
                                   **:.    .*..  *******:*::.**:**********************************

SP|P22304|IDS_HUMAN                LYPLENITLAPDPEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
TR|K6ZGI9|K6ZGI9_PANTR             LYPLENITLAPDPEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
TR|K7BKV4|K7BKV4_PANTR             LYPLENITLAPDPEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
TR|H9FTX2|H9FTX2_MACMU             LYPLENITLAPDSEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
TR|F7EJG2|F7EJG2_CALJA             LYPLENITLAPDPEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
TR|U3DTL8|U3DTL8_CALJA             LYPLENITLAPDPEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
TR|G7NRX7|G7NRX7_MACMU             LYPLENITLAPDSEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
TR|G7Q1V9|G7Q1V9_MACFA             LYPLENITLAPDSEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
TR|H2PX10|H2PX10_PONAB             LYPLENITLAPDPEVPDGLPPVAYNPWMDIRQREDVQALNISVPYGPIPVDFQQKIRQSY 300
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FIG. 2 continued

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TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB  LYPLENITLAPDSEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
TR|G1RST8|G1RST8_NOMLE          LYPLENITLAPDPEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
UPI0000D9F625                   LYPLENITLAPDSEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
UPI000274358B                   LYPLENITLAPDPEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
UPI00027F6FC5                   LYPLENITLAPDSEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
UPI00027FAE03                   LYPLENITLAPDPEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
UPI0003ABBF28                   LYPLENITLAPDSEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVEFQRKIRQSY 300
UPI000533297F                   LYPLENITLAPDSEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
UPI0005F40BD2                   LYPLENITLAPDSEVPDGLPPVAYNPWWMDIRQREDVQALNISVPYGPIPVDFQRKIRQSY 300
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SP|P22304|IDS_HUMAN             FASVSYLDTQVGRLLSALDDLQLANSTIIAFTSDHGWALGEHGEWAKYSNFDVATHVPLI 360
TR|K6ZGI9|K6ZGI9_PANTR          FASVSYLDTQVGRLLSALDDLQLANSTIIAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|K7BKV4|K7BKV4_PANTR          FASVSYLDTQVGRLLSALDDLQLANSTIIAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|H9FTX2|H9FTX2_MACMU          FASVSYLDTQVGRLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|F7EJG2|F7EJG2_CALJA          FASVSYLDTQVGHLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATRVPLM 360
TR|U3DTL8|U3DTL8_CALJA          FASVSYLDTQVGHLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATRVPLM 360
TR|G7NRX7|G7NRX7_MACMU          FASVSYLDTQVGRLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|G7Q1V9|G7Q1V9_MACFA          FASVSYLDTQVGHLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|H2PX10|H2PX10_PONAB          FASVSYLDTQVGRLLSTLDDLQLANSTIIAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB  FASVSYLDTQVGRLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
TR|G1RST8|G1RST8_NOMLE          FASVSYLDTQVGRLLSALDDLQLANSTIIAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
UPI0000D9F625                   FASVSYLDTQVGHLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
UPI000274358B                   FASVSYLDTQVGRLLSALDDLQLANSTIIAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
UPI00027F6FC5                   FASVSYLDTQVGRLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
UPI00027FAE03                   FASVSYLDTQVGHLLSALDDLHLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATRVPLM 360
UPI0003ABBF28                   FASVSYLDTQVGRLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
UPI000533297F                   FASVSYLDTQVGHLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
UPI0005F40BD2                   FASVSYLDTQVGHLLSALDDLQLANSTIVAFTSDHGWALGEHGEWAKYSNFDVATHVPLM 360
                                ********************: ***: ****: ******: **********************: ***:
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FIG. 2 continued

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SP|P22304|IDS_HUMAN                FYVPGRTASLPEAGEKLFPYLDPFDSASQLMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|K6ZGI9|K6ZGI9_PANTR             FYVPGRTASLPEAGEKLFPYLDPFDSASQLMEPGRQSMDLVELVSLFPTLAGLAGLQAPP 420
TR|K7BKV4|K7BKV4_PANTR             FYVPGRTASLPEAGEKLFPYLDPFDSASQLMEPGRQSMDLVELVSLFPTLAGLAGLQAPP 420
TR|H9FTX2|H9FTX2_MACMU             FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|F7EJG2|F7EJG2_CALJA             FYVPGRTASLPEADEKLFPYVDPFHSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|U3DTL8|U3DTL8_CALJA             FYVPGRTASLPEADEKLFPYVDPFHSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|G7NRX7|G7NRX7_MACMU             FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|G7Q1V9|G7Q1V9_MACFA             FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|H2PX10|H2PX10_PONAB             FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB     FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
TR|G1RST8|G1RST8_NOMLE             FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
UPI0000D9F625                      FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
UPI000274358B                      FYVPGRTASLPEAGEKLFPYLDPFDSASQLMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
UPI00027F6FC5                      FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
UPI00027FAE03                      FYVPGRTASLPETGEKLFPYVDPFHSASELMEPGRQSTDLVELVSLFPTLAGLAGLQVPP 420
UPI0003ABBF28                      FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
UPI000533297F                      FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
UPI0005F40BD2                      FYVPGRTASLPEAGEKLFPYLDPFDSASELMEPGRQSMDLVELVSLFPTLAGLAGLQVPP 420
                                   ************:.******:***.***:******** **********************.** 

SP|P22304|IDS_HUMAN                RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPSDIPQWNSDKP 480
TR|K6ZGI9|K6ZGI9_PANTR             RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPSDIPQWNSDKP 480
TR|K7BKV4|K7BKV4_PANTR             RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPSDIPQWNSDKP 480
TR|H9FTX2|H9FTX2_MACMU             RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
TR|F7EJG2|F7EJG2_CALJA             RCPVPSFHVELCREGKSLLKHFRFHGLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
TR|U3DTL8|U3DTL8_CALJA             RCPVPSFHVELCREGKSLLKHFRFHGLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
TR|G7NRX7|G7NRX7_MACMU             RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
TR|G7Q1V9|G7Q1V9_MACFA             RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
TR|H2PX10|H2PX10_PONAB             RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADIPQWNSDKP 480
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FIG. 2 continued

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TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB  RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
TR|G1RST8|G1RST8_NOMLE          RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADIPQWNSDKP 480
UPI0000D9F625                   RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
UPI000274358B                   RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPSDIPQWNSDKP 480
UPI00027F6FC5                   RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
UPI00027FAE03                   RCPVPSFHIELCREGKNLLKHFRFHGLEEDPYLPGNPRELIAYSQYPRPADFPQQNSDKP 480
UPI0003ABBF28                   RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
UPI000533297F                   RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
UPI0005F40BD2                   RCPVPSFHVELCREGKNLLKHFRFRDLEEDPYLPGNPRELIAYSQYPRPADFPQWNSDKP 480
                                ********:********.********:.**********************:*:** *****

SP|P22304|IDS_HUMAN             SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|K6ZGI9|K6ZGI9_PANTR          SLKDIKIMGYSIRTIDYRYTVWIGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|K7BKV4|K7BKV4_PANTR          SLKDIKIMGYSIRTIDYRYTVWIGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|H9FTX2|H9FTX2_MACMU          SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|F7EJG2|F7EJG2_CALJA          SLKYIKIMGYSIRTVDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|U3DTL8|U3DTL8_CALJA          SLKYIKIMGYSIRTVDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|G7NRX7|G7NRX7_MACMU          SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|G7Q1V9|G7Q1V9_MACFA          SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|H2PX10|H2PX10_PONAB          SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB  NLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
TR|G1RST8|G1RST8_NOMLE          SLKDIKIMGYSIRTIDYRYTVWVGFSPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
UPI0000D9F625                   SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
UPI000274358B                   SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
UPI00027F6FC5                   SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
UPI00027FAE03                   SLKYIKIMGYSIRTVDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
UPI0003ABBF28                   SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
UPI000533297F                   SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPFQDHNMYNDSQ 540
UPI0005F40BD2                   SLKDIKIMGYSIRTIDYRYTVWVGFNPDEFLANFSDIHAGELYFVDSDPLQDHNMYNDSQ 540
                                .** ***********:********:.**.**********************:********** 
```

FIG. 2 continued

```
SP|P22304|IDS_HUMAN                GGDLFQLLMP 550
TR|K6ZGI9|K6ZGI9_PANTR             GGDLFQLLMP 550
TR|K7BKV4|K7BKV4_PANTR             GGDLFQLLMP 550
TR|H9FTX2|H9FTX2_MACMU             GGDLFQLLMP 550
TR|F7EJG2|F7EJG2_CALJA             GGELFQSLMP 550
TR|U3DTL8|U3DTL8_CALJA             GGELFQSLMP 550
TR|G7NRX7|G7NRX7_MACMU             GGDLLQLLMP 550
TR|G7Q1V9|G7Q1V9_MACFA             GGDLFQLLMP 550
TR|H2PX10|H2PX10_PONAB             GGDLFQLLMP 550
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB     GGDLFQLLMP 550
TR|G1RST8|G1RST8_NOMLE             GGDLFQLLMP 550
UPI0000D9F625                      GGDLLQLLMP 550
UPI000274358B                      GGDLFQLLMP 550
UPI00027F6FC5                      GGDLFQLLMP 550
UPI00027FAE03                      GGELFQSLMP 550
UPI0003ABBF28                      GGDLFQLLMP 550
UPI000533297F                      GGDLFQLLMP 550
UPI0005F40BD2                      GGDLFQLLMP 550
                                   **:*:* ***

Species Legend:
SP|P22304|IDS_HUMAN [Homo sapiens]
TR|K6ZGI9|K6ZGI9_PANTR [Pan troglodytes (Chimpanzee)]
TR|K7BKV4|K7BKV4_PANTR [Pan troglodytes (Chimpanzee)]
TR|H9FTX2|H9FTX2_MACMU [Macaca mulatta (Rhesus macaque)]
TR|F7EJG2|F7EJG2_CALJA [Callithrix jacchus (White-tufted-ear marmoset)]
TR|U3DTL8|U3DTL8_CALJA [Callithrix jacchus (White-tufted-ear marmoset)]
TR|G7NRX7|G7NRX7_MACMU [Macaca mulatta (Rhesus macaque)]
TR|G7Q1V9|G7Q1V9_MACFA [Macaca fascicularis (Crab-eating macaque; Cynomologous monkey)]
```

FIG. 2 continued

TR|H2PX10|H2PX10_PONAB [Pongo abelii (Sumatran orangutan)]
TR|A0A0D9R4D1|A0A0D9R4D1_CHLSB [Chlorocebus sabaeus (Green monkey)]
TR|G1RST8|G1RST8_NOMLE [Nomascus leucogenys (Northern white-cheeked gibbon)]
UPI0000D9F625 [Macaca mulatta (Rhesus macaque)]
UPI000274358B [Pan paniscus (Pygmy chimpanzee; Bonobo)]
UPI00027F6FC5 [Papio Anubis (Olive baboon)]
UPI00027FAE03 [Saimiri boliviensis (Bolivian squirrel monkey)]
UPI0003ABBF28 [Macaca fascicularis (Crab-eating macaque; Cynomologous monkey)]
UPI000533297F [Rhinopithecus roxellana (Golden snub-nosed monkey; Pygathrix roxellana)]
UPI0005F40BD2 [Colobus angolensis palliates (Peters' Angolan colobus)]

FIG. 2 continued

hIDS MPS II Variants

L41P (mild);
41X (intermediate);
D45N (MPS2);
R48P (mild);
Y54D (severe);
N63D (mild/intermediate);
A68E (severe);
S71N (mild);
S71R (severe);
L73F (severe);
A79E (mild);
A82E (MPS2);
A82V (no significant enzyme activity);
A85S (severe);
A85T (mild to severe forms);
P86L (intermediate to severe forms);
P86Q (MPS2);
P86R (severe);
S87N (mild);
R88C (severe);
E125V (mild);
S132W (severe);
G134R (severe);
K135N (intermediate);
K135R (intermediate);
H138D (mild/intermediate);
G140V (MPS2; no significant enzyme activity);
S143F (MPS2);
D148H (intermediate);
H159P (severe);
159X (missing in MPS2; intermediate form;
P160R (MPS2);
N181I (mild);
L182P (intermediate);
C184F (mild/intermediate);
C184W (MPS2);
L196S (mild/intermediate);
D198G (mild);
A205P (intermediate);
L221P (intermediate);
D334G (severe);
D334N (mild);
H335R (intermediate);
G336E (severe);
G336R (severe);
W337R (intermediate);
L339R (severe);
G340D (mild);
E341K (severe);
H342Y (mild);
W345C (mild/severe);
A346D (mild/severe);
A346V (mild/severe);
K347I (MPS2);
K347Q (severe);
K347T (severe);
Y348H (MPS2);
S349I (severe);
P358R (severe);
L403R (intermediate);
L410P (MPS2);
C422G (mild);

FIG. 3

R88G (severe);
R88H (intermediate/severe form);
R88L (severe);
R88P (severe–total absence of residual activity);
V89F (MPS2);
L92P (severe);
G94D (mild);
R95G (intermediate);
R95T (mild);
95X (severe);
L102R (mild);
Y108C (mild);
Y108S (mild);
N115Y (MPS2);
S117Y (severe);
117X (missing in MPS2; severe form; deleterious mutation);
T118I (mild to severe; greatly reduced activity);
118X (missing in MPS2; severe form);
P120H (mild);
P120R (severe);
Q121H (severe);
Q121R (severe);

G224E (severe);
Y225D (intermediate);
K227M (intermediate);
K227Q (severe);
P228L (MPS2);
P228T (severe);
H229R (intermediate/severe);
H229Y (severe);
P231L (mild);
D252N (MPS2);
L259P (severe);
Y264N (MPS2);
N265I (intermediate; deleterious mutation);
P266H (mild);
P266R (MPS2);
D269V (MPS2);
Q293H (mild);
S299I (mild);
D308E (mild);
D308N (intermediate);
T309A (severe);
R313C (MPS2; unknown pathological significance);
L314P (severe);
S333L (severe);

C422R (severe);
C432Y (severe);
E434K (MPS2);
Q465P (severe);
P467L (severe);
R468G (mild/severe);
R468L (mild/severe);
R468Q (severe/intermediate; greatly reduced activity);
R468W (mild/severe);
P469H (mild);
D478G (mild);
D478Y (severe);
P480L (mild);
P480Q (mild);
P480R (severe);
I485K (MPS2);
I485R (severe);
MG488–489IA (intermediate);
Y490S (intermediate);
S491F (mild);
W502C (severe);
W502S (MPS2);
E521K (severe);
E521V (severe);
Y523C (mild).

FIG. 3 continued

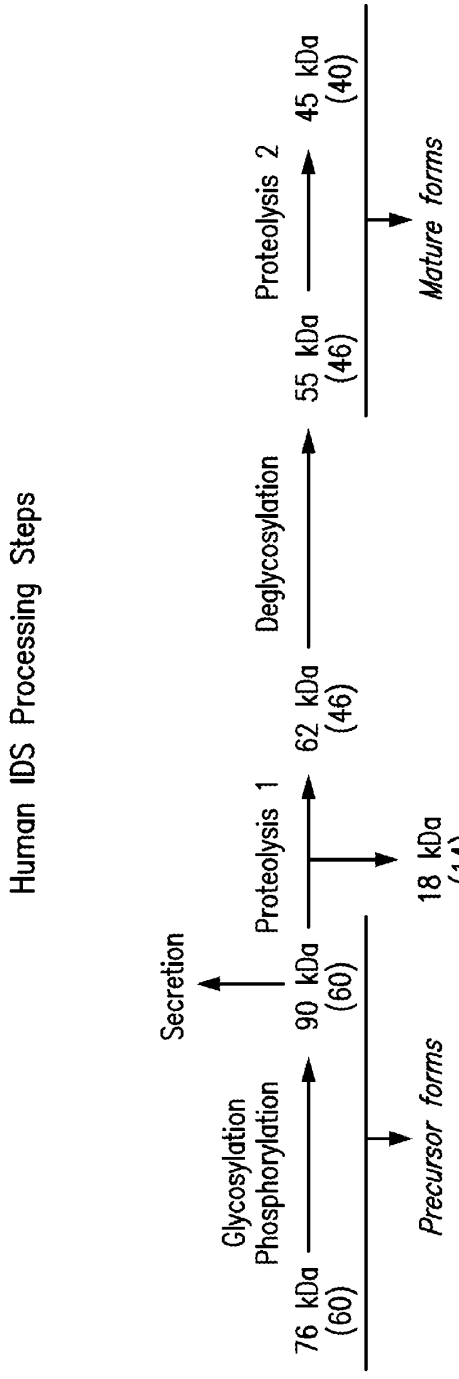


FIG. 7. IDS processing. Molecular mass of deglycosylated polypeptides is indicated in parentheses.

(From, Millat et al., 1997, Exp. Cell. Res. 230: 362–367 ("Millat 1997") Fig. 7).

FIG. 4

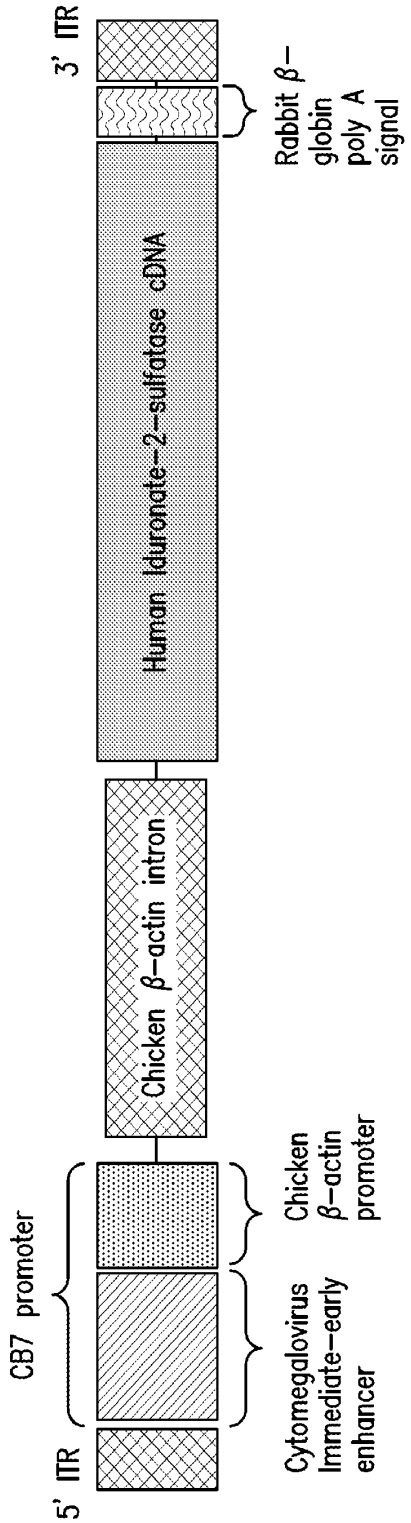

3' ITR
Rabbit β-globin poly A signal
Human Iduronate-2-sulfatase cDNA
Chicken β-actin intron
CB7 promoter
Chicken β-actin promoter
Cytomegalovirus Immediate-early enhancer
5' ITR

FIG. 5

