| | Arm A (n=6) | | Arm B (n=6) | | Arm C (n=6) | | Arm D (n=6) | | Arm E (n=6) | | Arm F (n=6) | | Arm G (n=6) | | Arm H (n=6) | | Arm I (n=6) | | Arm J (n=6) | | Arm K (n=6) | | Arm L (n=6) | | Arm M (n=6) | | Arm N (n=6) | | Arm O (n=6) | | Arm P (n=6) | | Arm Q (n=6) | | Arm R (n=6) | | Arm S (n=6) | | Arm T (n=6) | | Arm U (n=6) | | Arm V (n=6) | | Arm W (n=6) | | Arm X (n=6) | | Arm Y (n=6) | | Arm Z (n=6) | | Arm AA (n=6) | | Arm AB (n=6) | | Arm AC (n=6) | | Arm AD (n=6) | | Arm AE (n=6) | | Arm AF (n=6) | | Arm AG (n=6) | | Arm AH (n=6) | | Arm AI (n=6) | | Arm AJ (n=6) | | Arm AK (n=6) | | Arm AL (n=6) | | Arm AM (n=6) | | Arm AN (n=6) | | Arm AO (n=6) | | Arm AP (n=6) | | Arm AQ (n=6) | | Arm AR (n=6) | | Arm AS (n=6) | | Arm AT (n=6) | | Arm AU (n=6) | | Arm AV (n=6) | | Arm AW (n=6) | | Arm AX (n=6) | | Arm AY (n=6) | | Arm AZ (n=6) | | Arm BA (n=6) | | Arm BB (n=6) | | Arm BC (n=6) | | Arm BD (n=6) | | Arm BE (n=6) | | Arm BF (n=6) | | Arm BG (n=6) | | Arm BH (n=6) | | Arm BI (n=6) | | Arm BJ (n=6) | | Arm BK (n=6) | | Arm BL (n=6) | | Arm BM (n=6) | | Arm BN (n=6) | | Arm BO (n=6) | | Arm BP (n=6) | | Arm BQ (n=6) | | Arm BR (n=6) | | Arm BS (n=6) | | Arm BT (n=6) | | Arm BU (n=6) | | Arm BV (n=6) | | Arm BW (n=6) | | Arm BX (n=6) | | Arm BY (n=6) | | Arm BZ (n=6) | | Arm CA (n=6) | | Arm CB (n=6) | | Arm CC (n=6) | | Arm CD (n=6) | | Arm CE (n=6) | | Arm CF (n=6) | | Arm CG (n=6) | | Arm CH (n=6) | | Arm CI (n=6) | | Arm CJ (n=6) | | Arm CK (n=6) | | Arm CL (n=6) | | Arm CM (n=6) | | Arm CN (n=6) | | Arm CO (n=6) | | Arm CP (n=6) | | Arm CQ (n=6) | | Arm CR (n=6) | | Arm CS (n=6) | | Arm CT (n=6) | | Arm CU (n=6) | | Arm CV (n=6) | | Arm CW (n=6) | | Arm CX (n=6) | | Arm CY (n=6) | | Arm CZ (n=6) | | Arm DA (n=6) | | Arm DB (n=6) | | Arm DC (n=6) | | Arm DD (n=6) | | Arm DE (n=6) | | Arm DF (n=6) | | Arm DG (n=6) | | Arm DH (n=6) | | Arm DI (n=6) | | Arm DJ (n=6) | | Arm DK (n=6) | | Arm DL (n=6) | | Arm DM (n=6) | | Arm DN (n=6) | | Arm DO (n=6) | | Arm DP (n=6) | | Arm DQ (n=6) | | Arm DR (n=6) | | Arm DS (n=6) | | Arm DT (n=6) | | Arm DU (n=6) | | Arm DV (n=6) | | Arm DW (n=6) | | Arm DX (n=6) | | Arm DY (n=6) | | Arm DZ (n=6) | | Arm EA (n=6) | | Arm EB (n=6) | | Arm EC (n=6) | | Arm ED (n=6) | | Arm EE (n=6) | | Arm EF (n=6) | | Arm EG (n=6) | | Arm EH (n=6) | | Arm EI (n=6) | | Arm EJ (n=6) | | Arm EK (n=6) | | Arm EL (n=6) | | Arm EM (n=6) | | Arm EN (n=6) | | Arm EO (n=6) | | Arm EP (n=6) | | Arm EQ (n=6) | | Arm ER (n=6) | | Arm ES (n=6) | | Arm ET (n=6) | | Arm EU (n=6) | | Arm EV (n=6) | | Arm EW (n=6) | | Arm EX (n=6) | | Arm EY (n=6) | | Arm EZ (n=6) | | Arm FA (n=6) | | Arm FB (n=6) | | Arm FC (n=6) | | Arm FD (n=6) | | Arm FE (n=6) | | Arm FF (n=6) | | Arm FG (n=6) | | Arm FH (n=6) | | Arm FI (n=6) | | Arm FJ (n=6) | | Arm FK (n=6) | | Arm FL (n=6) | | Arm FM (n=6) | | Arm FN (n=6) | | Arm FO (n=6) | | Arm FP (n=6) | | Arm FQ (n=6) | | Arm FR (n=6) | | Arm FS (n=6) | | Arm FT (n=6) | | Arm FU (n=6) | | Arm FV (n=6) | | Arm FW (n=6) | | Arm FX (n=6) | | Arm FY (n=6) | | Arm FZ (n=6) | | Arm GA (n=6) | | Arm GB (n=6) | | Arm GC (n=6) | | Arm GD (n=6) | | Arm GE (n=6) | | Arm GF (n=6) | | Arm GG (n=6) | | Arm GH (n=6) | | Arm GI (n=6) | | Arm GJ (n=6) | | Arm GK (n=6) | | Arm GL (n=6) | | Arm GM (n=6) | | Arm GN (n=6) | | Arm GO (n=6) | | Arm GP (n=6) | | Arm GQ (n=6) | | Arm GR (n=6) | | Arm GS (n=6) | | Arm GT (n=6) | | Arm GU (n=6) | | Arm GV (n=6) | | Arm GW (n=6) | | Arm GX (n=6) | | Arm GY (n=6) | | Arm GZ (n=6) | | Arm HA (n=6) | | Arm HB (n=6) | | Arm HC (n=6) | | Arm HD (n=6) | | Arm HE (n=6) | | Arm HF (n=6) | | Arm HG (n=6) | | Arm HH (n=6) | | Arm HI (n=6) | | Arm HJ (n=6) | | Arm HK (n=6) | | Arm