```
          VP1 1-736 ⟶
AAV1      MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV2      MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLD 60
AAV3-3    MAADGYLPDWLEDNLSEGIREWWALKPGVPQPKANQQHQDNRRGLVLPGYKYLGPGNGLD 60
AAV4-4    -MTDGYLPDWLEDNLSEGVREWWALQPGAPKPKANQQHQDNARGLVLPGYKYLGPGNGLD 59
AV5       MSFVDHPPDWLEE-VGEGLREFLGLEAGPPKPKPNQQHQDQARGLVLPGYNYLGPGNGLD 59
AAV6      MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
AAV7      MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLD 60
AAV8      MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLD 60
hu31      MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPGNGLD 60
hu32      MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPGNGLD 60
AAV9      MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLD 60
SUBS      -STVDHP-----ETVG--V-QFLK-QA-P-K--PAERKK-DG--------N---F----
           MF               L   D E  V P        QS
                              G     Q          R

AAV1      KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV2      KGEPVNEADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
AAV3-3    KGEPVNEADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV4-4    KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQQRLQGDTSFGGNLGRAVFQ 119
AV5       RGEPVNRADEVAREHDISYNEQLEAGDNPYLKYNHADAEFQEKLADDTSFGGNLGKAVFQ 119
AAV6      KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV7      KGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
AAV8      KGEPVNAADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQ 120
hu31      KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
hu32      KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
AAV9      KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQ 120
SUBS      R-----E--EV-R---IS-NE--DS------R---------QK-QD---------K----
               R             R  E                    AG
                                Q
```

FIG. 6

```
                    VP2-138→ ┌--HVR1--┐
AAV1      AKKRVLEPLGLVEEGAKTAPGKKRPVEQSPQ-EPDSSSGIGKTGQQPAKKRLNFGQTGDS 179
AAV2      AKKRVLEPLGLVEEPVKTAPGKKRPVEHSPV-EPDSSSGTGKAGQQPARKRLNFGQTGDA 179
AAV3-3    AKKRILEPLGLVEEAAKTAPGKKGAVDQSPQ-EPDSSSGVGKSGKQPARKRLNFGQTGDS 179
AAV4-4    AKKRVLEPLGLVEQAGETAPGKKRPLIESPQ-QPDSSTGIGKKGKQPAKKKLVFEDETGA 178
AV5       AKKRVLEPFGLVEEGAKTAPTGKRIDDHFP----------KRKKARTEEDSKPSTSSDA 168
AAV6      AKKRVLEPFGLVEEGAKTAPGKKRPVEQSPQ-EPDSSSGIGKTGQQPAKKRLNFGQTGDS 179
AAV7      AKKRVLEPLGLVEEGAKTAPAKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDS 180
AAV8      AKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDS 180
hu31      AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQ-EPDSSAGIGKSGSQPAKKKLNFGQTGDT 179
hu32      AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQ-EPDSSAGIGKSGSQPAKKKLNFGQTGDT 179
AAV9      AKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQ-EPDSSAGIGKSGAQPAKKRLNFGQTGDT 179
SUBS      ----V--F----QGGE--TG-GIDDHF-V-S----S-T--KKQARTREKSVPEDETGA
             I        PV    A   ALIP    Q    T V  T K   E D K STSS S
                                  E            A S
                                               R A
```

FIG. 6 continued

```
                                                VP3203→
AAV1      ESVPD-PQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 238
AAV2      DSVPD-PQPLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDR 238
AAV3-3    ESVPD-PQPLGEPPAAPTSLGSNTMASGGGAPMADNNEGADGVGNSSGNWHCDSQWLGDR 238
AAV4-4    GDGP----PEGSTSGAMS--DDSEMRAAAGGAAVEGGQGADGVGNASGDWHCDSTWSEGH 232
AV5       EAGPSGSQQLQIPAQPASSLGADTMSAGGGGPLGDNNQGADGVGNASGDWHCDSTWMGDR 228
AAV6      ESVPD-PQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 238
AAV7      ESVPD-PQPLGEPPAAPSSVGSGTVAAGGGAPMADNNEGADGVGNASGNWHCDSTWLGDR 239
AAV8      ESVPD-PQPLGEPPAAPSGVGPNTMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDR 239
hu31      ESVPD-PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
hu32      ESVPD-PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
AAV9      ESVPD-PQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDR 238
SUBS      GDG-S-S-QLQQTSGTMASLDPNEVRAAA-GAMGEGGQ------NA--D-----T-MEGH
          DA       E S AQPATA  AG  ST S   LV                     S
                     I      — DT         A
                              TD
                               S

                                                HVR3
AAV1      VITTSTRTWALPTYNNHLYKQIS-SASTGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV2      VITTSTRTWALPTYNNHLYKQIS--SQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 296
AAV3-3    VITTSTRTWALPTYNNHLYKQIS--SQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 296
AAV4-4    VTTTSTRTWVLPTYNNHLYKRLG-----ESLQSNTYNGFSTPWGYFDFNRFHCHFSPRDW 287
AV5       VVTKSTRTWVLPSYNNHQYREIKS-GSVDGSNANAYFGYSTPWGYFDFNRFHSHWSPRDW 287
AAV6      VITTSTRTWALPTYNNHLYKQISSAST-GASNDNHYFGYSTPWGYFDFNRFHCHFSPRDW 297
AAV7      VITTSTRTWALPTYNNHLYKQISS-ETAGSTNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 298
AAV8      VITTSTRTWALPTYNNHLYKQISNGTSGGATNDNTYFGYSTPWGYFDFNRFHCHFSPRDW 299
hu31      VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
hu32      VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
AAV9      VITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDW 298
SUBS      -T-K-----V--S----Q-RRLGSGSQSDATQA-T----------------S-W-----
           V                  E K AATTEGL S H
                                G V
                                E A
```

FIG. 6 continued

```
AAV1      QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV2      QRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV3-3    QRLINNNWGFRPKKLSFKLFNIQVRGVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVLGS 356
AAV4-4    QRLINNNWGMRPKAMRVKIFNIQVKEVTTSNGETTVANNLTSTVQIFADSSYELPYVMDA 347
AV5       QRLINNYWGFRPRSLRVKIFNIQVKEVTVQDSTTTIANNLTSTVQVFTDDDYQLPYVVGN 347
AAV6      QRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYVLGS 357
AAV7      QRLINNNWGFRPKKLRFKLFNIQVKEVTTNDGVTTIANNLTSTIQVFSDSEYQLPYVLGS 358
AAV8      QRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGS 359
hu31      QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
hu32      QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
AAV9      QRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGS 358
SUBS      --------M--RAMRV-I--------VQDSTT--------I-I-S-DE-E----MDA
                    K S           QSE E             A  S
                    S
```

FIG. 6 continued

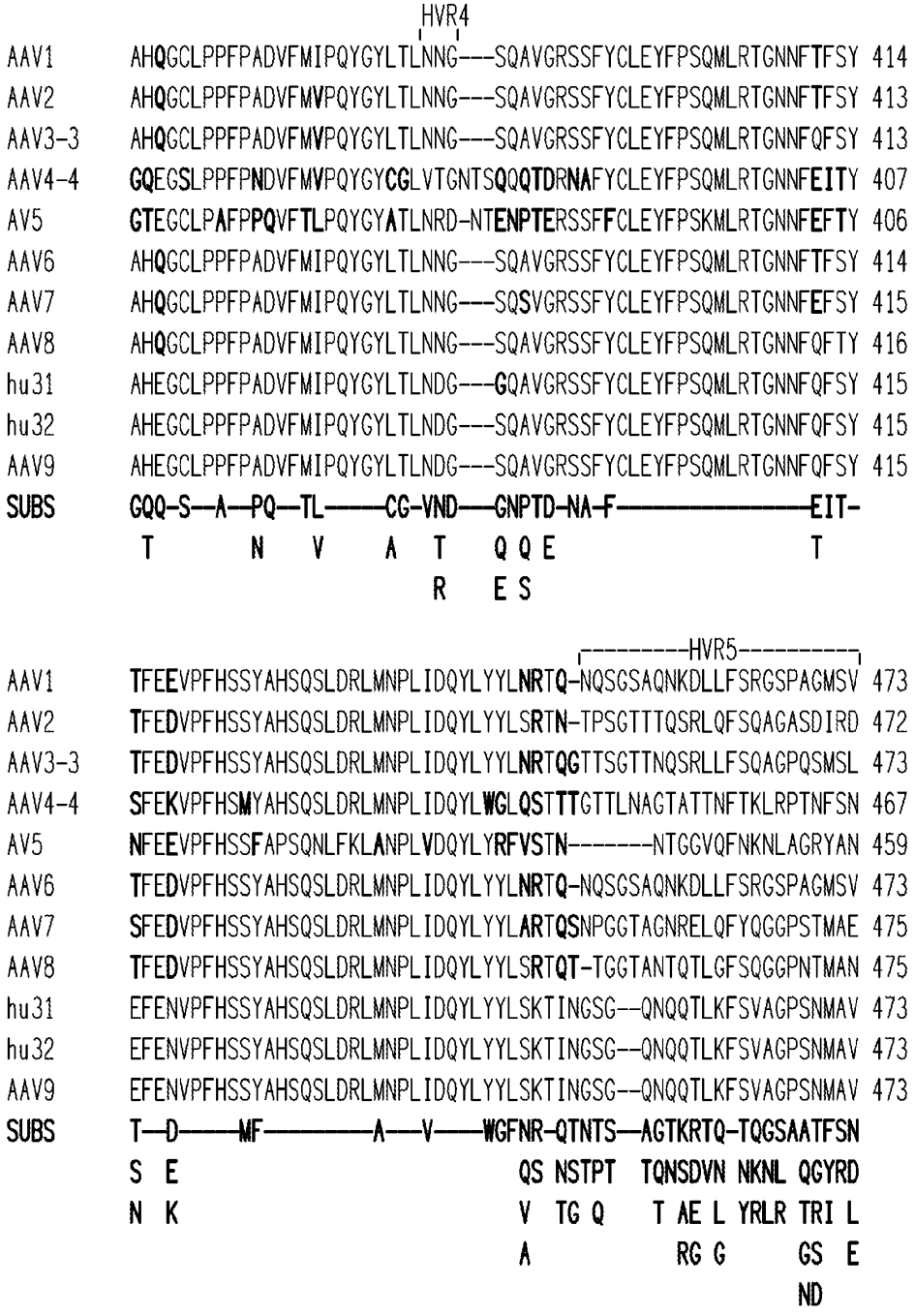


FIG. 6 continued

```
                 ┌--┐                ┌HVR6-┐        ┌HVR7-┐        ┌---HVR8--┐
AAV1     QPKNWLPGPCYRQQRVSKTKTDN-----NNSNFTWTGASKYNLNGRESIINPGTAMASHK 528
AAV2     QSRNWLPGPCYRQQRVSKTSADN-----NNSEYSWTGATKYHLNGRDSLVNPGPAMASHK 527
AAV3-3   QARNWLPGPCYRQQRLSKTANDN-----NNSNFPWTAASKYHLNGRDSLVNPGPAMASHK 528
AAV4-4   FKKNWLPGPSIKQQGFSKTANQNYKIPATGSDSLIKYETHSTLDGRWSALTPGPPMATAG 527
AV5      TYKNWFPGPMGRTQGWNLGSGVN-----RASVSAFATTNRMELEGASYQVPPQPNGMTNN 514
AAV6     QPKNWLPGPCYRQQRVSKTKTDN-----NNSNFTWTGASKYNLNGRESIINPGTAMASHK 528
AAV7     QAKNWLPGPCFRQQRVSKTLDQN-----NNSNFAWTGATKYHLNGRNSLVNPGVAMATHK 530
AAV8     QAKNWLPGPCYRQQRVSTTTGQN-----NNSNFAWTAGTKYHLNGRNSLANPGIAMATHK 530
hu31     QGRNYIPGPSYRQQRVSTTVTQN-----NNSEFAWPGASSWALNGRNSLMNPGPAMASHK 528
hu32     QGRNYIPGPSYRQQRVSTTVTQN-----NNSEFAWPGASSWALNGRNSLMNPGPAMASHK 528
AAV9     QGRNYIPGPSYRQQRVSTTVTQN-----NNSEFAWPGASSWALNGRNSLMNPGPAMASHK 528
SUBS     FAK-WL---CIKT-GWNLGSGV-------TG-DSLIKYETHST-D-ASYQVP-QTPGMTAG
         TP  F  MG   F K AND     RA NYTFATTNRME E  D ALT  VN   NN
          K      F   L  KA        V P TAG KYN   W II  I
          Y                LD        S      H   E  A
          S                T
```

FIG. 6 continued

```
                  ┌----------HVR9----------┐                          ┌──┐
AAV1      DDEDKFFPMSGVMIFGKESA--GASNTALD-NVMITDEEEIKATNPVATERFGTVAVNFQ 585
AAV2      DDEEKFFPQSGVLIFGKQGS--EKTNVDIE-KVMITDEEEIRTTNPVATEQYGSVSTNLQ 584
AAV3-3    DDEEKFFPMHGNLIFGKEGT--TASNAELD-NVMITDEEEIRTTNPVATEQYGTVANNLQ 585
AAV4-4    PADSKFS-NSQLIFAGPKQN--GNTATVPG-TLIFTSEEELAATNATDTDMWGNLPGGDQ 583
AV5       LQGSNTYALENTMIFNSQPANPGTTATYLEGNMLITSESETQPVNRVAYNVGGQMATNNQ 574
AAV6      DDKDKFFPMSGVMIFGKESA--GASNTALD-NVMITDEEEIKATNPVATERFGTVAVNLQ 585
AAV7      DDEDRFFPSSGVLIFGKTGA--TN-KTTLE-NVLMTNEEEIRPTNPVATEEYGIVSSNLQ 586
AAV8      DDEERFFPSNGILIFGKQNA--ARDNADYS-DVMLTSEEEIKTTNPVATEEYGIVADNLQ 587
hu31      EGEDRFFPLSGSLIFGKQGT--GRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNHQ 585
hu32      EGEDRFFPLSGSLIFGKQGT--GRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNHQ 585
AAV9      EGEDRFFPLSGSLIFGKQGT--GRDNVDAD-KVMITNEEEIKTTNPVATESYGQVATNHQ 585
SUBS      LQGSNTYAMENTMFANPKQN--TNTATVPG-TLIF-S-S-TQPV-ATDYDMW-NLPGGD-
          PADEK S QHQLI   SESA  EASKAALE-NMLM D    RA  R   NVF TMSN L
          DDK     NN V     TPS  AK  KTY     L     A        QG I  V N
                  S  I      N        EI                     E  S  S F
                     N               Y                     R     D

                ┌--HVR10--┐
AAV1      SSSTDPATGDVHAMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKNPPP 645
AAV2      RGNRQAATADVNTQGVLPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPP 644
AAV3-3    SSNTAPTTGTVNHQGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPP 645
AAV4-4    SNSNLPTVDRLTALGAVPGMVWQNRDIYYQGPIWAKIPHTDGHFHPSPLIGGFGLKHPPP 643
AV5       SSTTAPATGTYNLQEIVPGSVWMERDVYLQGPIWAKIPETGAHFHPSPAMGGFGLKHPPP 634
AAV6      SSSTDPATGDVHVMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPP 645
AAV7      AANTAAQTQVVNNQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPP 646
AAV8      QQNTAPQIGTVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPP 647
hu31      SAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPP 645
hu32      SAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPP 645
AAV9      SAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPP 645
SUBS      RNSNLPTVDRLTALEAV--S--ME--I----------E-CAH-----AI---L-N--
          ASNTA AIADYHTM V       N
          QGTRD   QT NH
           Q       V  L
                      V
                      S
```

FIG. 6 continued

```
                    ┌--HVR11--┐
AAV1      QILIKNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNY 705
AAV2      QILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 704
AAV3-3    QIMIKNTPVPANPPTTFSPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV4-4    QIFIKNTPVPANPATTFSSTPVNSFITQYSTGQVSVQIDWEIQKERSKRWNPEVQFTSNY 703
AV5       MMLIKNTPVPGNI-TSFSDVPVSSFITQYSTGQVTVEMEWELKKENSKRWNPEIQYTNNY 693
AAV6      QILIKNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNY 705
AAV7      QILIKNTPVPANPPEVFTPAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNF 706
AAV8      QILIKNTPVPADPPTTFNQSKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 707
hu31      QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
hu32      QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
AAV9      QILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY 705
SUBS      MMM------G-IAAE-SDVPVS----------QMD--IK--R------V-----
           F          SET TAA FA
                       S  PT
                       V  QS
                          S
```

FIG. 6 continued

	-----HVR12-----	
AAV1	AKSANVDFTVDNNGLY**T**EPRPIGTRYLTR**P**L	736 (SEQ ID NO. 16)
AAV2	NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL	735 (SEQ ID NO. 17)
AAV3-3	NKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL	736 (SEQ ID NO. 18)
AAV4-4	GQQNSLLWAPDAAGKY**T**EPR**A**IGTRYLT**HH**L	734 (SEQ ID NO. 19)
AV5	NDPQFVDFAPDSTGEY**RTT**RPIGTRYLTR**P**L	724 (SEQ ID NO. 20)
AAV6	AKSANVDFTVDNNGLY**T**EPRPIGTRYLTR**P**L	736 (SEQ ID NO. 21)
AAV7	EKQTGVDFAVDSQGVYSEPRPIGTRYLTRNL	737 (SEQ ID NO. 22)