HL (n=6) | | Arm HM (n=6) | | Arm HN (n=6) | | Arm HO (n=6) | | Arm HP (n=6) | | Arm HQ (n=6) | | Arm HR (n=6) | | Arm HS (n=6) | | Arm HT (n=6) | | Arm HU (n=6) | | Arm HV (n=6) | | Arm HW (n=6) | | Arm HX (n=6) | | Arm HY (n=6) | | Arm HZ (n=6) | | Arm IA (n=6) | | Arm IB (n=6) | | Arm IC (n=6) | | Arm ID (n=6) | | Arm IE (n=6) | | Arm IF (n=6) | | Arm IG (n=6) | | Arm IH (n=6) | | Arm II (n=6) | | Arm IJ (n=6) | | Arm IK (n=6) | | Arm IL (n=6) | | Arm IM (n=6) | | Arm IN (n=6) | | Arm IO (n=6) | | Arm IP (n=6) | | Arm IQ (n=6) | | Arm IR (n=6) | | Arm IS (n=6) | | Arm IT (n=6) | | Arm IU (n=6) | | Arm IV (n=6) | | Arm IW (n=6) | | Arm IX (n=6) | | Arm IY (n=6) | | Arm IZ (n=6) | | Arm JA (n=6) | | Arm JB (n=6) | | Arm JC (n=6) | | Arm JD (n=6) | | Arm JE (n=6) | | Arm JF (n=6) | | Arm JG (n=6) | | Arm JH (n=6) | | Arm JI (n=6) | | Arm JJ (n=6) | | Arm JK (n=6) | | Arm JL (n=6) | | Arm JM (n=6) | | Arm JN (n=6) | | Arm JO (n=6) | | Arm JP (n=6) | | Arm JQ (n=6) | | Arm JR (n=6) | | Arm JS (n=6) | | Arm JT (n=6) | | Arm JU (n=6) | | Arm JV (n=6) | | Arm JW (n=6) | | Arm JX (n=6) | | Arm JY (n=6) | | Arm JZ (n=6) | | Arm KA (n=6) | | Arm KB (n=6) | | Arm KC (n=6) | | Arm KD (n=6) | | Arm KE (n=6) | | Arm KF (n=6) | | Arm KG (n=6) | | Arm KH (n=6) | | Arm KI (n=6) | | Arm KJ (n=6) | | Arm KK (n=6) | | Arm KL (n=6) | | Arm KM (n=6) | | Arm KN (n=6) | | Arm KO (n=6) | | Arm KP (n=6) | | Arm KQ (n=6) | | Arm KR (n=6) | | Arm KS (n=6) | | Arm KT (n=6) | | Arm KU (n=6) | | Arm KV (n=6) | | Arm KW (n=6) | | Arm KX (n=6) | | Arm KY (n=6) | | Arm KZ (n=6) | | Arm LA (n=6) | | Arm LB (n=6) | | Arm LC (n=6) | | Arm LD (n=6) | | Arm LE (n=6) | | Arm LF (n=6) | | Arm LG (n=6) | | Arm LH (n=6) | | Arm LI (n=6) | | Arm LJ (n=6) | | Arm LK (n=6) | | Arm LL (n=6) | | Arm LM (n=6) | | Arm LN (n=6) | | Arm LO (n=6) | | Arm LP (n=6) | | Arm LQ (n=6) | | Arm LR (n=6) | | Arm LS (n=6) | | Arm LT (n=6) | | Arm LU (n=6) | | Arm LV (n=6) | | Arm LW (n=6) | | Arm LX (n=6) | | Arm LY (n=6) | | Arm LZ (n=6) | | Arm MA (n=6) | | Arm MB (n=6) | | Arm MC (n=6) | | Arm MD (n=6) | | Arm ME (n=6) | | Arm MF (n=6) | | Arm MG (n=6) | | Arm MH (n=6) | | Arm MI (n=6) | | Arm MJ (n=6) | | Arm MK (n=6) | | Arm ML (n=6) | | Arm MM (n=6) | | Arm MN (n=6) | | Arm MO (n=6) | | Arm MP (n=6) | | Arm MQ (n=6) | | Arm MR (n=6) | | Arm MS (n=6) | | Arm MT (n=6) | | Arm MU (n=6) | | Arm MV (n=6) | | Arm MW (n=6) | | Arm MX (n=6) | | Arm MY (n=6) | | Arm MZ (n=6) | | Arm NA (n=6) | | Arm NB (n=6) | | Arm NC (n=6) | | Arm ND (n=6) | | Arm NE (n=6) | | Arm NF (n=6) | | Arm NG (n=6) | | Arm NH (n=6) | | Arm NI (n=6) | | Arm NJ (n=6) | | Arm NK (n=6) | | Arm NL (n=6) | | Arm NM (n=6) | | Arm NN (n=6) | | Arm NO (n=6) | | Arm NP (n=6) | | Arm NQ (n=6) | | Arm NR (n=6) | | Arm NS (n=6) | | Arm NT (n=6) | | Arm NU (n=6) | | Arm NV (n=6) | | Arm NW (n=6) | | Arm NX (n=6) | | Arm NY (n=6) | | Arm NZ (n=6) | | Arm OA (n=6) | | Arm OB (n=6) | | Arm OC (n=6) | | Arm OD (n=6) | | Arm OE (n=6) | | Arm OF (n=6) | | Arm OG (n=6) | | Arm OH (n=6) | | Arm OI (n=6) | | Arm OJ (n=6) | | Arm OK (n=6) | | Arm OL (n=6) | | Arm OM (n=6) | | Arm ON (n=6) | | Arm OO (n=6) | | Arm OP (n=6) | | Arm OQ (n=6) | | Arm OR (n=6) | | Arm OS (n=6) | | Arm OT (n=6) | | Arm OU (n=6) | | Arm OV (n=6) | | Arm OW (n=6) | | Arm OX (n=6) | | Arm OY (n=6) | | Arm OZ (n=6) | | Arm PA (n=6) | | Arm PB (n=6) | | Arm PC (n=6) | | Arm PD (n=6) | | Arm PE (n=6) | | Arm PF (n=6) | | Arm PG (n=6) | | Arm PH (n=6) | | Arm PI (n=6) | | Arm PJ (n=6) | | Arm PK (n=6) | | Arm PL (n=6) | | Arm PM (n=6) | | Arm PN (n=6) | | Arm PO (n=6) | | Arm PP (n=6) | | Arm PQ (n=6) | | Arm PR (n=6) | | Arm PS (n=6) | | Arm PT (n=6) | | Arm PU (n=6) | | Arm PV (n=6) | | Arm PW (n=6) | | Arm PX (n=6) | | Arm PY (n=6) | | Arm PZ (n=6) | | Arm QA (n=6) | | Arm QB (n=6) | | Arm QC (n=6) | | Arm QD (n=6) | | Arm QE (n=6) | | Arm QF (n=6) | | Arm QG (n=6) | | Arm QH (n=6) | | Arm QI (n=6) | | Arm QJ (n=6) | | Arm QK (n=6) | | Arm QL (n=6) | | Arm QM (n=6) | | Arm QN (n=6) | | Arm QO (n=6) | | Arm QP (n=6) | | Arm QQ (n=6) | | Arm QR (n=6) | | Arm QS (n=6) | | Arm QT (n=6) | | Arm QU (n=6) | | Arm QV (n=6) | | Arm QW (n=6) | | Arm QX (n=6) | | Arm QY (n=6) | | Arm QZ (n=6) | | Arm RA (n=6) | | Arm RB (n=6) | | Arm RC (n=6) | | Arm RD (n=6) | | Arm RE (n=6) | | Arm RF (n=6) | | Arm RG (n=6) | | Arm RH (n=6) | | Arm RI (n=6) | | Arm RJ (n=6) | | Arm RK (n=6) | | Arm RL (n=6) | | Arm RM (n=6) | | Arm RN (n=6) | | Arm RO (n=6) | | Arm RP (n=6) | | Arm RQ (n=6) | | Arm RR (n=6) | | Arm RS (n=6) | | Arm RT (n=6) | | Arm RU (n=6) | | Arm RV (n=6) | | Arm RW (n=6) | | Arm RX (n=6) | | Arm RY (n=6) | | Arm RZ (n=6) | | Arm SA (n=6) | | Arm SB (n=6) | | Arm SC (n=6) | | Arm SD (n=6) | | Arm SE (n=6) | | Arm SF (n=6) | | Arm SG (n=6) | | Arm SH (n=6) | | Arm SI (n=6) | | Arm SJ (n=6) | | Arm SK (n=6) | | Arm SL (n=6) | | Arm SM (n=6) | | Arm SN (n=6) | | Arm SO (n=6) | | Arm SP (n=6) | | Arm SQ (n=6) | | Arm SR (n=6) | | Arm SS (n=6) | | Arm ST (n=6) | | Arm SU (n=6) | | Arm SV (n=6) | | Arm SW (n=6) | | Arm SX (n=6) | | Arm SY (n=6) | | Arm SZ (n=6) | | Arm TA (n=6) | | Arm TB (n=6) | | Arm TC (n=6) | | Arm TD (n=6) | | Arm TE (n=6) | | Arm TF (n=6) | | Arm TG (n=6) | | Arm TH (n=6) | | Arm TI (n=6) | | Arm TJ (n=6) | | Arm TK (n=6) | | Arm TL (n=6) | | Arm TM (n=6) | | Arm TN (n=6) | | Arm TO (n=6) | | Arm TP (n=6) | | Arm TQ (n=6) | | Arm TR (n=6) | | Arm TS (n=6) | | Arm TT (n=6) | | Arm TU (n=6) | | Arm TV (n=6) | | Arm TW (n=6) | | Arm TX (n=6) | | Arm TY (n=6) | | Arm TZ (n=6) | | Arm UA (n=6) | | Arm UB (n=6) | | Arm UC (n=6) | | Arm UD (n=6) | | Arm UE (n=6) | | Arm UF (n=6) | | Arm UG (n=6) | | Arm UH (n=6) | | Arm UI (n=6) | | Arm UJ (n=6) | | Arm UK (n=6) | | Arm UL (n=6) | | Arm UM (n=6) | | Arm UN (n=6) | | Arm UO (n=6) | | Arm UP (n=6) | | Arm UQ (n=6) | | Arm UR (n=6) | | Arm US (n=6) | | Arm UT (n=6) | | Arm UU (n=6) | | Arm UV (n=6) | | Arm UW (n=6) | | Arm UX (n=6) | | Arm UY (n=6) | | Arm UZ (n=6) | | Arm VA (n=6) | | Arm VB (n=6) | | Arm VC (n=6) | | Arm VD (n=6) | | Arm VE (n=6) | | Arm VF (n=6) | | Arm VG (n=6) | | Arm VH (n=6) | | Arm VI (n=6) | | Arm VJ (n=6) | | Arm VK (n=6) | | Arm VL (n=6) | | Arm VM (n=6) | | Arm VN (n=6) | | Arm VO (n=6) | | Arm VP (n=6) | | Arm VQ (n=6) | | Arm VR (n=6) | | Arm VS (n=6) | | Arm VT (n=6) | | Arm VU (n=6) | | Arm VV (n=6) | | Arm VW (n=6) | | Arm VX (n=6) | | Arm VY (n=6) | | Arm VZ (n=6) | | Arm WA (n=6) | | Arm WB (n=6) | | Arm WC (n=6) | | Arm WD (n=6) | | Arm WE (n=6) | | Arm WF (n=6) | | Arm WG (n=6) | | Arm WH (n=6) | | Arm WI (n=6) | | Arm WJ (n=6) | | Arm WK (n=6) | | Arm WL (n=6) | | Arm WM (n=6) | | Arm WN (n=6) | | Arm WO (n=6) | | Arm WP (n=6) | | Arm WQ (n=6) | | Arm WR (n=6) | | Arm WS (n=6) | | Arm WT (n=6) | | Arm WU (n=6) | | Arm WV (n=6) | | Arm WW (n=6) | | Arm WX (n=6) | | Arm WY (n=6) | | Arm WZ (n=6) | | Arm XA (n=6) | | Arm XB (n=6) | | Arm XC (n=6) | | Arm XD (n=6) | | Arm XE (n=6) | | Arm XF (n=6) | | Arm XG (n=6) | | Arm XH (n=6) | | Arm XI (n=6) | | Arm XJ (n=6) | | Arm XK (n=6) | | Arm XL (n=6) | | Arm XM (n=6) | | Arm XN (n=6) | | Arm XO (n=6) | | Arm XP (n=6) | | Arm XQ (n=6) | | Arm XR (n=6) | | Arm XS (n=6) | | Arm XT (n=6) | | Arm XU (n=6) | | Arm XV (n=6) | | Arm XW (n=6) | | Arm XX (n=6) | | Arm XY (n=6) | | Arm XZ (n=6) | | Arm YA (n=6) | | Arm YB (n=6) | | Arm YC (n=6) | | Arm YD (n=6) | | Arm