AAV8	YKSTSVDFAVNTEGVYSEPRPIGTRYLTRNL	738 (SEQ ID NO. 23)
hu31	YKSNNVEFAVSTEGVYSEPRPIGTRYLTRNL	736 (SEQ ID NO. 24)
hu32	YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL	736 (SEQ ID NO. 25)
AAV9	YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL	736 (SEQ ID NO. 26)
SUBS	**GQQVSLLWTPDAA-K-RTT-A------HP-**	
	NDPQF D SSN E T H	
	A TG NQ L	
	E A T	

FIG. 6 continued

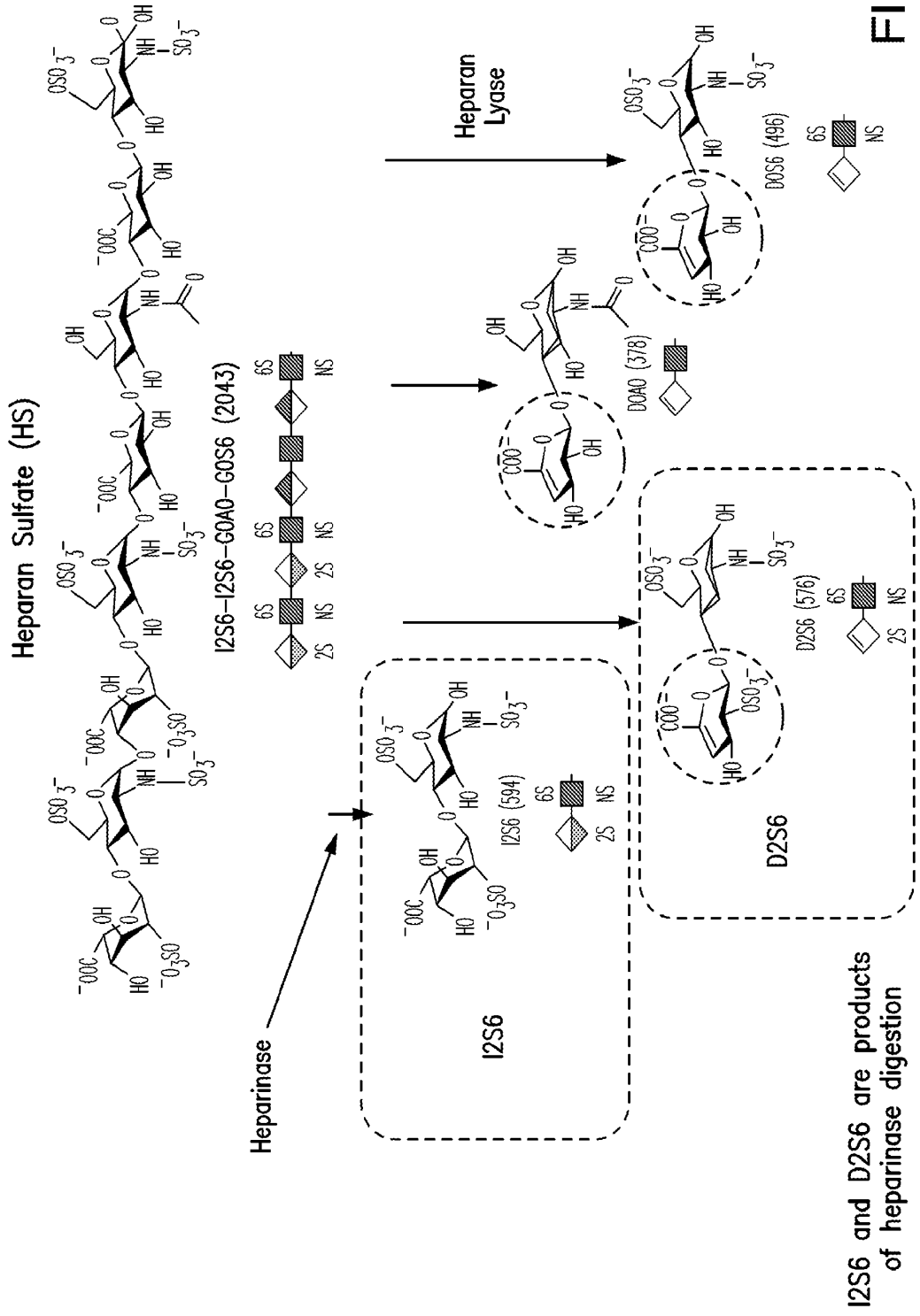

Heparan Sulfate (HS)
I2S6–I2S6–GOA0–GOS6 (2043)
6S
6S
6S
2S NS 2S NS NS
Heparinase
I2S6
I2S6 (594)
6S
2S NS
Heparan Lyase
DOA0 (378)
DOS6 (496)
6S
NS
D2S6
D2S6 (576)
6S
2S NS
I2S6 and D2S6 are products of heparinase digestion

FIG. 7

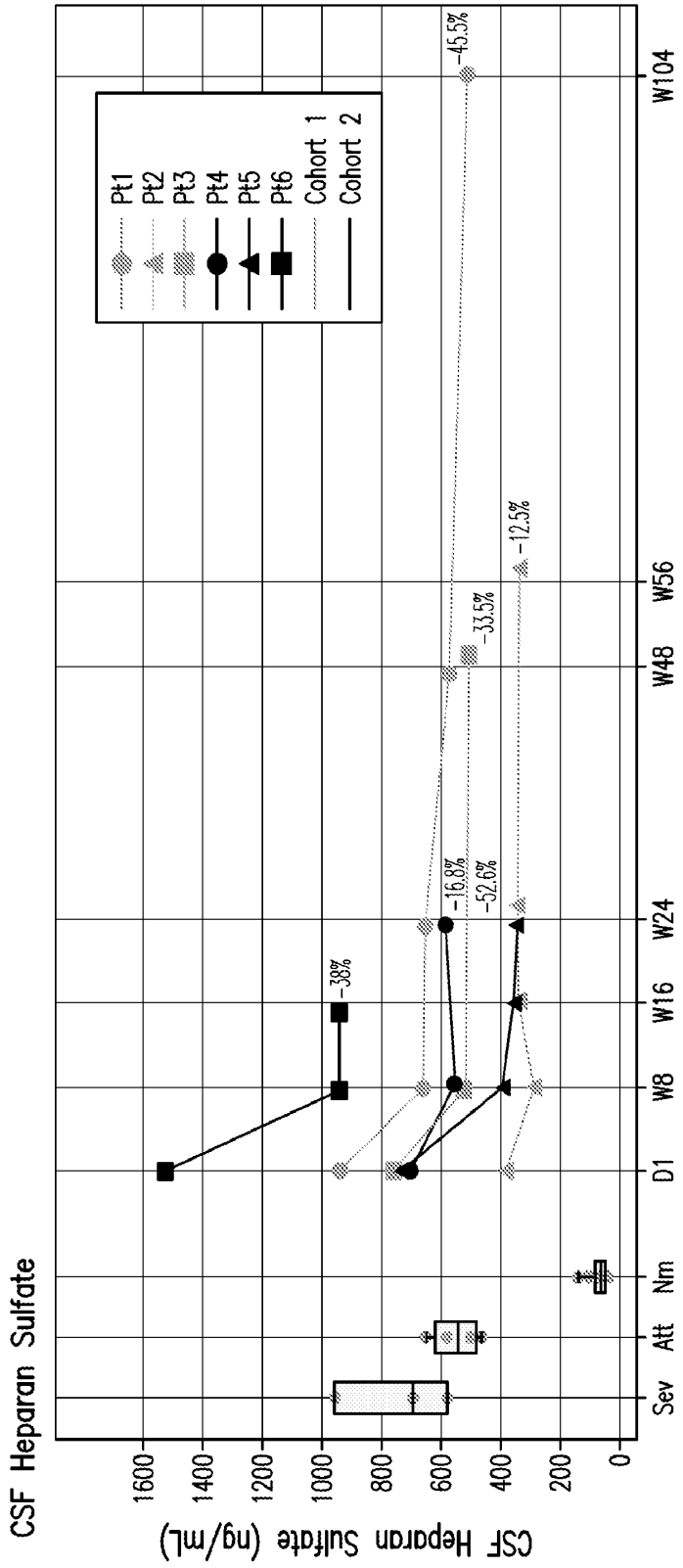

CSF Heparan Sulfate
CSF Heparan Sulfate (ng/mL)
1600
1400
1200
1000
800
600
400
200
0
Sev
Att
Nm
D1
W8
W16
W24
W48
W56
W104
Pt1
Pt2
Pt3
Pt4
Pt5
Pt6
Cohort 1
Cohort 2
-38%
-16.8%
-52.6%
-33.5%
-12.5%
-45.5%

FIG. 8

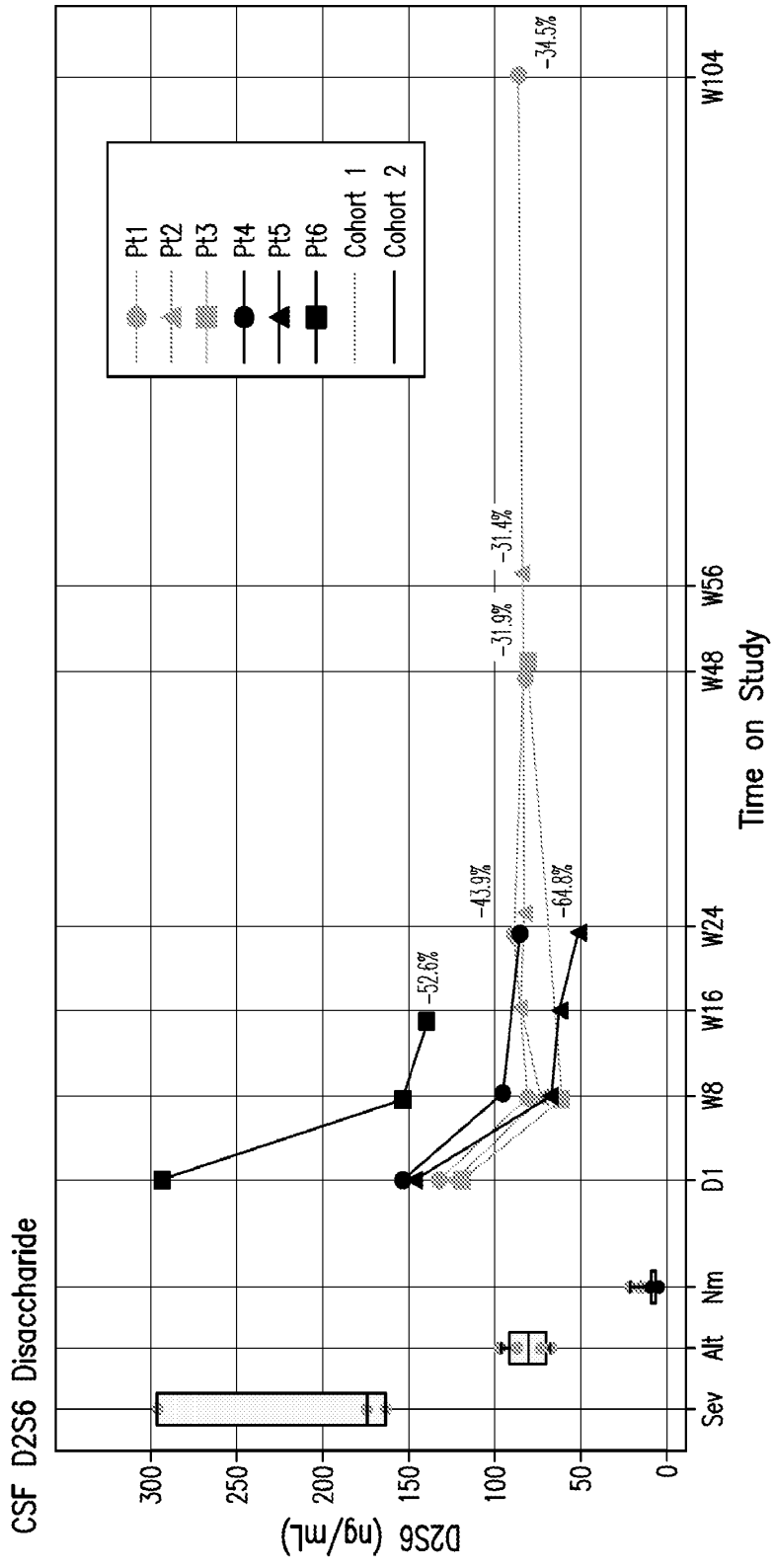

CSF D2S6 Disaccharide
D2S6 (ng/mL)
300
250
200
150
100
50
0
Sev
Alt
Nm
D1
W8
W16
W24
W48
W56
W104
Time on Study
Pt1
Pt2
Pt3
Pt4
Pt5
Pt6
Cohort 1
Cohort 2
-52.6%
-43.9%
-64.8%
-31.9%
-31.4%
-34.5%

FIG. 9

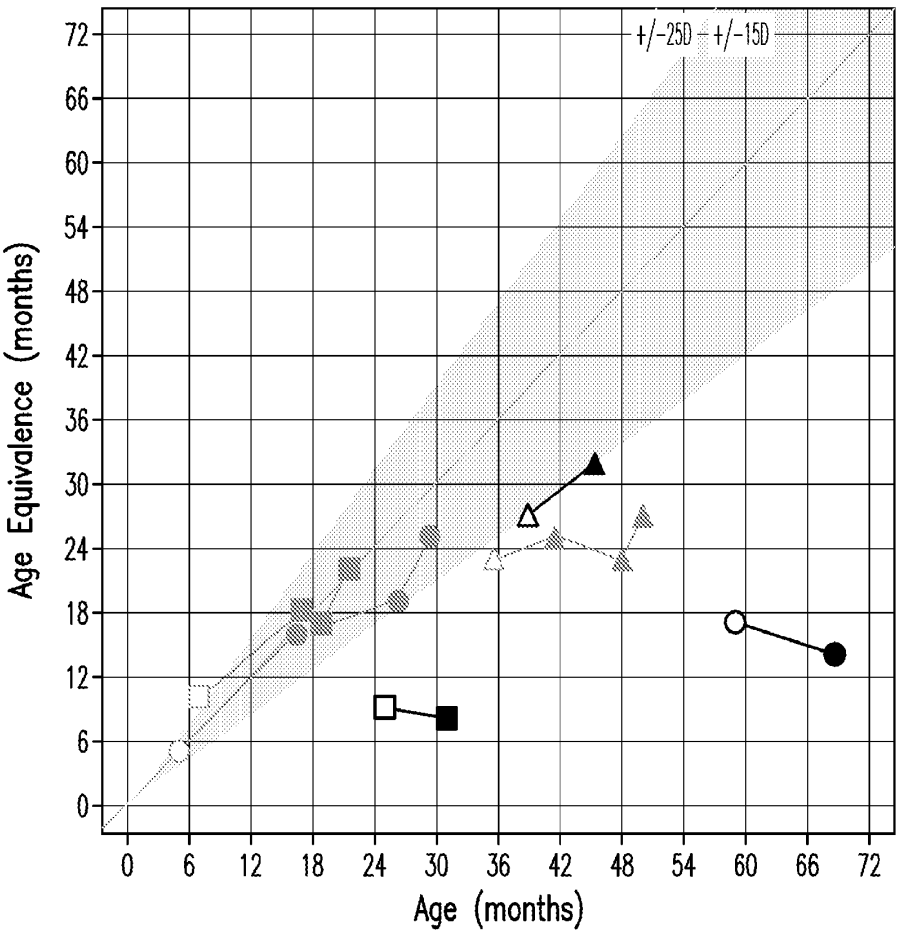

+/-25D
+/-15D
Age Equivalence (months)
Age (months)
0
6
12
18
24
30
36
42
48
54
60
66
72
Pt1
Pt2
Pt3
Pt4
Pt5
Pt6
Pre-dose

FIG. 10A

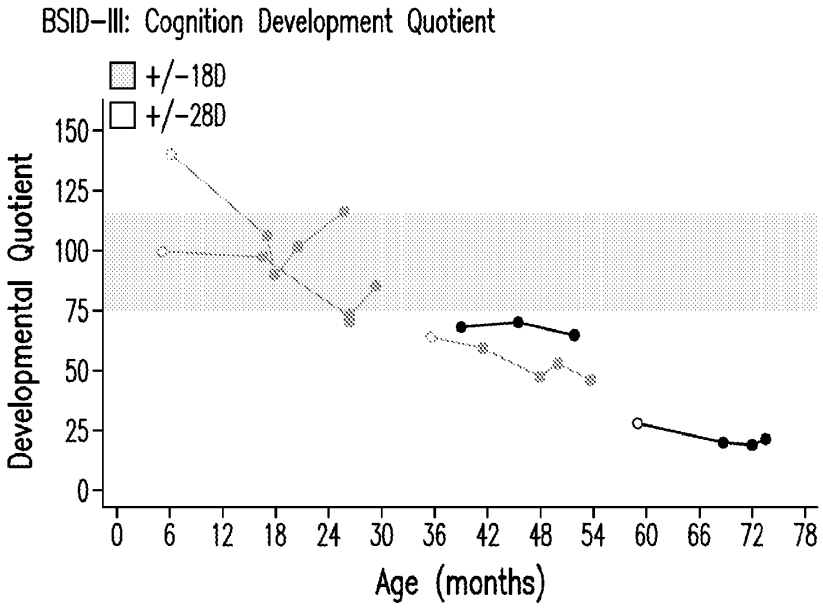


FIG. 10B

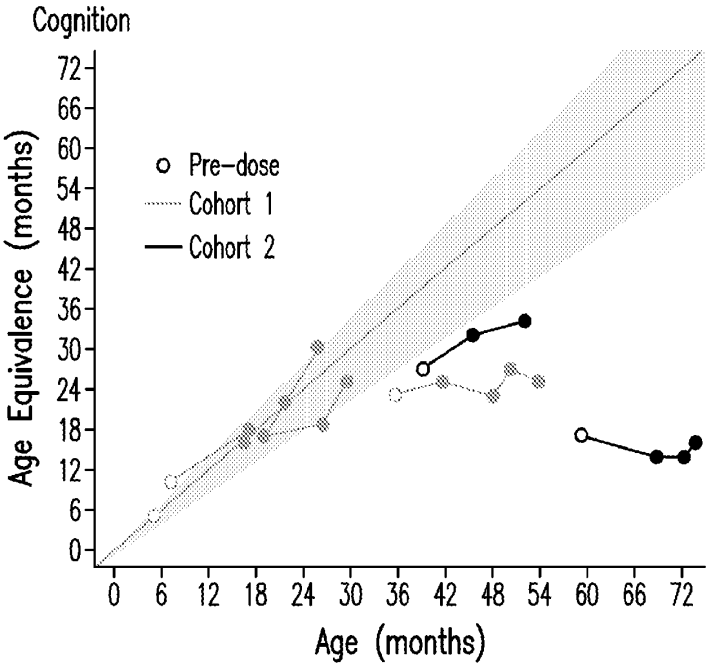


FIG. 10C

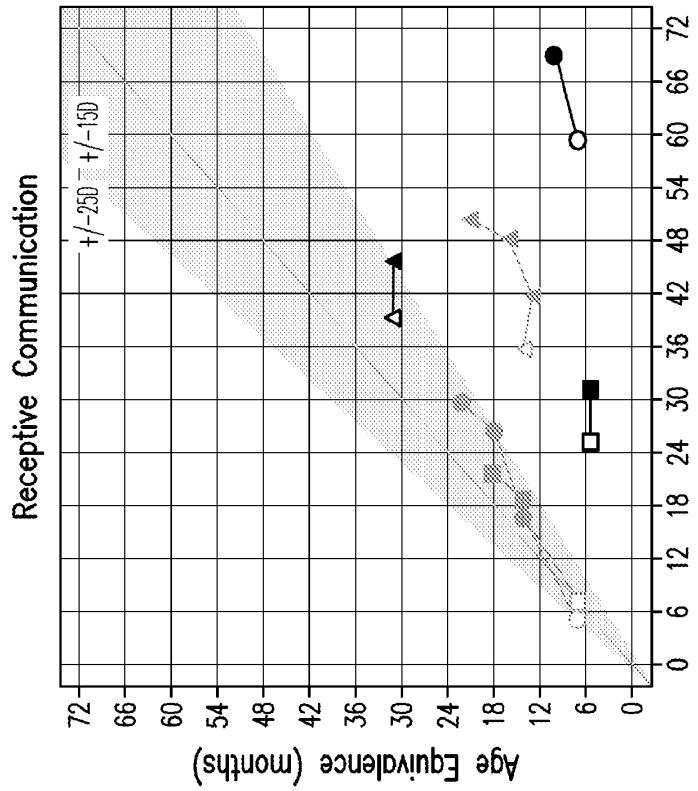


FIG. 11B

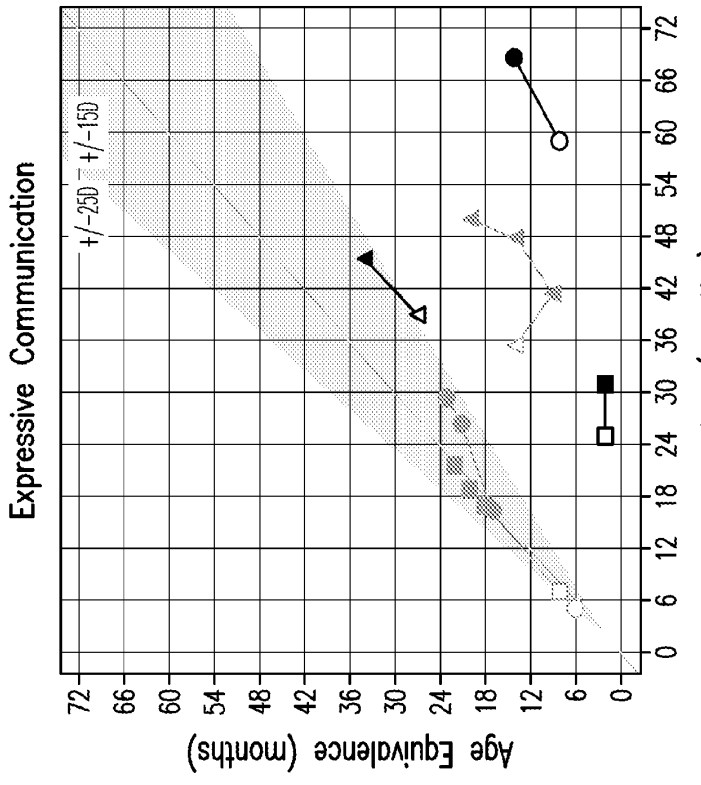


FIG. 11A

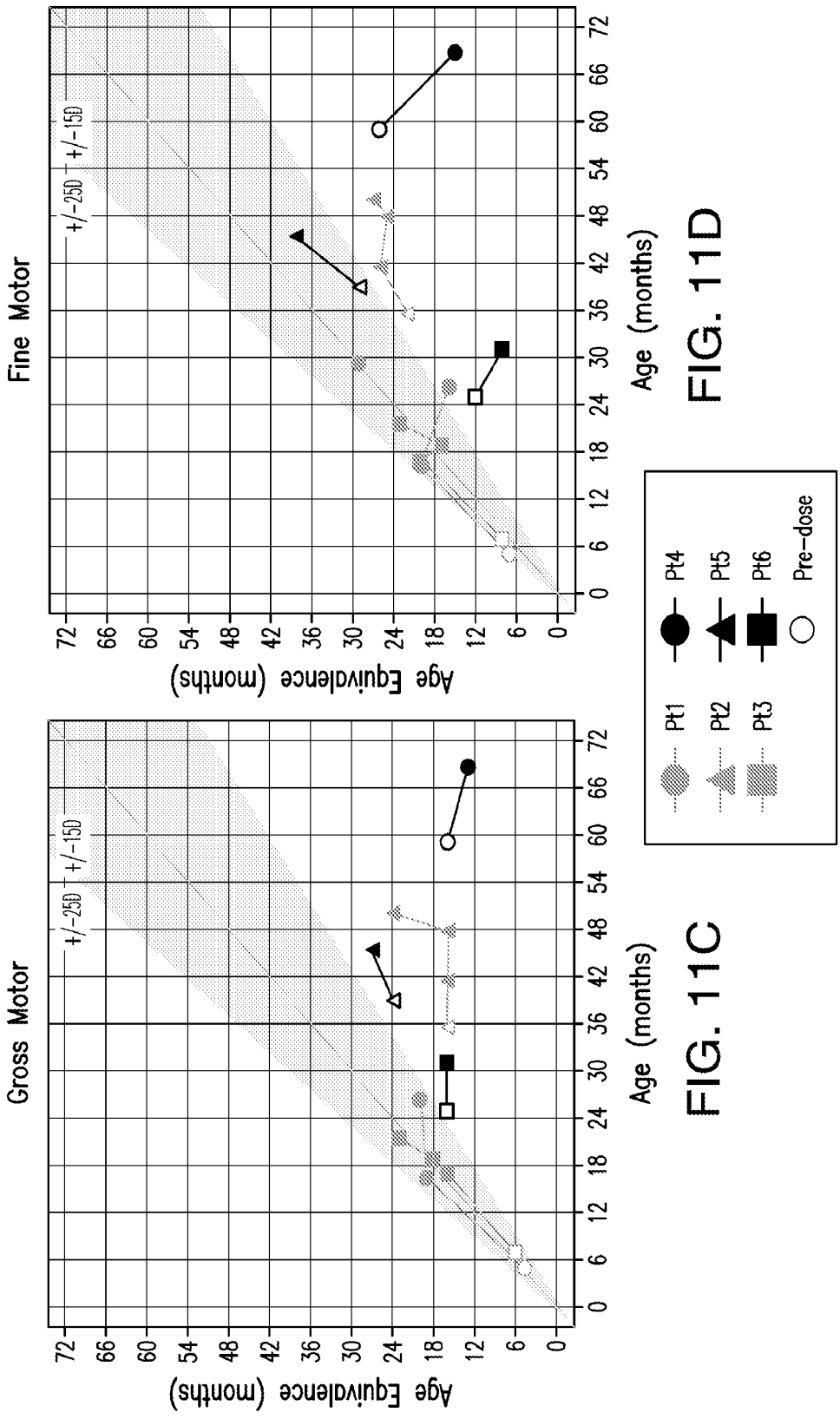