YE (n=6) | | Arm YF (n=6) | | Arm YG (n=6) | | Arm YH (n=6) | | Arm YI (n=6) | | Arm YJ (n=6) | | Arm YK (n=6) | | Arm YL (n=6) | | Arm YM (n=6) | | Arm YN (n=6) | | Arm YO (n=6) | | Arm YP (n=6) | | Arm YQ (n=6) | | Arm YR (n=6) | | Arm YS (n=6) | | Arm YT (n=6) | | Arm YU (n=6) | | Arm YV (n=6) | | Arm YW (n=6) | | Arm YX (n=6) | | Arm YY (n=6) | | Arm YZ (n=6) | | Arm ZA (n=6) | | Arm ZB (n=6) | | Arm ZC (n=6) | | Arm ZD (n=6) | | Arm ZE (n=6) | | Arm ZF (n=6) | | Arm ZG (n=6) | | Arm ZH (n=6) | | Arm ZI (n=6) | | Arm ZJ (n=6) | | Arm ZK (n=6) | | Arm ZL (n=6) | | Arm ZM (n=6) | | Arm ZN (n=6) | | Arm ZO (n=6) | | Arm ZP (n=6) | | Arm ZQ (n=6) | | Arm ZR (n=6) | | Arm ZS (n=6) | | Arm ZT (n=6) | | Arm ZU (n=6) | | Arm ZV (n=6) | | Arm ZW (n=6) | | Arm ZX (n=6) | | Arm ZY (n=6) | | Arm ZZ (n=6) | | Arm AAA (n=6) | | Arm AAB (n=6) | | Arm AAC (n=6) | | Arm AAD (n=6) | | Arm AAE (n=6) | | Arm AAF (n=6) | | Arm AAG (n=6) | | Arm AAH (n=6) | | Arm AAI (n=6) | | Arm AAJ (n=6) | | Arm AAK (n=6) | | Arm AAL (n=6) | | Arm AAM (n=6) | | Arm AAN (n=6) | | Arm AAO (n=6) | | Arm AAP (n=6) | | Arm AAQ (n=6) | | Arm AAR (n=6) | | Arm AAS (n=6) | | Arm AAT (n=6) | | Arm AAU (n=6) | | Arm AAV (n=6) | | Arm AAW (n=6) | | Arm AAX (n=6) | | Arm AAY (n=6) | | Arm AAZ (n=6) | | Arm ABA (n=6) | | Arm ABB (n=6) | | Arm ABC (n=6) | | Arm ABD (n=6) | | Arm ABE (n=6) | | Arm ABF (n=6) | | Arm ABG (n=6) | | Arm ABH (n=6) | | Arm ABI (n=6) | | Arm ABJ (n=6) | | Arm ABK (n=6) | | Arm ABL (n=6) | | Arm ABM (n=6) | | Arm ABN (n=6) | | Arm ABO (n=6) | | Arm ABP (n=6) | | Arm ABQ (n=6) | | Arm ABR (n=6) | | Arm ABS (n=6) | | Arm ABT (n=6) | | Arm ABU (n=6) | | Arm ABV (n=6) | | Arm ABW (n=6) | | Arm ABX (n=6) | | Arm ABY (n=6) | | Arm ABZ (n=6) | | Arm ACA (n=6) | | Arm ACB (n=6) | | Arm ACC (n=6) | | Arm ACD (n=6) | | Arm ACE (n=6) | | Arm ACF (n=6) | | Arm ACG (n=6) | | Arm ACH (n=6) | | Arm ACI (n=6) | | Arm ACJ (n=6) | | Arm ACK (n=6) | | Arm ACL (n=6) | | Arm ACM (n=6) | | Arm ACN (n=6) | | Arm ACO (n=6) | | Arm ACP (n=6) | | Arm ACQ (n=6) | | Arm ACR (n=6) | | Arm ACS (n=6) | | Arm ACT (n=6) | | Arm ACU (n=6) | | Arm ACV (n=6) | | Arm ACW (n=6) | | Arm ACX (n=6) | | Arm ACY (n=6) | | Arm ACZ (n=6) | | Arm ADA (n=6) | | Arm ADB (n=6) | | Arm ADC (n=6) | | Arm ADD (n=6) | | Arm ADE (n=6) | | Arm ADF (n=6) | | Arm ADG (n=6) | | Arm ADH (n=6) | | Arm ADI (n=6) | | Arm ADJ (n=6) | | Arm ADK (n=6) | | Arm ADL (n=6) | | Arm ADM (n=6) | | Arm ADN (n=6) | | Arm ADO (n=6) | | Arm ADP (n=6) | | Arm ADQ (n=6) | | Arm ADR (n=6) | | Arm ADS (n=6) | | Arm ADT (n=6) | | Arm ADU (n=6) | | Arm ADV (n=6) | | Arm ADW (n=6) | | Arm ADX (n=6) | | Arm ADY (n=6) | | Arm ADZ (n=6) | | Arm AEA (n=6) | | Arm AEB (n=6) | | Arm AEC (n=6) | | Arm AED (n=6) | | Arm AEE (n=6) | | Arm AEF (n=6) | | Arm AEG (n=6) | | Arm AEH (n=6) | | Arm AEI (n=6) | | Arm AEJ (n=6) | | Arm AEK (n=6) | | Arm AEL (n=6) | | Arm AEM (n=6) | | Arm AEN (n=6) | | Arm AEO (n=6) | | Arm AEP (n=6) | | Arm AEQ (n=6) | | Arm AER (n=6) | | Arm AES (n=6) | | Arm AET (n=6) | | Arm AEU (n=6) | | Arm AEV (n=6) | | Arm AEW (n=6) | | Arm AEX (n=6) | | Arm AEY (n=6) | | Arm AEZ (n=6) | | Arm AFA (n=6) | | Arm AFB (n=6) | | Arm AFC (n=6) | | Arm AFD (n=6) | | Arm AFE (n=6) | | Arm AFF (n=6) | | Arm AFG (n=6) | | Arm AFH (n=6) | | Arm AFI (n=6) | | Arm AFJ (n=6) | | Arm AFK (n=6) | | Arm AFL (n=6) | | Arm AFM (n=6) | | Arm AFN (n=6) | | Arm AFO (n=6) | | Arm AFP (n=6) | | Arm AFQ (n=6) | | Arm AFR (n=6) | | Arm AFS (n=6) | | Arm AFT (n=6) | | Arm AFU (n=6) | | Arm AFV (n=6) | | Arm AFW (n=6) | | Arm AFX (n=6) | | Arm AFY (n=6) | | Arm AFZ (n=6) | | Arm AGA (n=6) | | Arm AGB (n=6) | | Arm AGC (n=6) | | Arm AGD (n=6) | | Arm