FIG. 11C

FIG. 11D

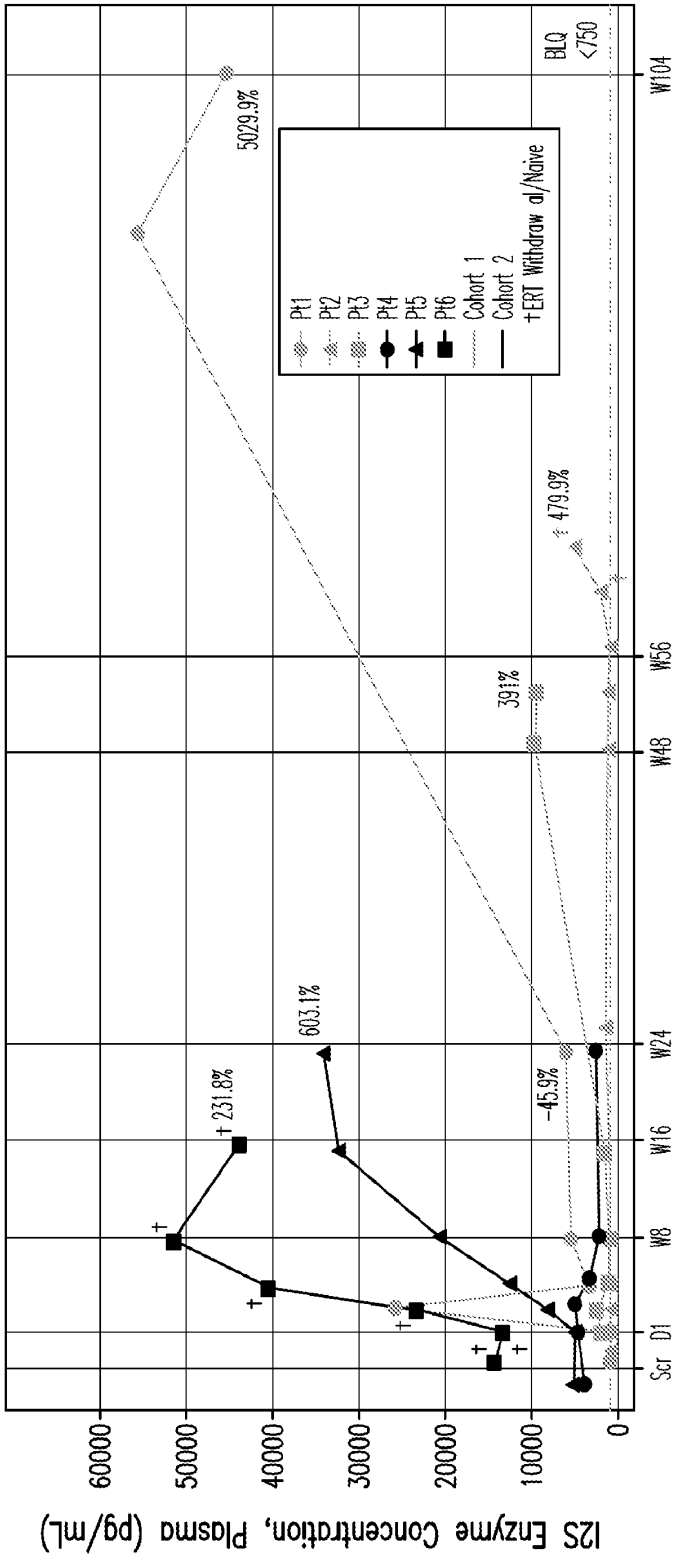

I2S Enzyme Concentration, Plasma (pg/mL)
60000
50000
40000
30000
20000
10000
0
Scr
D1
W8
W16
W24
W48
W56
W104
Time on Study
Pt1
Pt2
Pt3
Pt4
Pt5
Pt6
Cohort 1
Cohort 2
+ERT Withdraw d/Naive
BLQ
<750
5029.9%
479.9%
391%
603.1%
+ 231.8%
-45.9%

FIG. 12

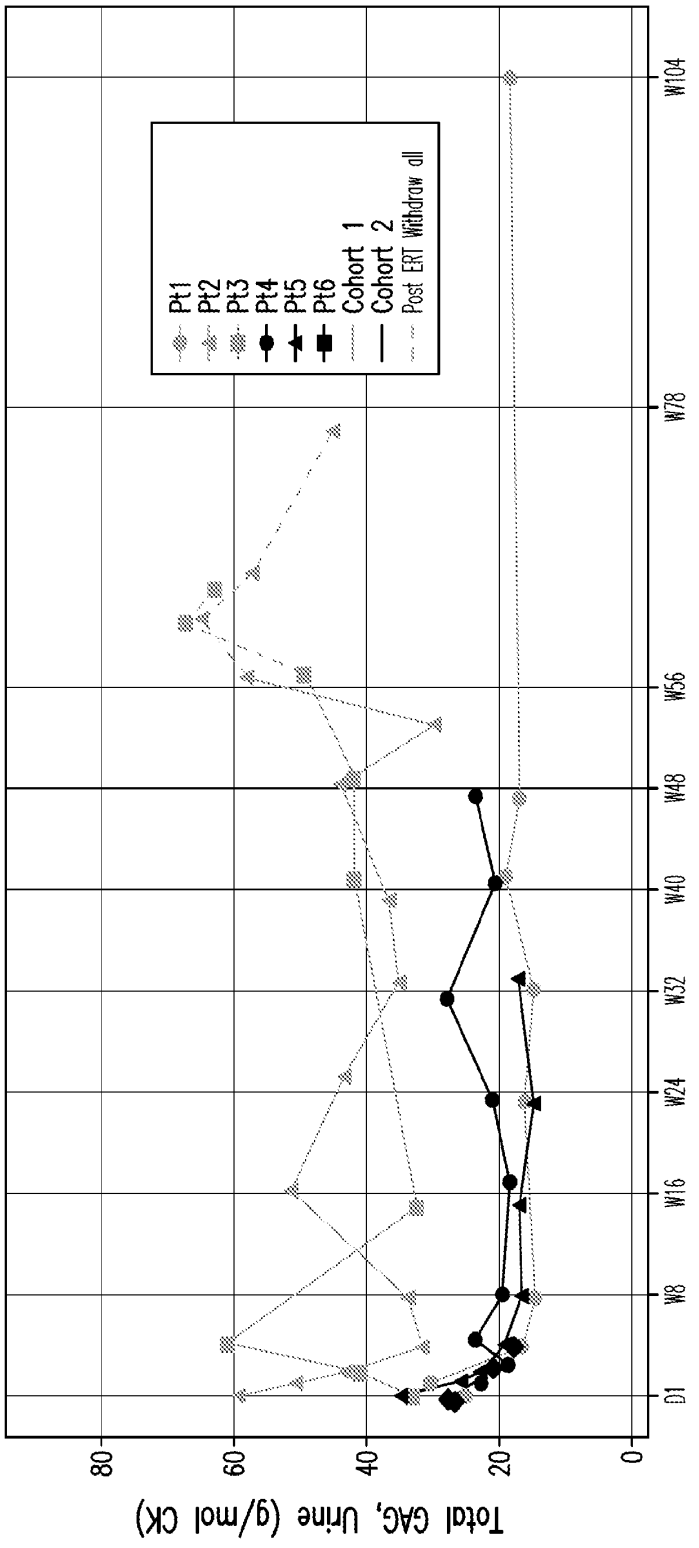

Total GAG, Urine (g/mol Ck)
0
20
40
60
80
D1
W8
W16
W24
W32
W40
W48
W56
W78
W104
Time on Study
Pt1
Pt2
Pt3
Pt4
Pt5
Pt6
Cohort 1
Cohort 2
Post ERT Withdraw dll

FIG. 13

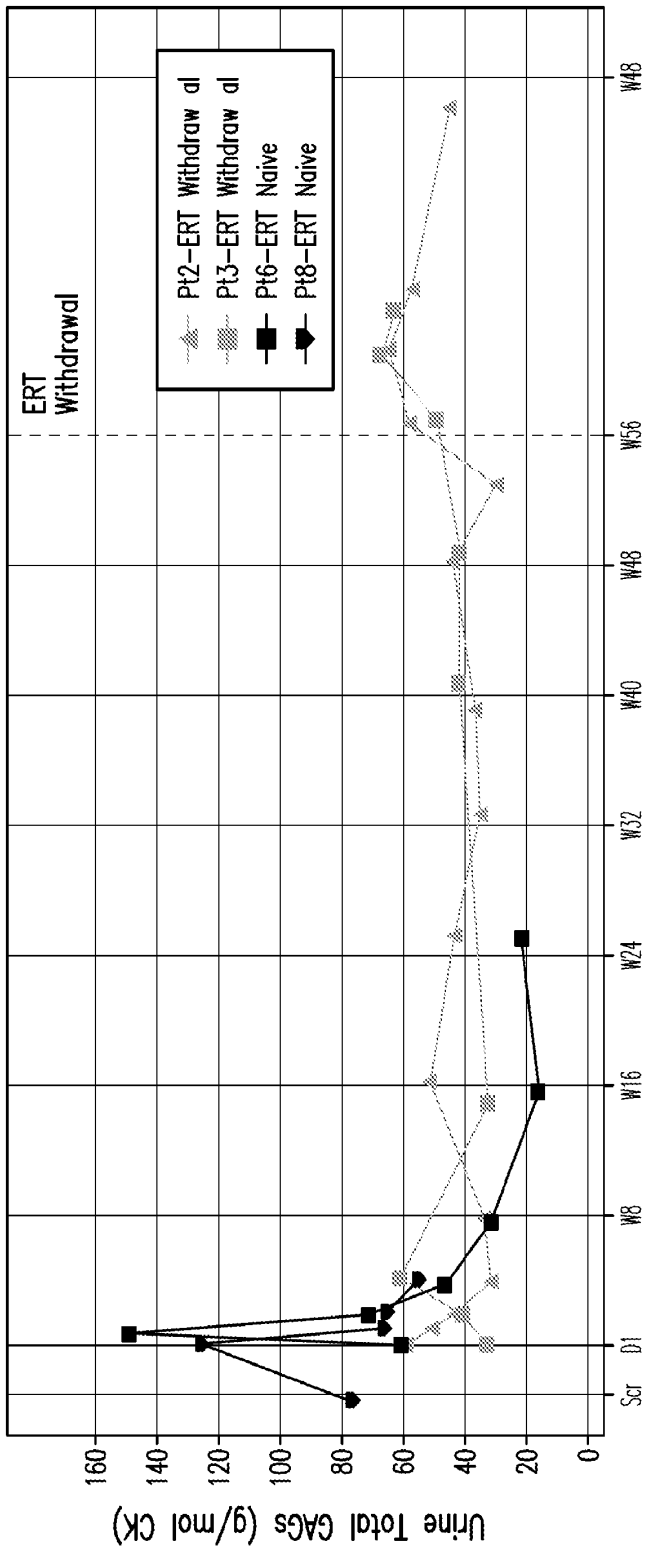

Urine Total GAGs (g/mol CK)
0
20
40
60
80
100
120
140
160
Scr
D1
W8
W16
W24
W32
W40
W48
W56
W48
Time on Study
ERT
Withdrawal
Pt2-ERT Withdraw al
Pt3-ERT Withdraw al
Pt6-ERT Naive
Pt8-ERT Naive

FIG. 14

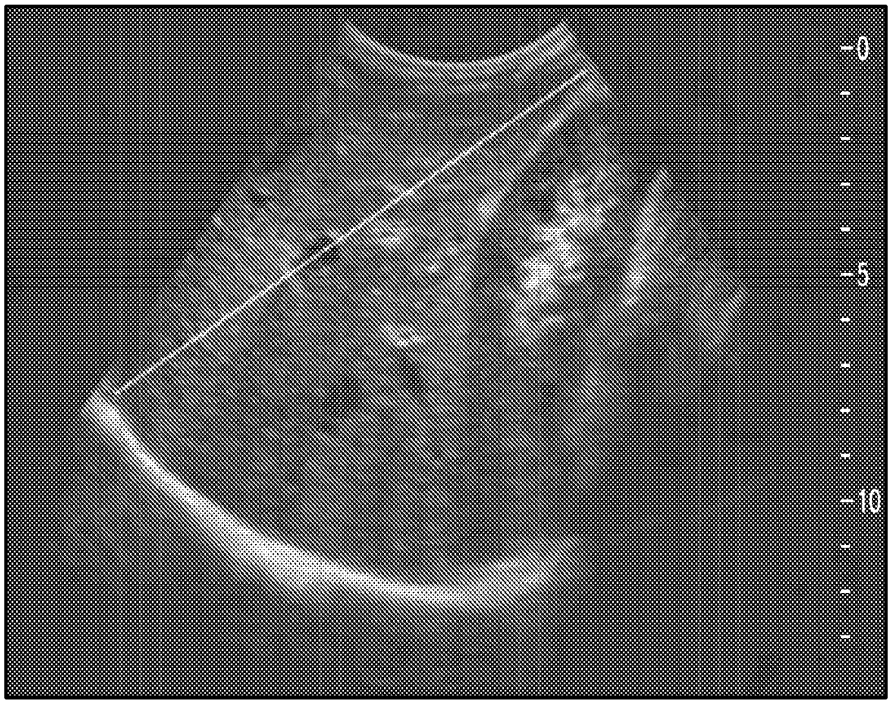


FIG. 15

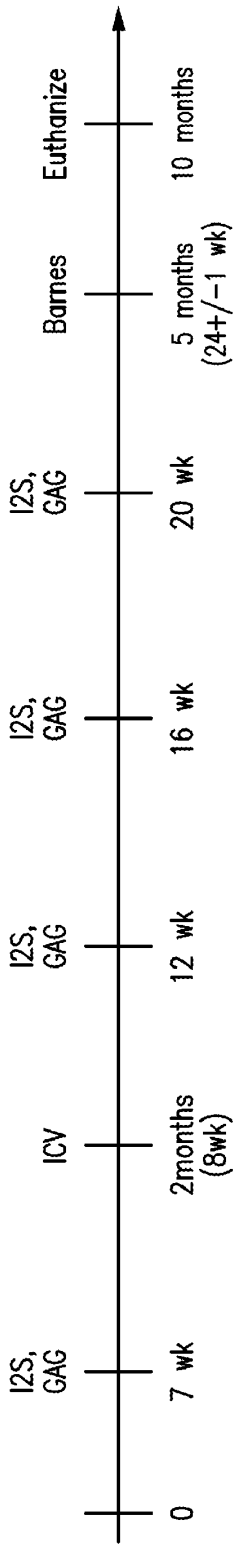

I2S, GAG
ICV
I2S, GAG
I2S, GAG
Barnes
Euthanize
0
7 wk
2months (8wk)
12 wk
16 wk
20 wk
5 months (24+/−1 wk)
10 months

FIG. 16

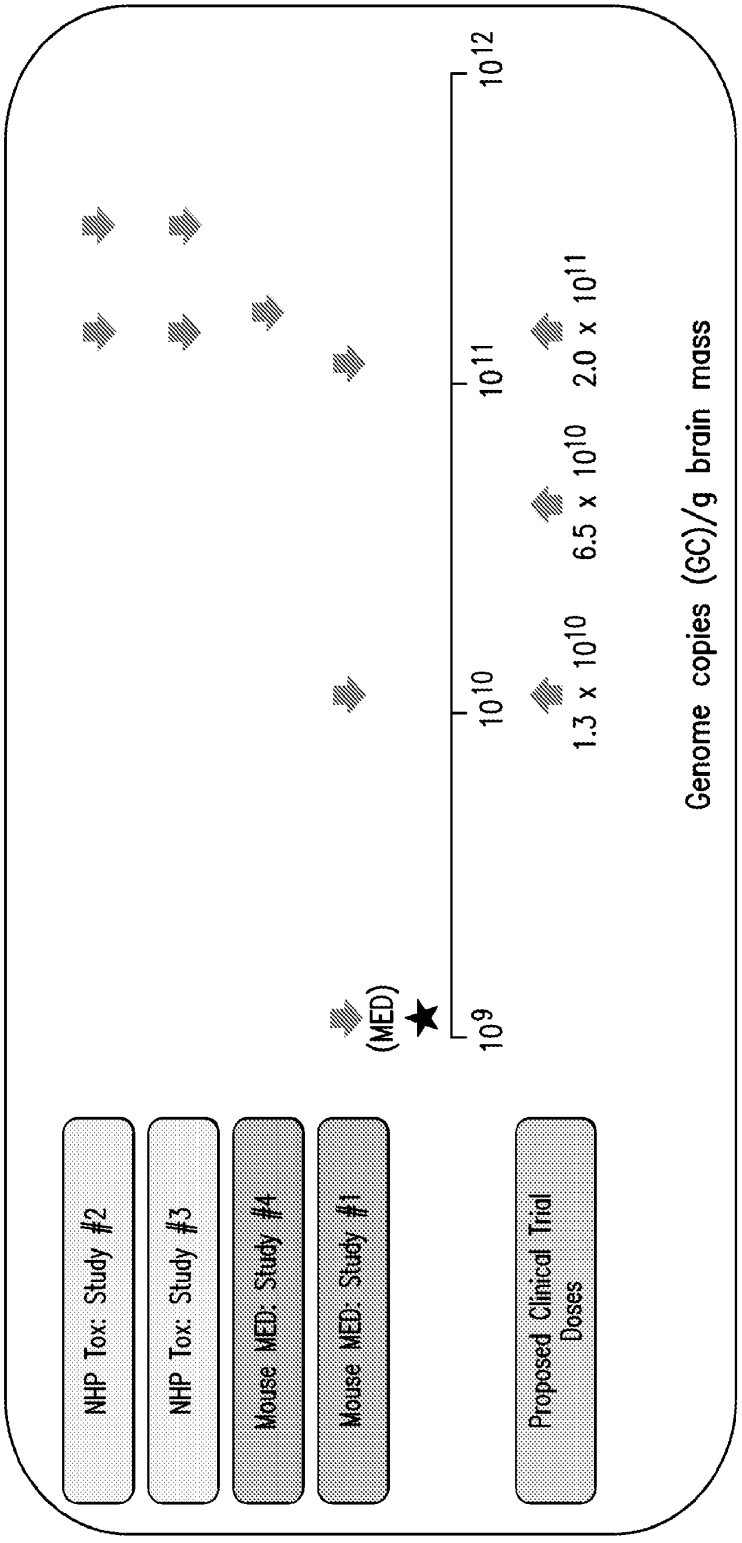

NHP Tox: Study #2
NHP Tox: Study #3
Mouse MED: Study #4
Mouse MED: Study #1
Proposed Clinical Trial Doses
(MED)
10^9
10^{10}
10^{11}
10^{12}
1.3×10^{10}
6.5×10^{10}
2.0×10^{11}
Genome copies (GC)/g brain mass

FIG. 17

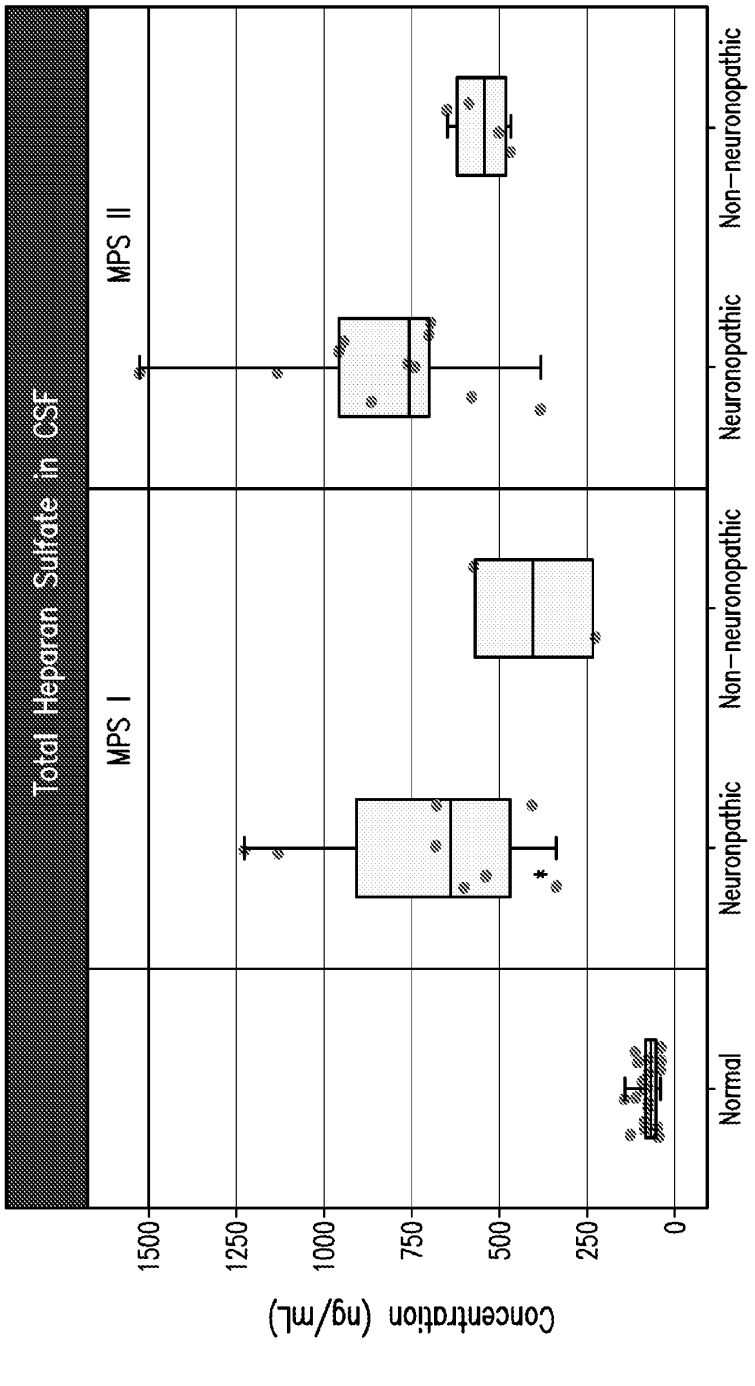

Total Heparan Sulfate in CSF
MPS I
MPS II
Concentration (ng/mL)
1500
1250
1000
750
500
250
0
Normal
Neuronpathic
Non-neuronopathic
Neuronopathic
Non-neuronopathic
Sample size
n=29*
n=8
n=2
11
4
Mean
72.3
700.2
400
844.2
551.7

FIG. 18

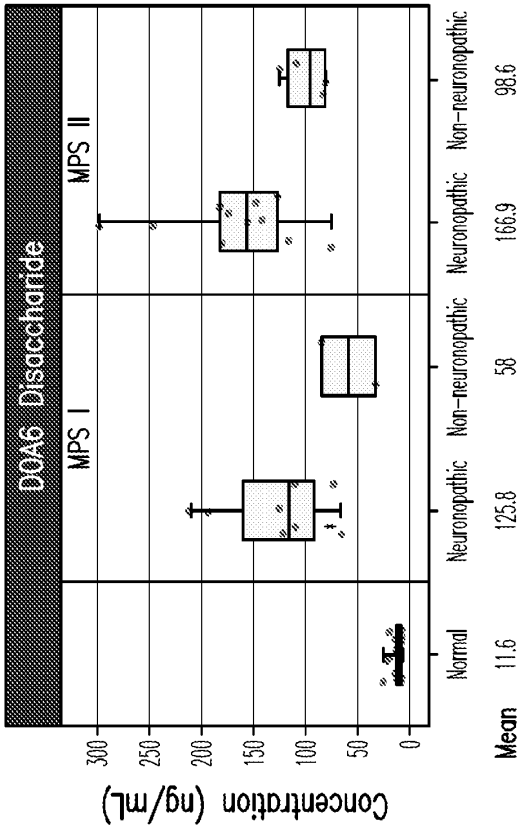


FIG. 19B

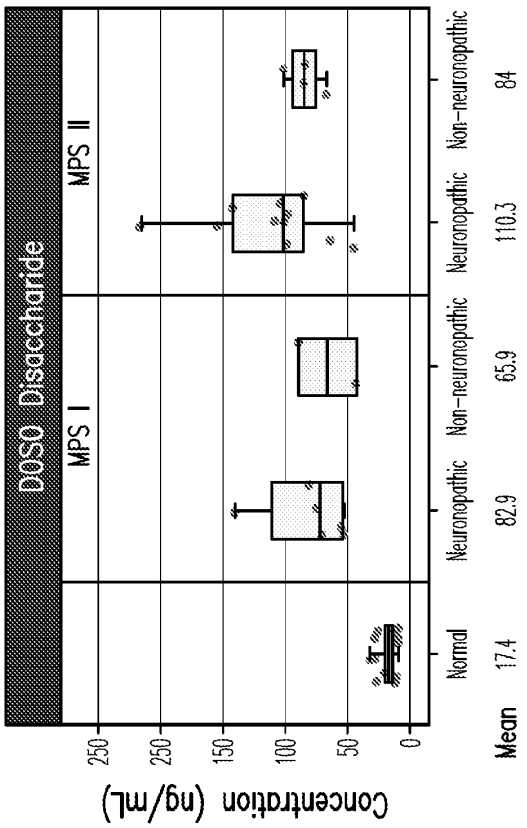


FIG. 19A

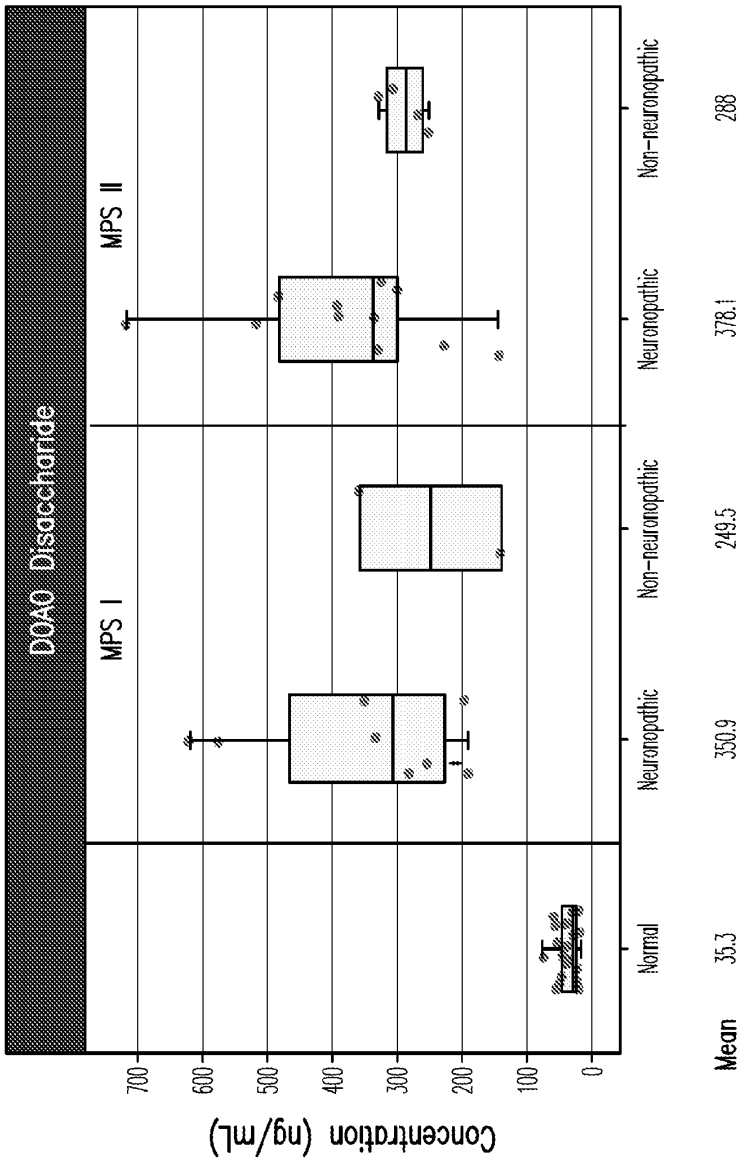

DOA0 Disaccharide
MPS I
MPS II
Concentration (ng/mL)
700
600
500
400
300
200
100
0
Mean
Normal
35.3
Neuronopathic
350.9
Non-neuronopathic
249.5
Neuronopathic
378.1
Non-neuronopathic
288

FIG. 19C

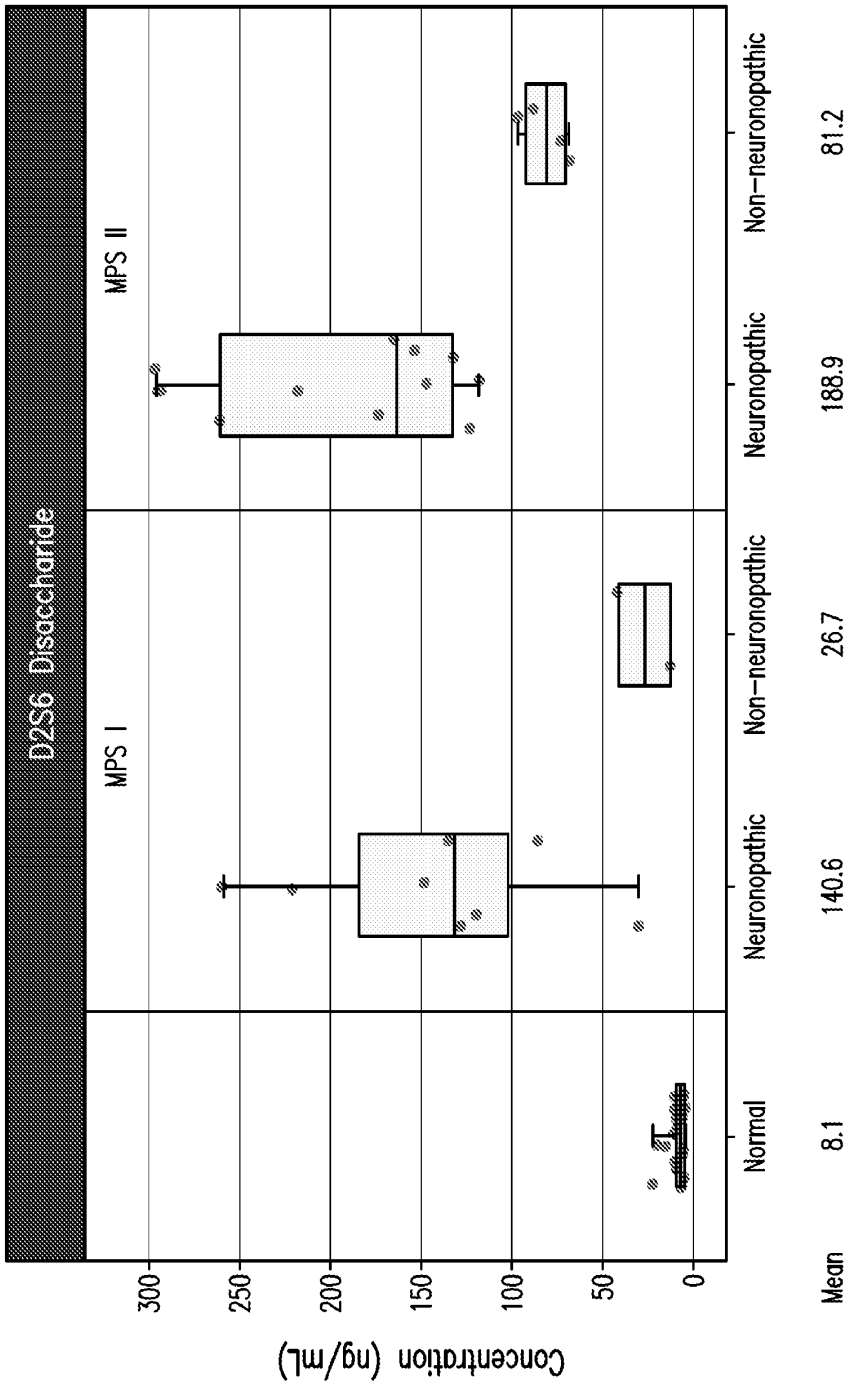

D2S6 Disaccharide
MPS I
MPS II
Concentration (ng/mL)
300
250
200
150
100
50
0
Normal
Neuronopathic
Non-neuronopathic
Neuronopathic
Non-neuronopathic
Mean
8.1
140.6
26.7
188.9
81.2

FIG. 20

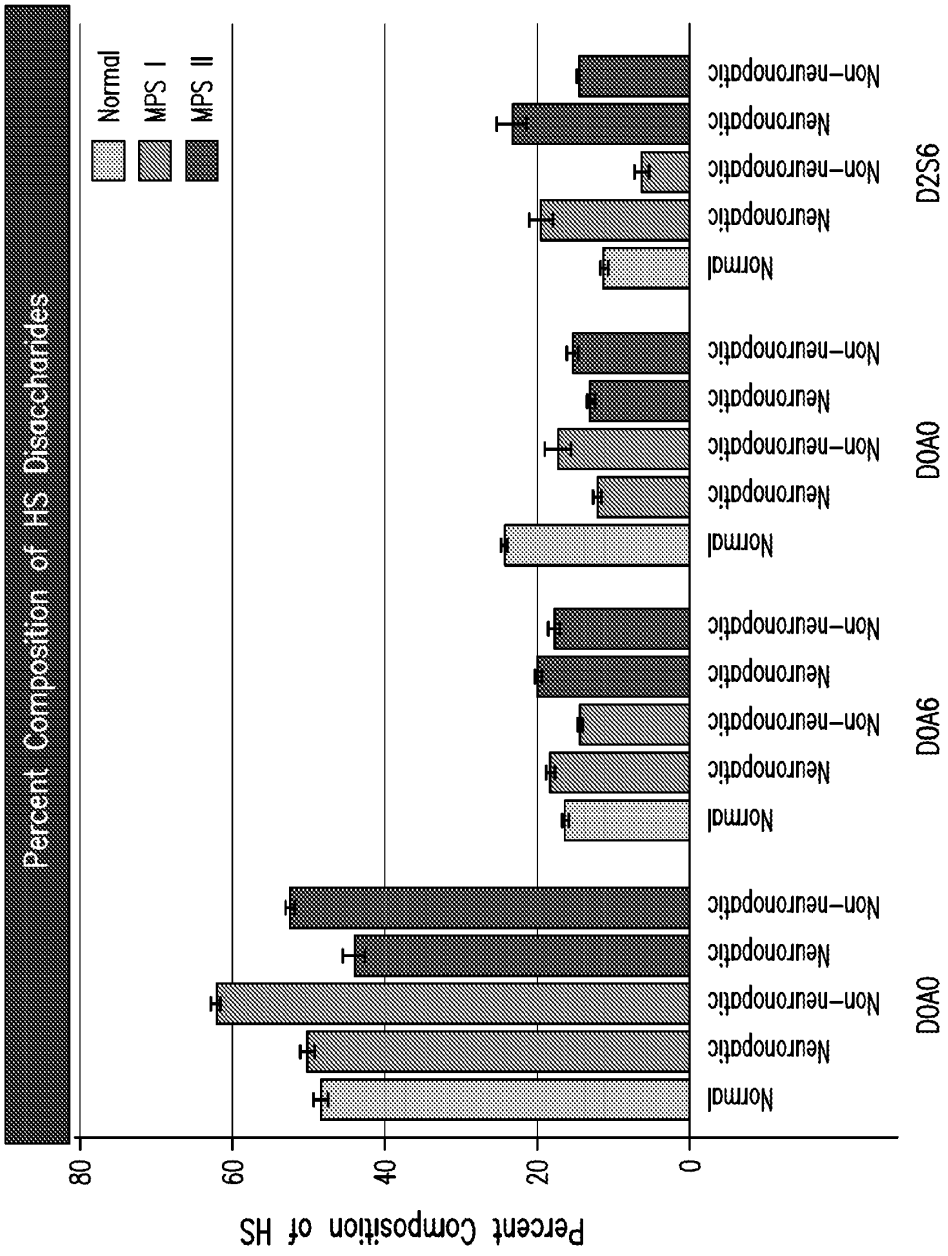

Percent Composition of HS Disaccharides
Normal
MPS I
MPS II
Percent Composition of HS
0
20
40
60
80
Normal
Neuronopathic
Non–neuronopathic
D0A0
Normal
Neuronopathic
Non–neuronopathic
D0A6
Normal
Neuronopathic
Non–neuronopathic
D0A0
Normal
Neuronopathic
Non–neuronopathic
D2S6

FIG. 21

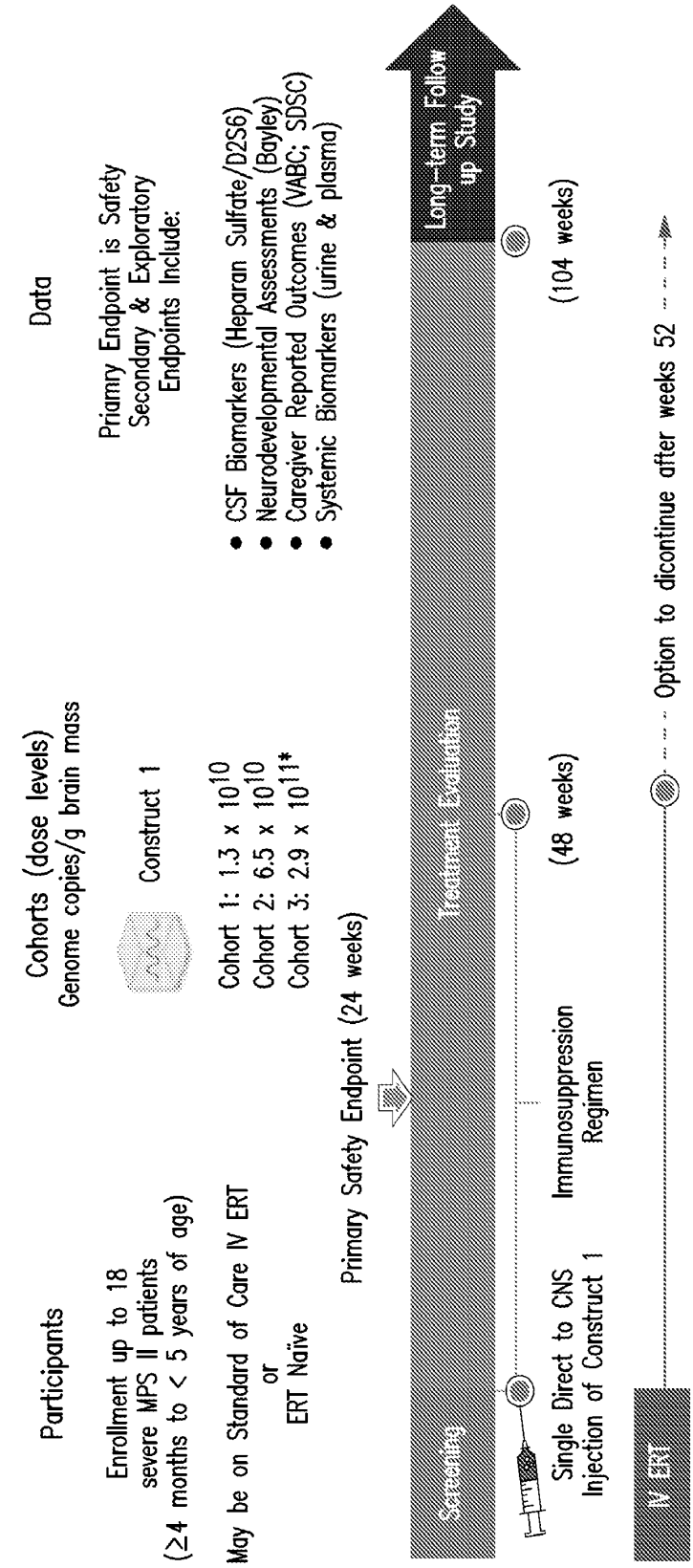

Participants
Enrollment up to 18
severe MPS II patients
(≥4 months to < 5 years of age)
May be on Standard of Care IV ERT
or
ERT Naïve
Cohorts (dose levels)
Genome copies/g brain mass
Construct 1
Cohort 1: 1.3 x 10^10
Cohort 2: 6.5 x 10^10
Cohort 3: 2.9 x 10^11*
Data
Priamry Endpoint is Safety
Secondary & Exploratory
Endpoints Include:
• CSF Biomarkers (Heparan Sulfate/D2S6)
• Neurodevelopmental Assessments (Bayley)
• Caregiver Reported Outcomes (VABC; SDSC)
• Systemic Biomarkers (urine & plasma)
Primary Safety Endpoint (24 weeks)
Screening
Treatment Evaluation
Long-term Follow up Study
Single Direct to CNS
Injection of Construct 1
Immunosuppression
Regimen