AGE (n=6) | | Arm AGF (n=6) | | Arm AGG (n=6) | | Arm AGH (n=6) | | Arm AGI (n=6) | | Arm AGJ (n=6) | | Arm AGK (n=6) | | Arm AGL (n=6) | | Arm AGM (n=6) | | Arm AGN (n=6) | | Arm AGO (n=6) | | Arm AGP (n=6) | | Arm AGQ (n=6) | | Arm AGR (n=6) | | Arm AGS (n=6) | | Arm AGT (n=6) | | Arm AGU (n=6) | | Arm AGV (n=6) | | Arm AGW (n=6) | | Arm AGX (n=6) | | Arm AGY (n=6) | | Arm AGZ (n=6) | | Arm AHA (n=6) | | Arm AHB (n=6) | | Arm AHC (n=6) | | Arm AHD (n=6) | | Arm AHE (n=6) | | Arm AHF (n=6) | | Arm AHG (n=6) | | Arm AHH (n=6) | | Arm AHI (n=6) | | Arm AHJ (n=6) | | Arm AHK (n=6) | | Arm AHL (n=6) | | Arm AHM (n=6) | | Arm AHN (n=6) | | Arm AHO (n=6) | | Arm AHP (n=6) | | Arm AHQ (n=6) | | Arm AHR (n=6) | | Arm AHS (n=6) | | Arm AHT (n=6) | | Arm AHU (n=6) | | Arm AHV (n=6) | | Arm AHW (n=6) | | Arm AHX (n=6) | | Arm AHY (n=6) | | Arm AHZ (n=6) | | Arm AIA (n=6) | | Arm AIB (n=6) | | Arm AIC (n=6) | | Arm AID (n=6) | | Arm AIE (n=6) | | Arm AIF (n=6) | | Arm AIG (n=6) | | Arm AIH (n=6) | | Arm AII (n=6) | | Arm AIJ (n=6) | | Arm AIK (n=6) | | Arm AIL (n=6) | | Arm AIM (n=6) | | Arm AIN (n=6) | | Arm AIO (n=6) | | Arm AIP (n=6) | | Arm AIQ (n=6) | | Arm AIR (n=6) | | Arm AIS (n=6) | | Arm AIT (n=6) | | Arm AIU (n=6) | | Arm AIV (n=6) | | Arm AIW (n=6) | | Arm AIX (n=6) | | Arm AIY (n=6) | | Arm AIZ (n=6) | | Arm AJA (n=6) | | Arm AJB (n=6) | | Arm AJC (n=6) | | Arm AJD (n=6) | | Arm AJE (n=6) | | Arm AJF (n=6) | | Arm AJG (n=6) | | Arm AJH (n=6) | | Arm AJI (n=6) | | Arm AJJ (n=6) | | Arm AJK (n=6) | | Arm AJL (n=6) | | Arm AJM (n=6) | | Arm AJN (n=6) | | Arm AJO (n=6) | | Arm AJP (n=6) | | Arm AJQ (n=6) | | Arm AJR (n=6) | | Arm AJS (n=6) | | Arm AJT (n=6) | | Arm AJU (n=6) | | Arm AJV (n=6) | | Arm AJW (n=6) | | Arm AJX (n=6) | | Arm AJY (n=6) | | Arm AJZ (n=6) | | Arm AKA (n=6) | | Arm AKB (n=6) | | Arm AKC (n=6) | | Arm AKD (n=6) | | Arm AKE (n=6) | | Arm AKF (n=6) | | Arm AKG (n=6) | | Arm AKH (n=6) | | Arm AKI (n=6) | | Arm AKJ (n=6) | | Arm AKK (n=6) | | Arm AKL (n=6) | | Arm AKM (n=6) | | Arm AKN (n=6) | | Arm AKO (n=6) | | Arm AKP (n=6) | | Arm AKQ (n=6) | | Arm AKR (n=6) | | Arm AKS (n=6) | | Arm AKT (n=6) | | Arm AKU (n=6) | | Arm AKV (n=6) | | Arm AKW (n=6) | | Arm AKX (n=6) | | Arm AKY (n=6) | | Arm AKZ (n=6) | | Arm ALA (n=6) | | Arm ALB (n=6) | | Arm ALC (n=6) | | Arm ALD (n=6) | | Arm ALE (n=6) | | Arm ALF (n=6) | | Arm ALG (n=6) | | Arm ALH (n=6) | | Arm ALI (n=6) | | Arm ALJ (n=6) | | Arm ALK (n=6) | | Arm ALL (n=6) | | Arm ALM (n=6) | | Arm ALN (n=6) | | Arm ALO (n=6) | | Arm ALP (n=6) | | Arm ALQ (n=6) | | Arm ALR (n=6) | | Arm ALS (n=6) | | Arm ALT (n=6) | | Arm ALU (n=6) | | Arm ALV (n=6) | | Arm ALW (n=6) | | Arm ALX (n=6) | | Arm ALY (n=6) | | Arm ALZ (n=6) | | Arm AMA (n=6) | | Arm AMB (n=6) | | Arm AMC (n=6) | | Arm AMD (n=6) | | Arm AME (n=6) | | Arm AMF (n=6) | | Arm AMG (n=6) | | Arm AMH (n=6) | | Arm AMI (n=6) | | Arm AMJ (n=6) | | Arm AMK (n=6) | | Arm AML (n=6) | | Arm AMM (n=6) | | Arm AMN (n=6) | | Arm AMO (n=6) | | Arm AMP (n=6) | | Arm AMQ (n=6) | | Arm AMR (n=6) | | Arm AMS (n=6) | | Arm AMT (n=6) | | Arm AMU (n=6) | | Arm AMV (n=6) | | Arm AMW (n=6) | | Arm AMX (n=6) | | Arm AMY (n=6) | | Arm AMZ (n=6) | | Arm ANA (n=6) | | Arm ANB (n=6) | | Arm ANC (n=6) | | Arm AND (n=6) | | Arm ANE (n=6) | | Arm ANF (n=6) | | Arm ANG (n=6) | | Arm ANH (n=6) | | Arm ANI (n=6) | | Arm ANJ (n=6) | | Arm ANK (n=6) | | Arm ANL (n=6) | | Arm ANM (n=6) | | Arm ANN (n=6) | | Arm ANO (n=6) | | Arm ANP (n=6) | | Arm ANQ (n=6) | | Arm ANR (n=6) | | Arm ANS (n=6) | | Arm ANT (n=6) | | Arm ANU (n=6) | | Arm ANV (n=6) | | Arm ANW (n=6) | | Arm ANX (n=6) | | Arm ANY (n=6) | | Arm ANZ (n=6) | | Arm AOA (n=6) | | Arm AOB (n=6) | | Arm AOC (n=6) | | Arm AOD (n=6) | | Arm AOE (n=6) | | Arm AOF (n=6) | | Arm AOG (n=6) | | Arm AOH (n=6) | | Arm AOI (n=6) | | Arm AOJ (n=6) | | Arm AOK (n=6) | | Arm AOL (n=6) | | Arm AOM (n=6) | | Arm AON (n=6) | | Arm AOO (n=6) | | Arm AOP (n=6) | | Arm AOQ (n=6) | | Arm AOR (n=6) | | Arm AOS (n=6) | | Arm AOT (n=6) | | Arm AOU (n=6) | | Arm AOV (n=6) | | Arm AOW (n=6) | | Arm AOX (n=6) | | Arm AOY (n=6) | | Arm AOZ (n=6) | | Arm APA (n=6) | | Arm APB (n=6) | | Arm APC (n=6) | | Arm APD (n=6) | | Arm APE (n=6) | | Arm APF (n=6) | | Arm APG (n=6) | | Arm APH (n=6) | | Arm API (n=6) | | Arm APJ (n=6) | | Arm APK (n=6) | | Arm APL (n=6) | | Arm APM (n=6) | | Arm APN (n=6) | | Arm APO (n=6) | | Arm APP (n=6) | | Arm APQ (n=6) | | Arm APR (n=6) | | Arm APS (n=6) | | Arm APT (n=6) | | Arm APU (n=6) | | Arm APV (n=6) | | Arm APW (n=6) | | Arm APX (n=6) | | Arm APY (n=6) | | Arm APZ (n=6) | | Arm AQA (n=6) | | Arm AQB (n=6) | | Arm AQC (n=6) | | Arm AQD (n=6) | | Arm AQE (n=6) | | Arm AQF (n=6) | | Arm AQG (n=6) | | Arm AQH (n=6) | | Arm AQI (n=6) | | Arm AQJ (n=6) | | Arm AQK (n=6) | | Arm AQL (n=6) | | Arm AQM (n=6) | | Arm AQN (n=6) | | Arm AQO (n=6) | | Arm AQP (n=6) | | Arm AQQ (n=6) | | Arm AQR (n=6) | | Arm AQS (n=6) | | Arm AQT (n=6) | | Arm AQU (n=6) | | Arm AQV (n=6) | | Arm AQW (n=6) | | Arm AQX (n=6) | | Arm AQY (n=6) | | Arm AQZ (n=6) | | Arm ARA (n=6) | | Arm ARB (n=6) | | Arm ARC (n=6) | | Arm ARD (n=6) | | Arm ARE (n=6) | | Arm ARF (n=6) | | Arm ARG (n=6) | | Arm ARH (n=6) | | Arm ARI (n=6) | | Arm ARJ (n=6) | | Arm ARK (n=6) | | Arm ARL (n=6) | | Arm ARM (n=6) | | Arm ARN (n=6) | | Arm ARO (n=6) | | Arm ARP (n=6) | | Arm ARQ (n=6) | | Arm ARR (n=6) | | Arm ARS (n=6) | | Arm ART (n=6) | | Arm ARU (n=6) | | Arm ARV (n=6) | | Arm ARW (n=6) | | Arm ARX (n=6) | | Arm ARY (n=6) | | Arm ARZ (n=6) | | Arm ASA (n=6) | | Arm ASB (n=6) | | Arm ASC (n=6) | | Arm ASD (n=6) | | Arm ASE (n=6) | | Arm ASF (n=6) | | Arm ASG (n=6) | | Arm ASH (n=6) | | Arm ASI (n=6) | | Arm ASJ (n=6) | | Arm ASK (n=6) | | Arm ASL (n=6) | | Arm ASM (n=6) | | Arm ASN (n=6) | | Arm ASO (n=6) | | Arm ASP (n=6) | | Arm ASQ (n=6) | | Arm ASR (n=6) | | Arm ASS (n=6) | | Arm AST (n=6) | | Arm ASU (n=6) | | Arm ASV (n=6) | | Arm ASW (n=6) | | Arm ASX (n=6) | | Arm ASY (n=6) | | Arm ASZ (n=6) | | Arm ATA (n=6) | | Arm ATB (n=6) | | Arm ATC (n=6) | | Arm ATD (n=6) | | Arm ATE (n=6) | | Arm ATF (n=6) | | Arm ATG (n=6) | | Arm ATH (n=6) | | Arm ATI (n=6) | | Arm ATJ (n=6) | | Arm ATK (n=6) | | Arm ATL (n=6) | | Arm ATM (n=6) | | Arm ATN (n=6) | | Arm ATO (n=6) | | Arm ATP (n=6) | | Arm ATQ (n=6) | | Arm ATR (n=6) | | Arm ATS (n=6) | | Arm ATT (n=6) | | Arm ATU (n=6) | | Arm ATV (n=6) | | Arm ATW (n=6) | | Arm ATX (n=6) | | Arm ATY (n=6) | | Arm ATZ (n=6) | | Arm AUA (n=6) | | Arm AUB (n=6) | | Arm AUC (n=6) | | Arm AUD (n=6) | | Arm AUE (n=6) | | Arm AUF (n=6) | | Arm AUG (n=6) | | Arm AUH (n=6) | | Arm AUI (n=6) | | Arm AUJ (n=6) | | Arm AUK (n=6) | | Arm AUL (n=6) | | Arm AUM (n=6) | | Arm AUN (n=6) | | Arm AUO (n=6) | | Arm AUP (n=6) | | Arm AUQ (n=6) | | Arm AUR (n=6) | | Arm AUS (n=6) | | Arm AUT (n=6) | | Arm AUU (n=6) | | Arm AUV (n=6) | | Arm AUW (n=6) | | Arm AUX (n=6) | | Arm AUY (n=6) | | Arm AUZ (n=6) | | Arm AVA (n=6) | | Arm AVB (n=6) | | Arm AVC (n=6) | | Arm AVD (n=6) | | Arm AVE (n=6) | | Arm AVF (n=6) | | Arm AVG (n=6) | | Arm AVH (n=6) | | Arm AVI (n=6) | | Arm AVJ (n=6) | | Arm AVK (n=6) | | Arm AVL (n=6) | | Arm AVM (n=6) | | Arm AVN (n=6) | | Arm AVO (n=6) | | Arm AVP (n=6) | | Arm AVQ (n=6) | | Arm AVR (n=6) | | Arm AVS (n=6) | | Arm AVT (n=6) | | Arm AVU (n=6) | | Arm AVV (n=6) | | Arm AVW (n=6) | | Arm AVX (n=6) | | Arm AVY (n=6) |