(48 weeks)
(104 weeks)
IV ERT
Option to discontinue after weeks 52

FIG. 22

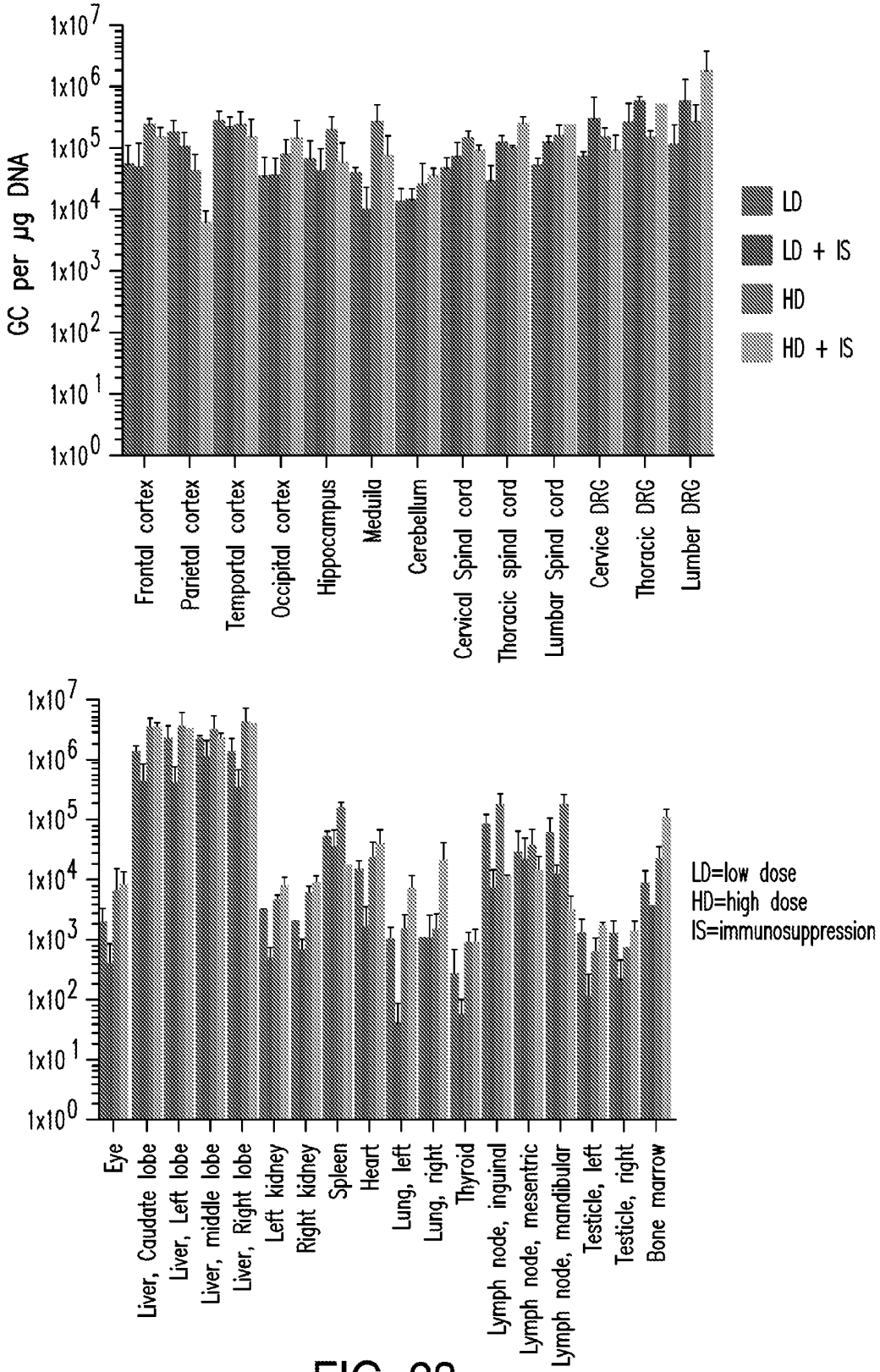

GC per µg DNA
1x10^7
1x10^6
1x10^5
1x10^4
1x10^3
1x10^2
1x10^1
1x10^0
LD
LD + IS
HD
HD + IS
Frontal cortex
Parietal cortex
Temportal cortex
Occipital cortex
Hippocampus
Medulla
Cerebellum
Cervical Spinal cord
Thoracic spinal cord
Lumbar Spinal cord
Cervice DRG
Thoracic DRG
Lumber DRG
Eye
Liver, Caudate lobe
Liver, Left lobe
Liver, middle lobe
Liver, Right lobe
Left kidney
Right kidney
Spleen
Heart
Lung, left
Lung, right
Thyroid
Lymph node, inguinal
Lymph node, mesentric
Lymph node, mandibular
Testicle, left
Testicle, right
Bone marrow
LD=low dose
HD=high dose
IS=immunosuppression

FIG. 23

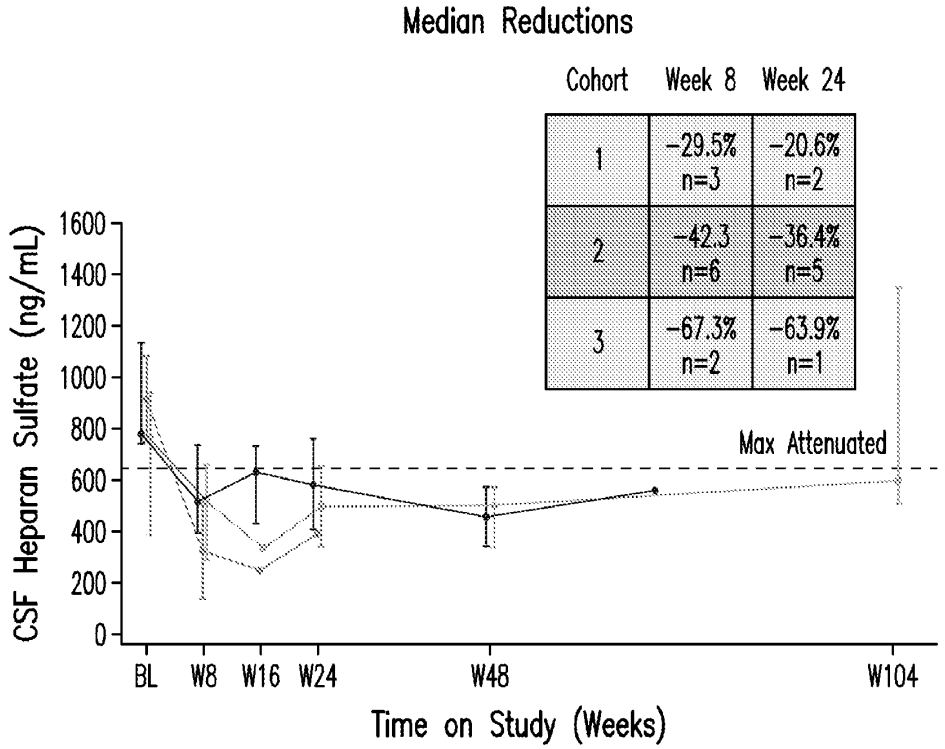


FIG. 24A

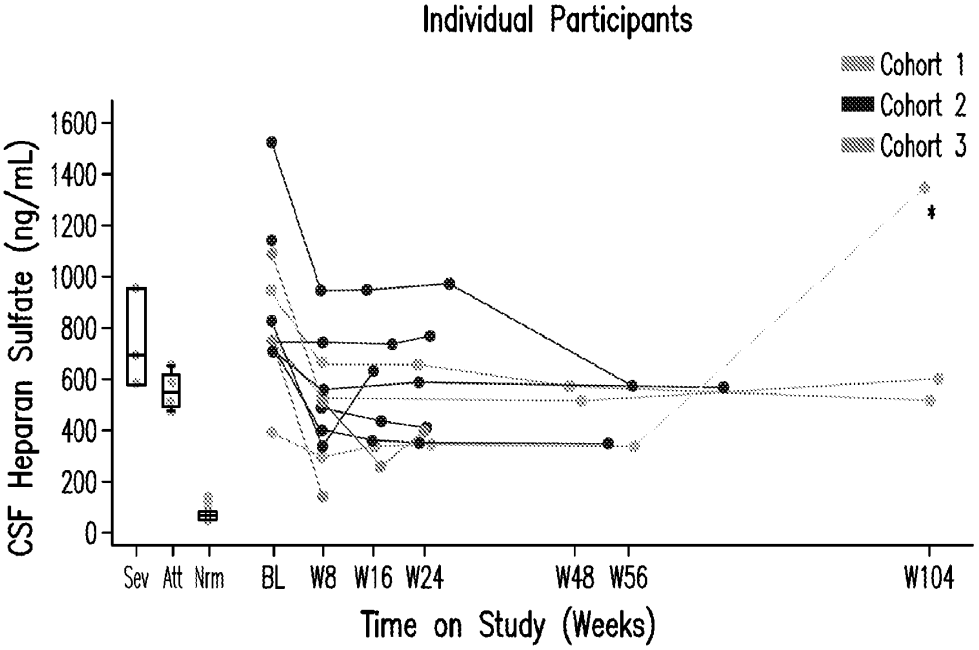


FIG. 24B

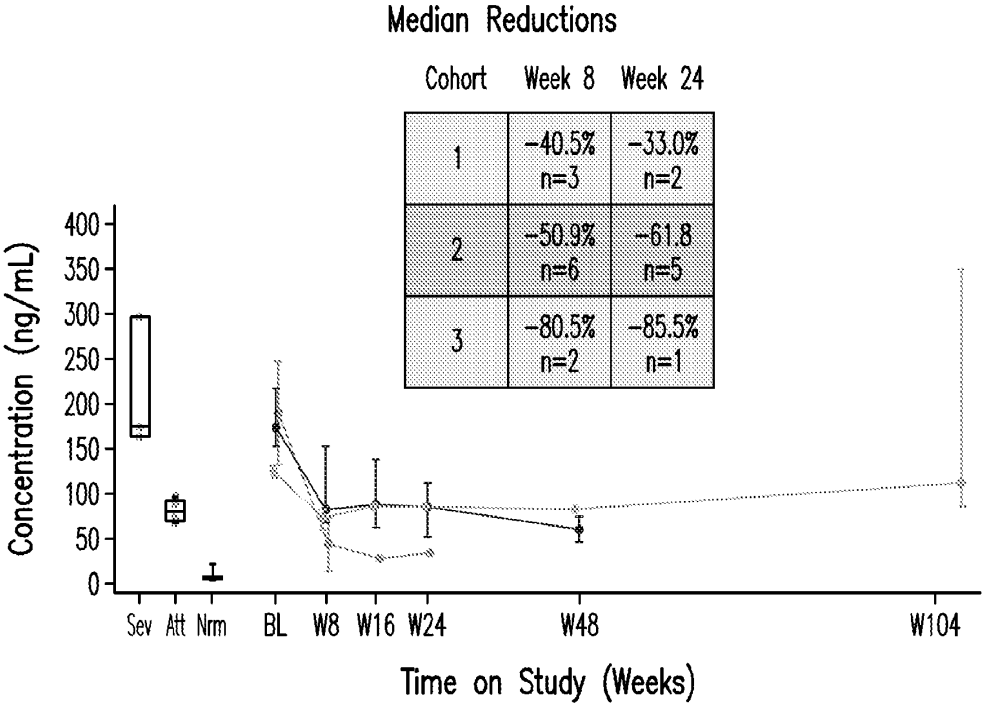


FIG. 25A

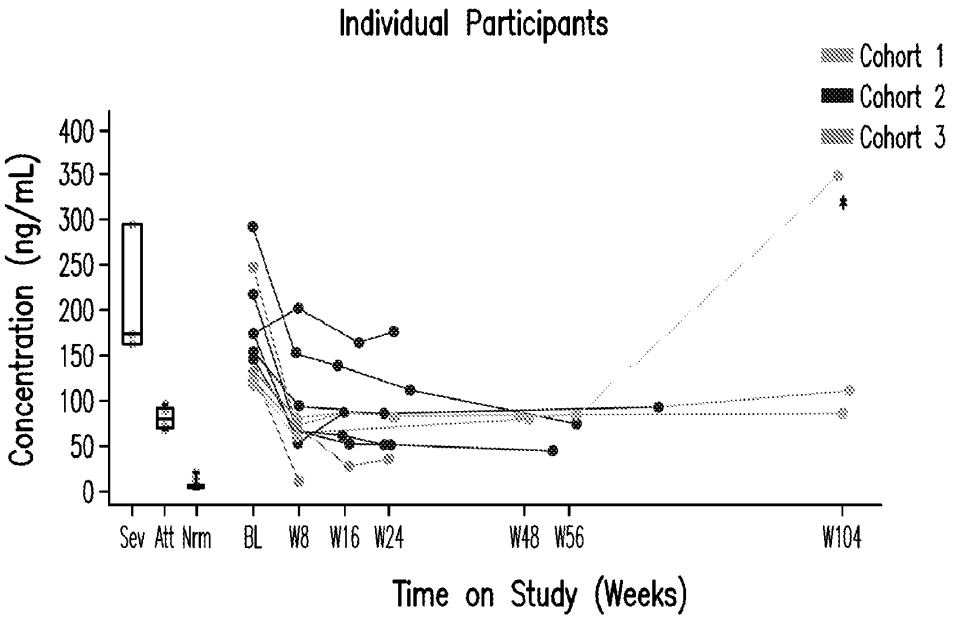


FIG. 25B

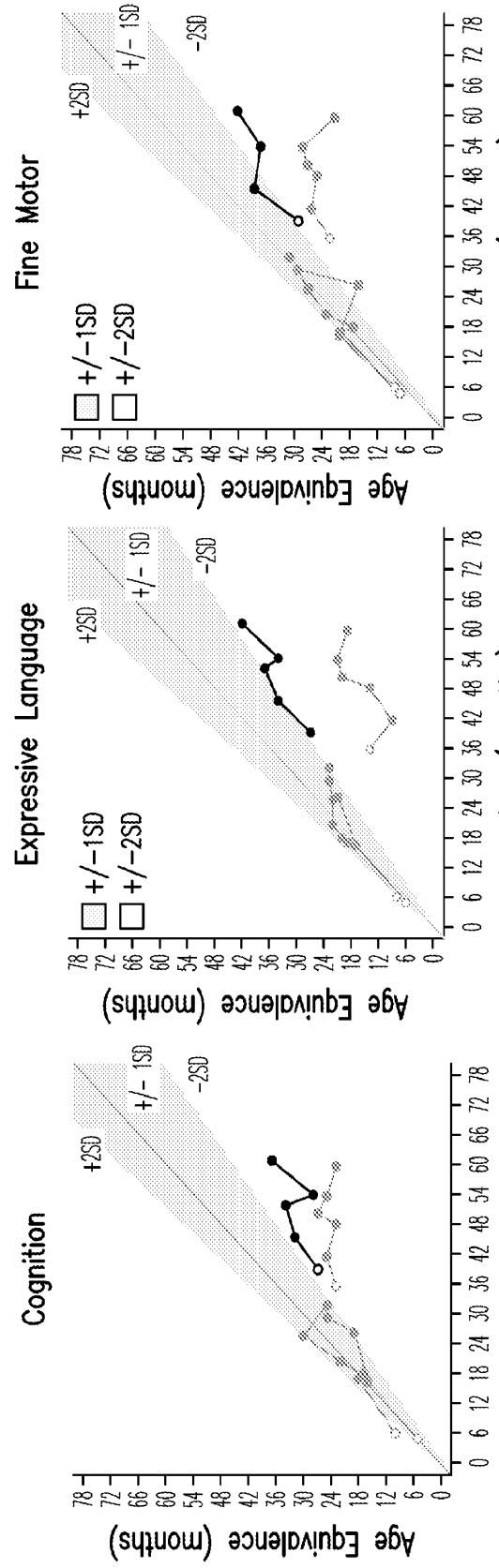


FIG. 26A

FIG. 26B

FIG. 26C

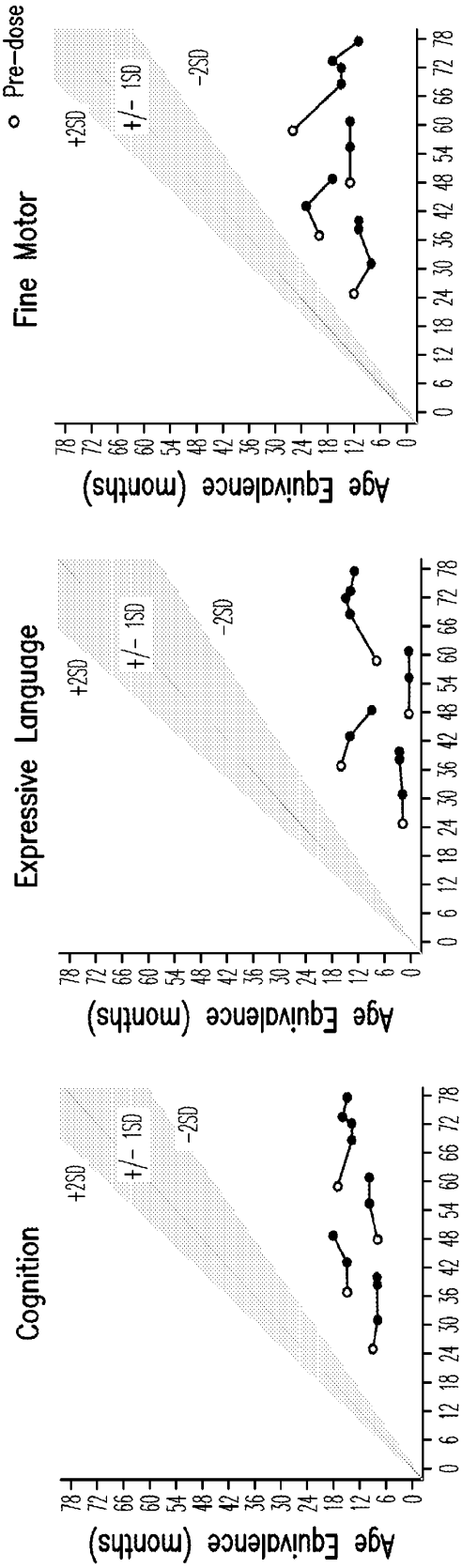


FIG. 27A FIG. 27B

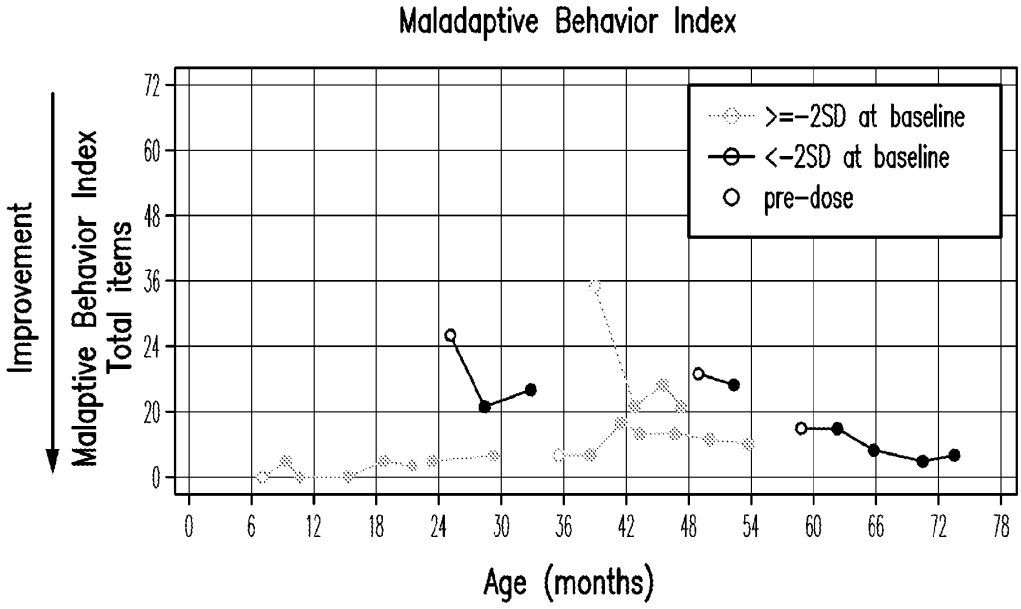


FIG. 28A

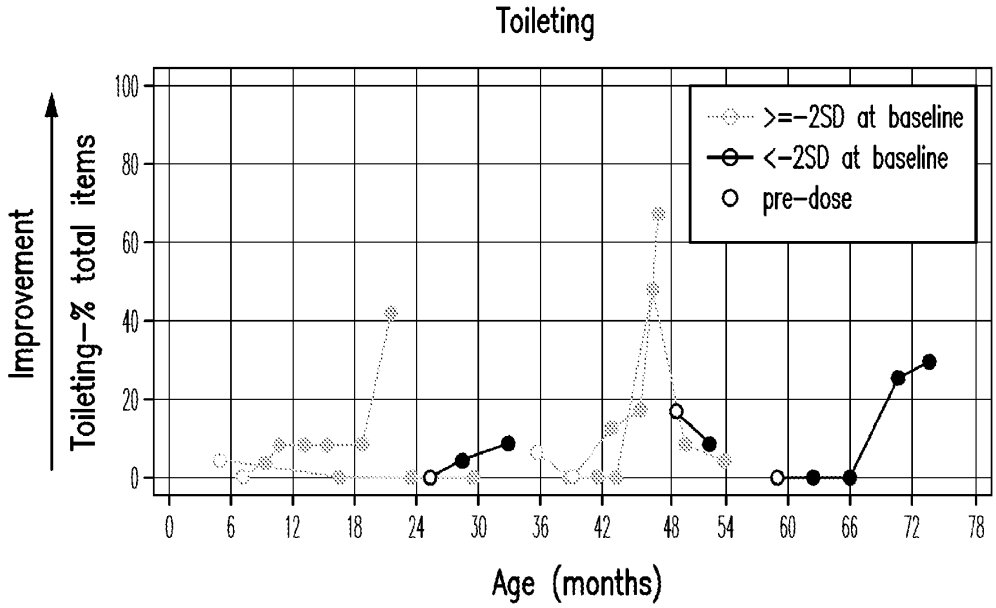


FIG. 28B

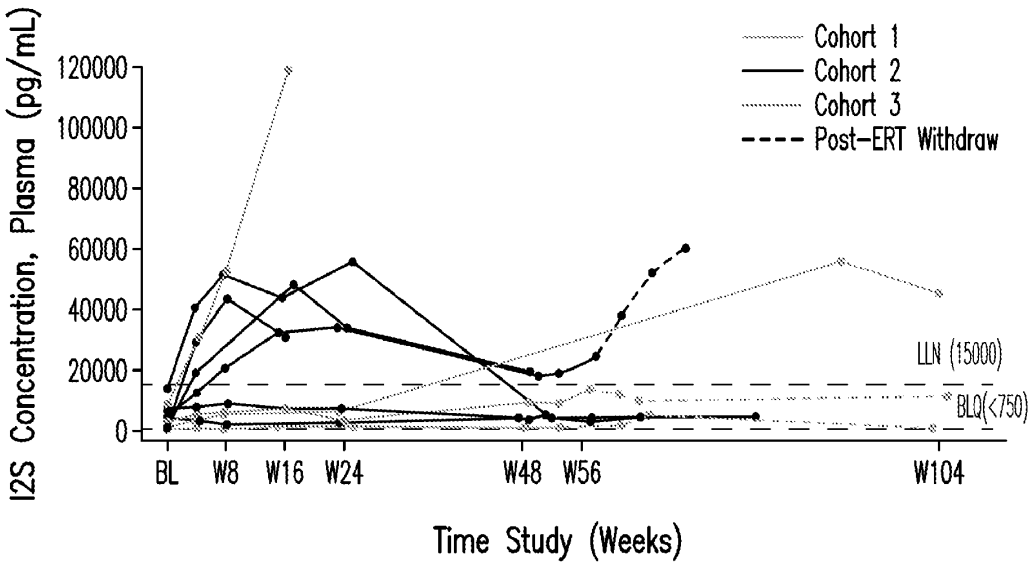


FIG. 29A

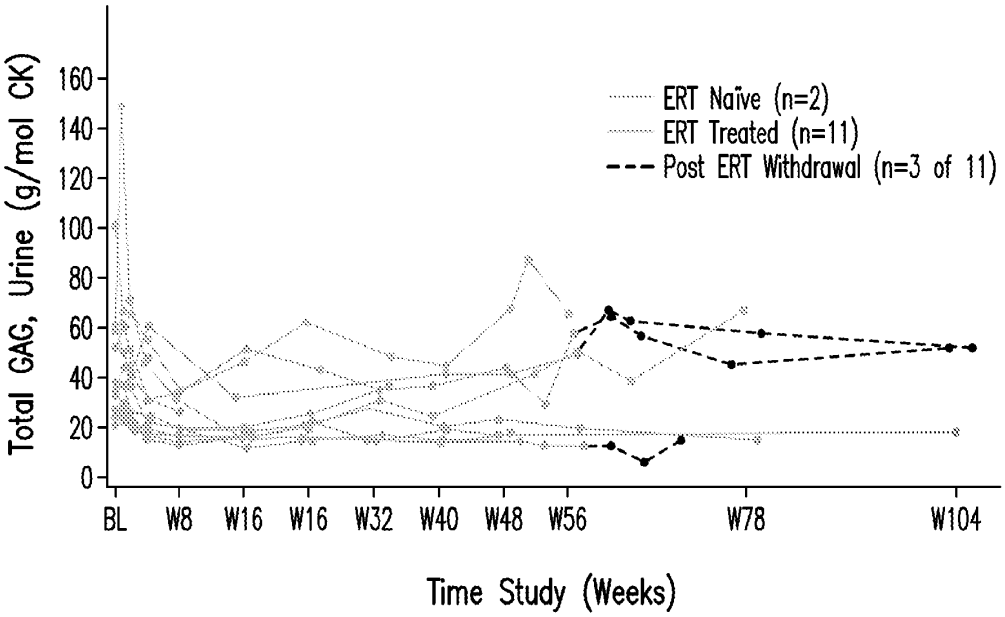


FIG. 29B

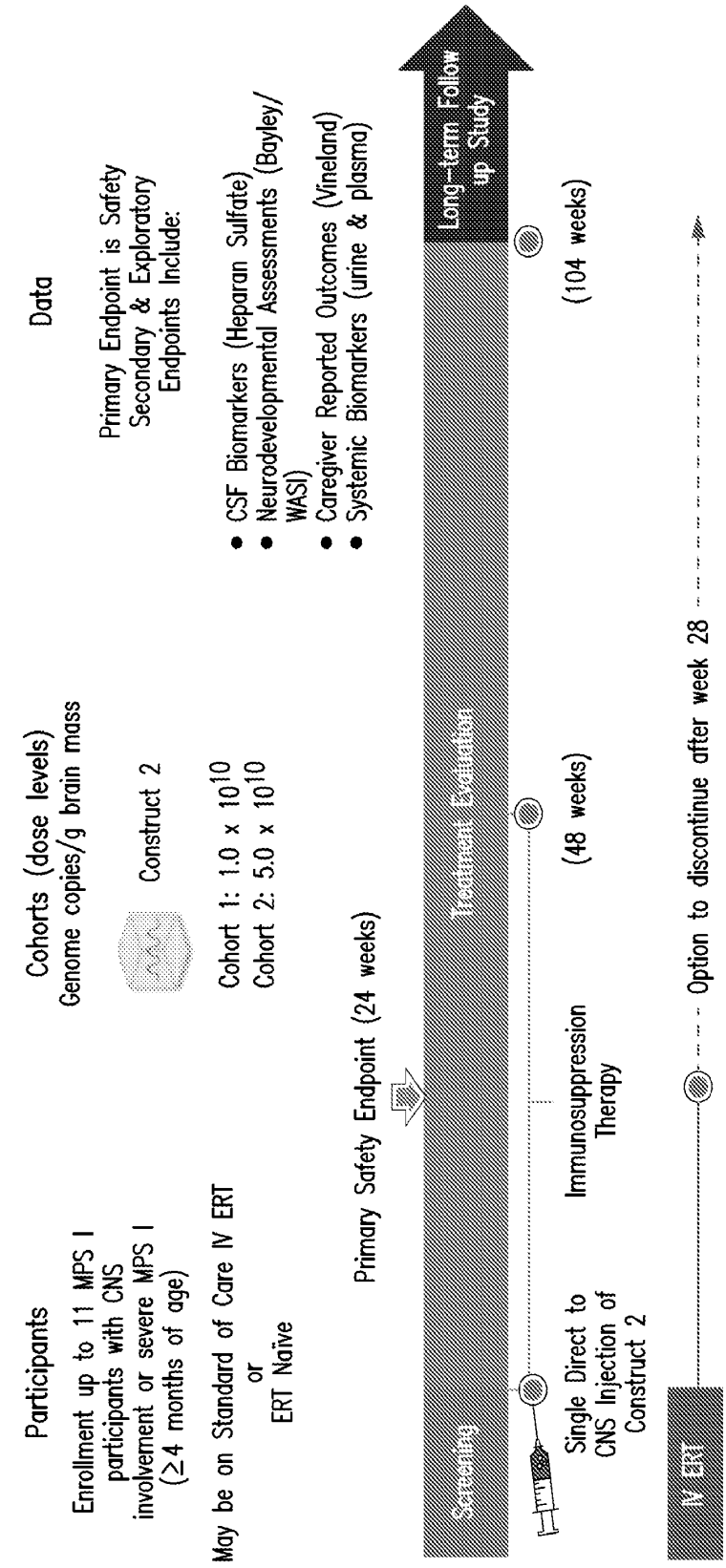

Participants
Enrollment up to 11 MPS I participants with CNS involvement or severe MPS I (≥4 months of age)
May be on Standard of Care IV ERT or ERT Naïve
Cohorts (dose levels)
Genome copies/g brain mass
Construct 2
Cohort 1: 1.0 x 10^10
Cohort 2: 5.0 x 10^10
Data