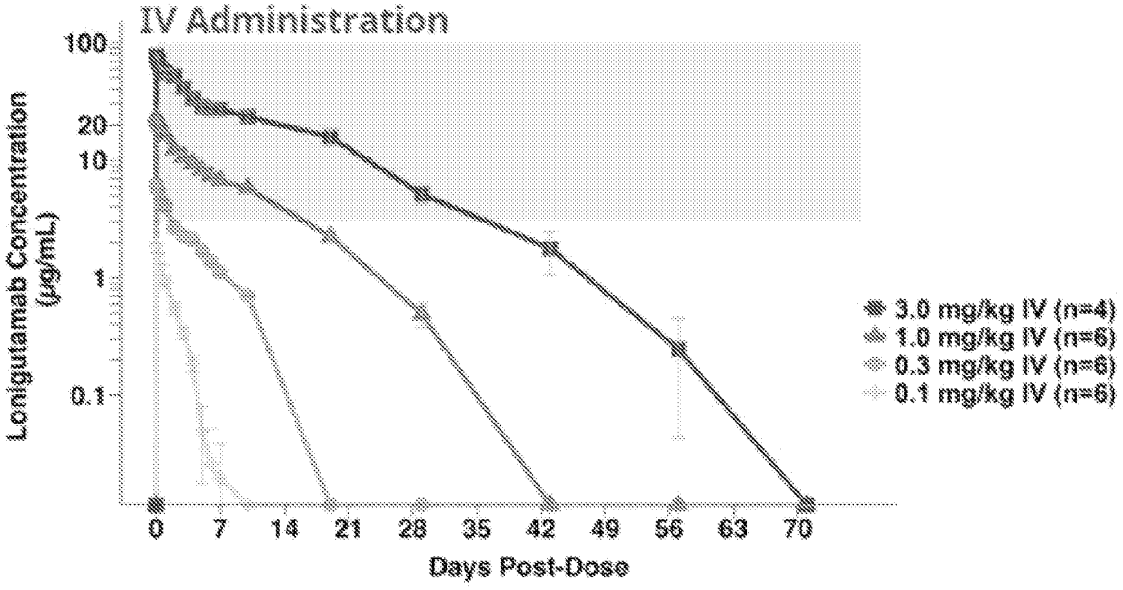

IV Administration
Lonigutamab Concentration (µg/mL)
100
20
10
1
0.1
0
7
14
21
28
35
42
49
56
63
70
Days Post-Dose
3.0 mg/kg IV (n=4)
1.0 mg/kg IV (n=6)
0.3 mg/kg IV (n=6)
0.1 mg/kg IV (n=6)

FIG. 2

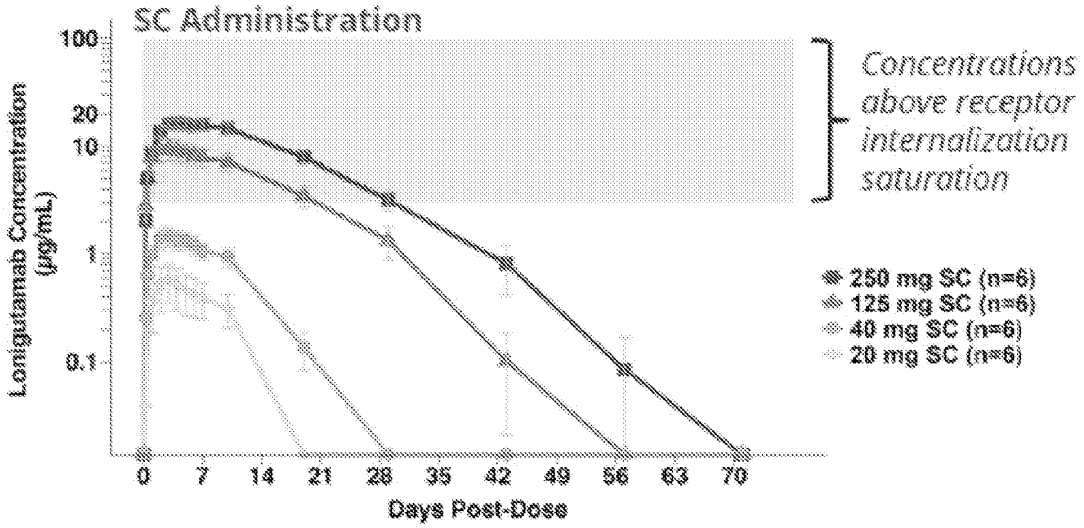

SC Administration
Lonigutamab Concentration (µg/mL)
100
20
10
1
0.1
0
7
14
21
28
35
42
49
56
63
70
Days Post-Dose
Concentrations above receptor internalization saturation
250 mg SC (n=6)
125 mg SC (n=6)
40 mg SC (n=6)
20 mg SC (n=6)

FIG. 3

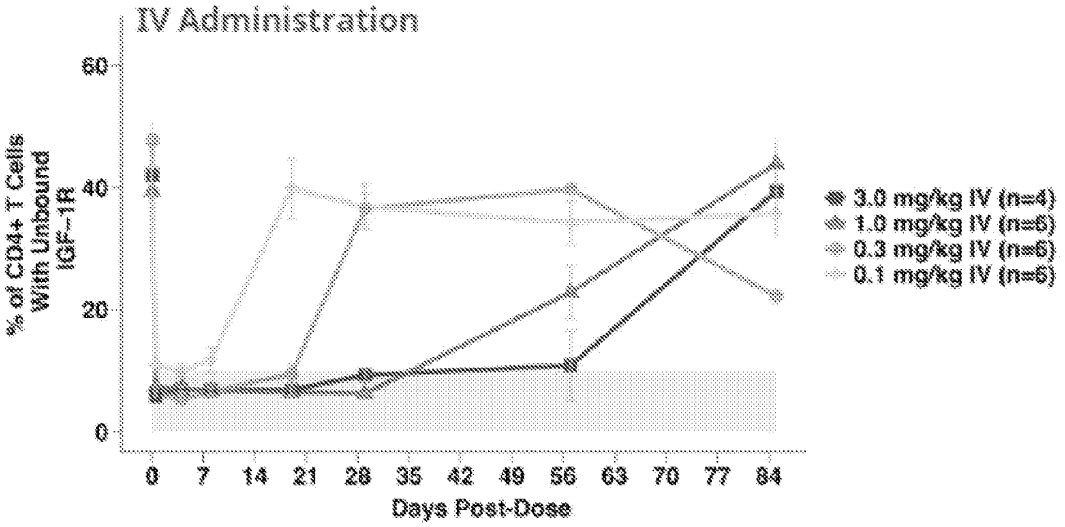

IV Administration
% of CD4+ T Cells With Unbound IGF-1R
60
40
20
0
0 7 14 21 28 35 42 49 56 63 70 77 84
Days Post-Dose
3.0 mg/kg IV (n=4)
1.0 mg/kg IV (n=6)
0.3 mg/kg IV (n=6)
0.1 mg/kg IV (n=6)