Primary Endpoint is Safety
Secondary & Exploratory Endpoints Include:
• CSF Biomarkers (Heparan Sulfate)
• Neurodevelopmental Assessments (Bayley/WASI)
• Caregiver Reported Outcomes (Vineland)
• Systemic Biomarkers (urine & plasma)
Primary Safety Endpoint (24 weeks)
Screening
Treatment Evaluation
Long-term Follow up Study
Single Direct to CNS Injection of Construct 2
Immunosuppression Therapy
(48 weeks)
(104 weeks)
IV ERT
Option to discontinue after week 28

FIG. 30

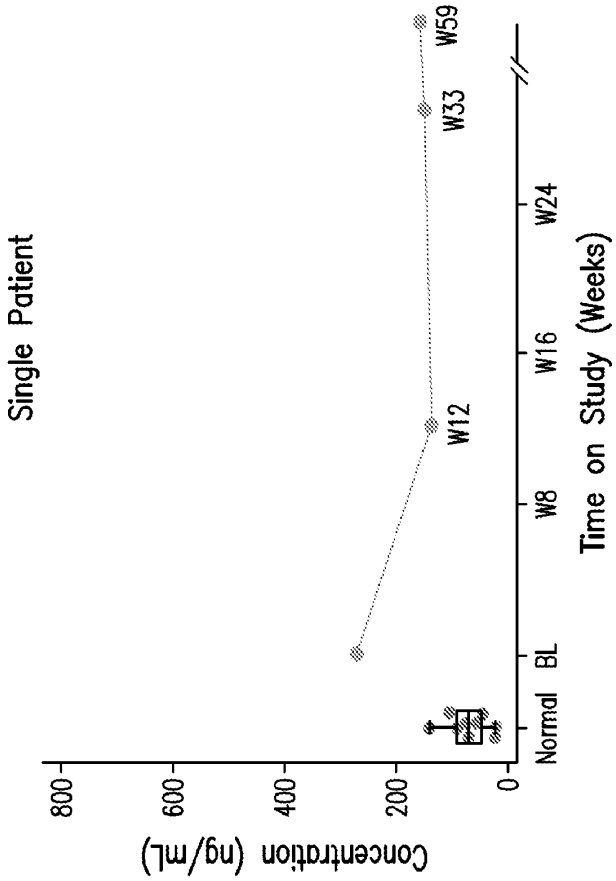


FIG. 31B

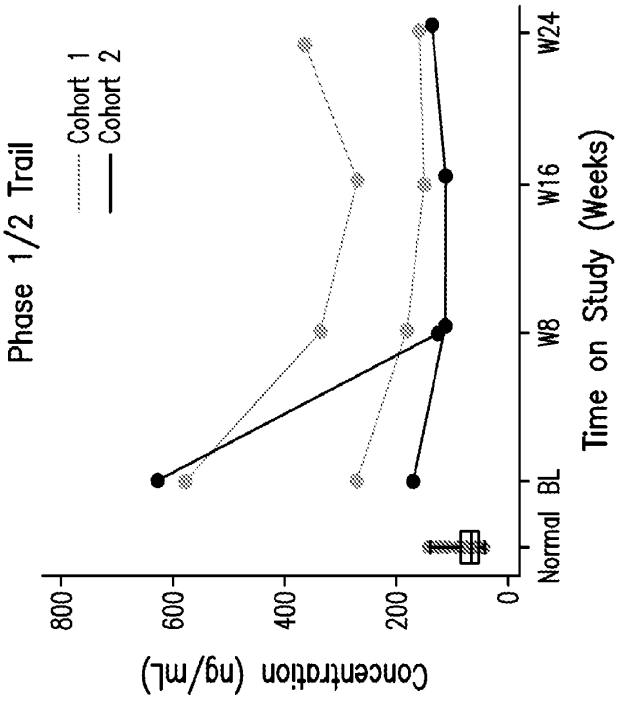


FIG. 31A

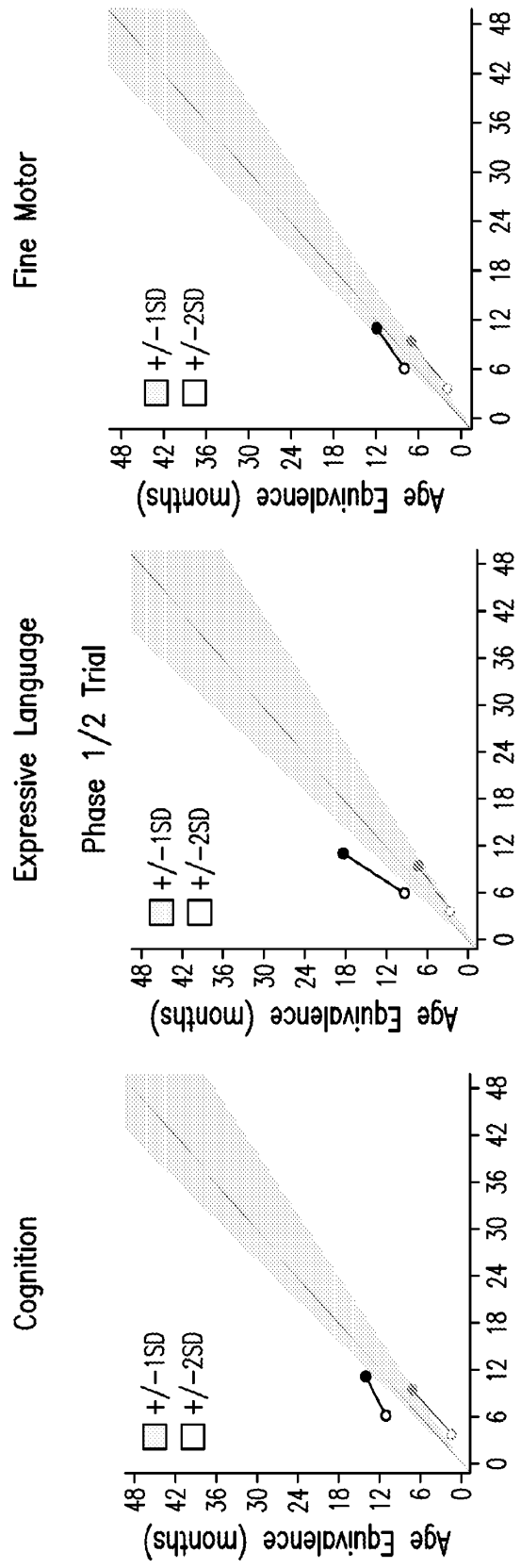


FIG. 32A

FIG. 32B

FIG. 32C

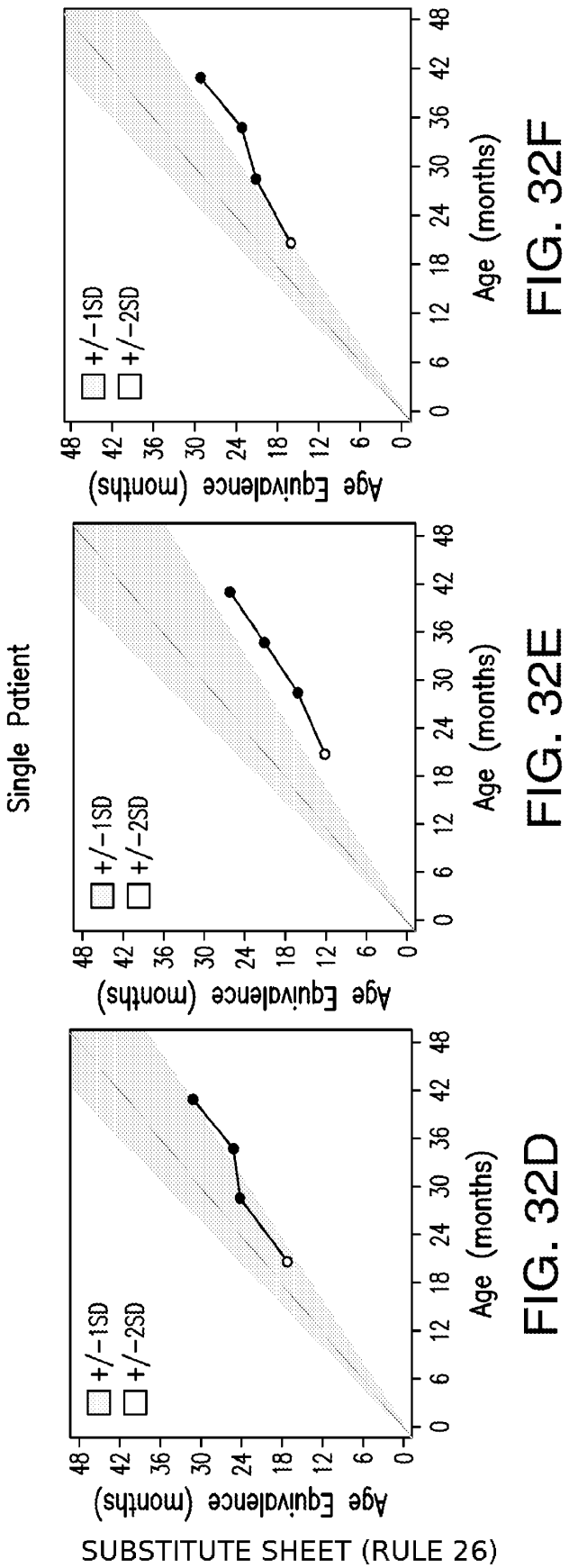


FIG. 32D

FIG. 32E

FIG. 32F

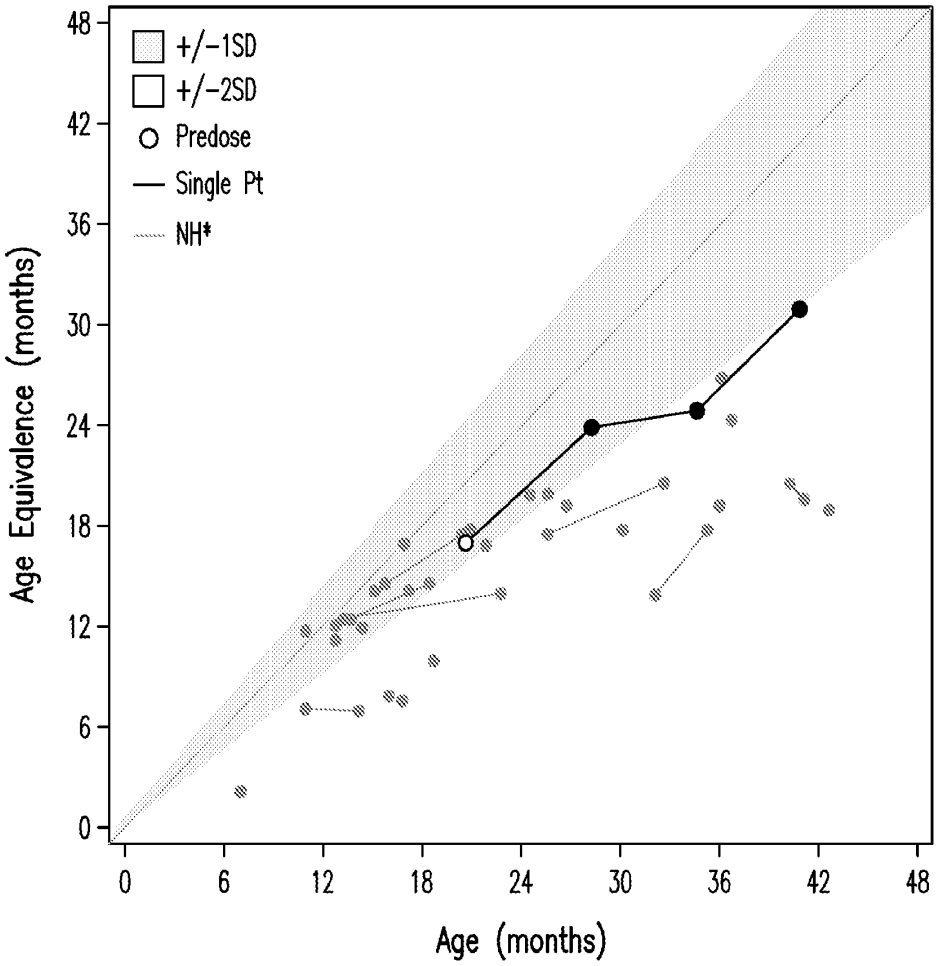

+/−1SD
+/−2SD
Predose
Single Pt
NH*
Age Equivalence (months)
Age (months)
0
6
12
18
24
30
36
42
48

FIG. 33

VABS–III Age Equivalent Scores (year:month)		
	Baseline Chronological Age 13y	Week 52 Chronological Age 14y
Personal (dressing, feeding, toileting, and washing/hygiene)	4:1	7:10
Domestic	7:7	6:7
Community	7:4	6:10
Interpersonal Relationships	5:10	7:4
Play and Leisure	8:1	8:1
Coping Skill	3:4	9:10
Adaptive Behavior	6:3	7:10
Fine Motor	5:7	6:4
Gross Motor	4:0	4:6

WASI–II Full Scale Composite		
	Baseline Chronological Age 13y	Week 52 Chronological Age 14y
Mean 100 (SD 15)	43	47

FIG. 34

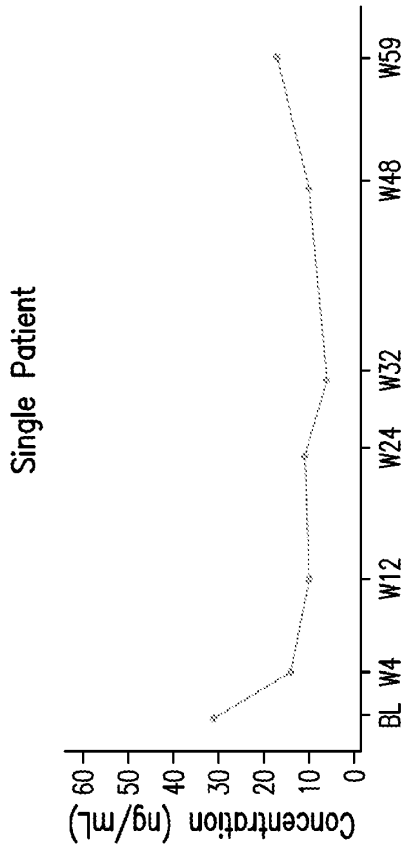


FIG. 35B

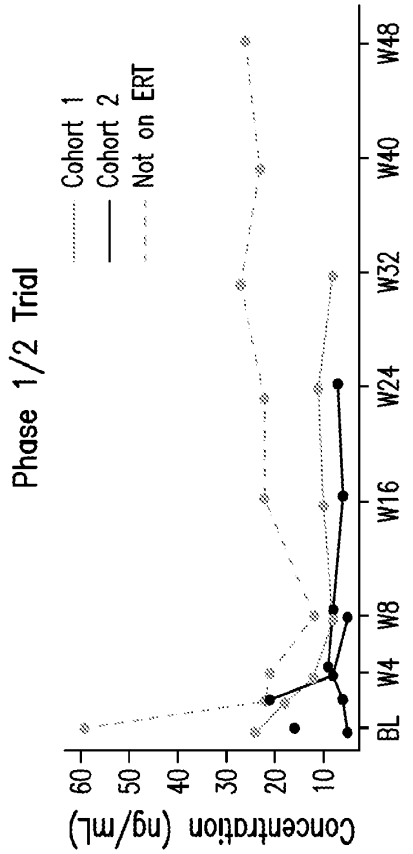


FIG. 35A

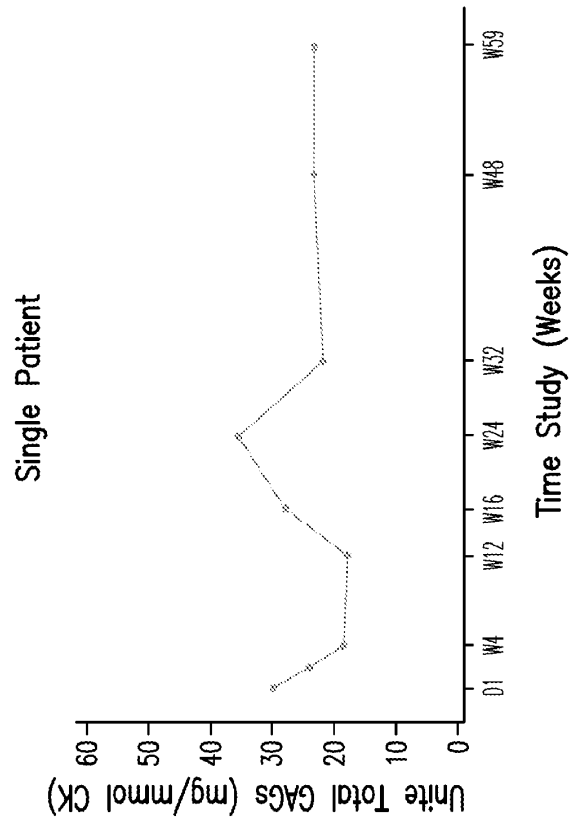


FIG. 36B

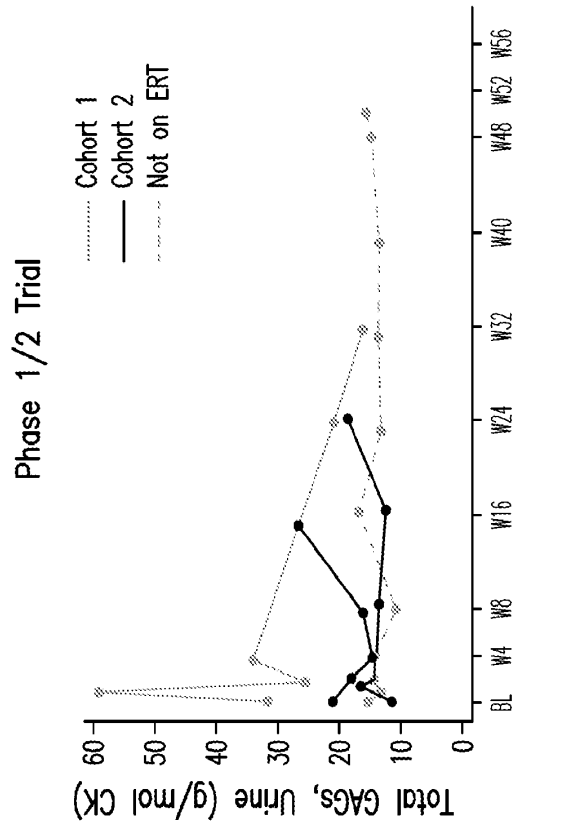


FIG. 36A