FIG. 4

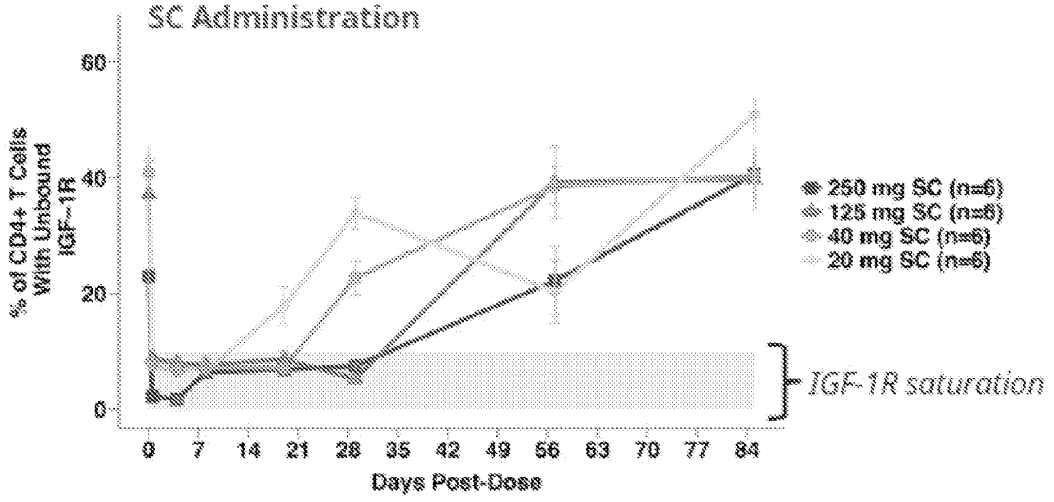
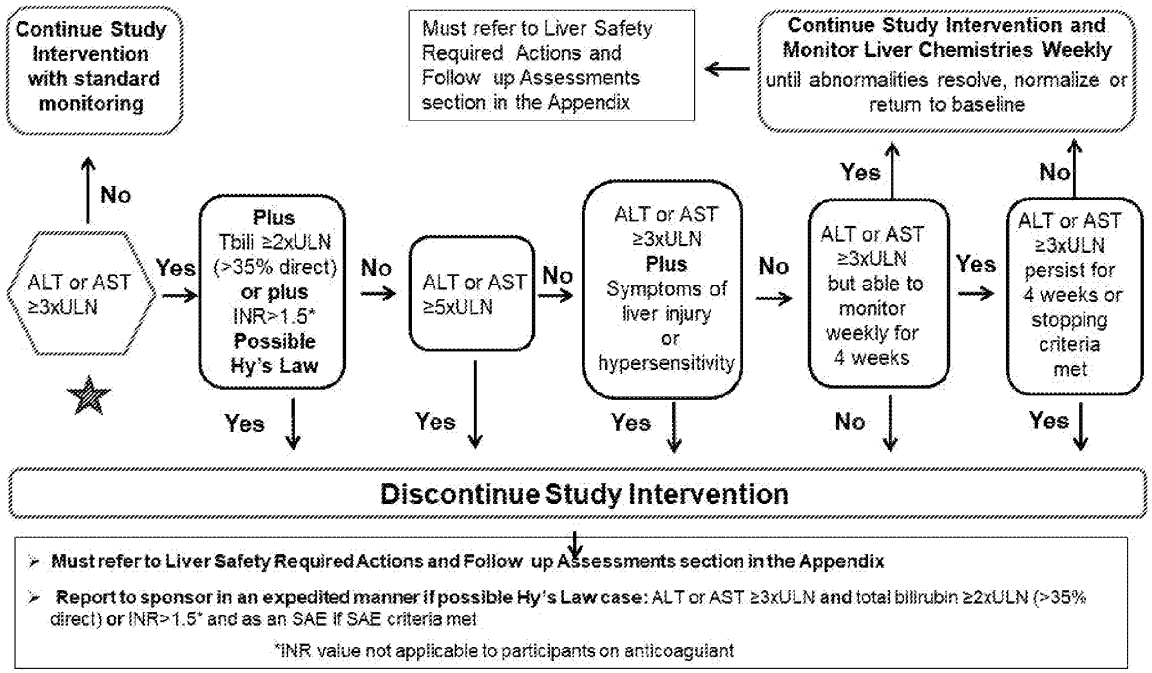

SC Administration
% of CD4+ T Cells With Unbound IGF-1R
60
40
20
0
0 7 14 21 28 35 42 49 56 63 70 77 84
Days Post-Dose
250 mg SC (n=6)
125 mg SC (n=6)
40 mg SC (n=6)
20 mg SC (n=6)
IGF-1R saturation

FIG. 5

Phase 1 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm[a]



ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin; ULN = upper limit of normal

[a] Liver Safety: Required actions and follow-up assessments can be found as described in the present disclosure.

FIG. 6

APPENDIX 2. GRAVES' OPHTHALMOPATHY QUALITY OF LIFE

GO-Quality Of Life Questionnaire ☐ Initial ☐ Follow-up Date

The following questions deal specifically with your thyroid eye disease. Please focus on the past week while answering th questions.

During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?

Tick the box that matches your answer. The boxes correspond with the answers above them.
Please tick only one box for each question.

	Yes seriously limited	Yes a little limited	No not at all limited
1) Bicycling (never learned to ride a bike☐)	☐	☐	☐
2) Driving (no driver's license ☐)	☐	☐	☐
3) Moving around the house	☐	☐	☐
4) Walking outdoors	☐	☐	☐
5) Reading	☐	☐	☐
6) Watching TV	☐	☐	☐
7) Hobby or pastime, i.e.	☐	☐	☐

	Yes severely hindered	Yes a little hindered	No not at all hindered	
8) During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	☐	☐	☐	Score

The following questions deal with your thyroid eye disease in general

	Yes, very much so	Yes a little	No not at all	
9) Do you feel that you appearance has changed because of your thyroid eye disease?	☐	☐	☐	
10) Do you feel that you are stared at in the streets because of thyroid eye disease	☐	☐	☐	
11) Do you feel that people react unpleasantly because of your thyroid eye disease?	☐	☐	☐	
12) Do you feel that your thyroid eye disease has an influence on your self-confidence?	☐	☐	☐	
13) Do you feel socially isolated because of your thyroid eye disease	☐	☐	☐	
14) Do you feel that your thyroid eye disease has an influence on making friends?	☐	☐	☐	
15) Do you feel that you appear less often on photos than before you had thyroid eye disease?	☐	☐	☐	
16) Do you try mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐	Score

FIG. 7

Lonigutamab Uniquely Impacts the IGF-1R axis and has shown improved therapeutic and clinical differentiation relative to prior therapies for TED

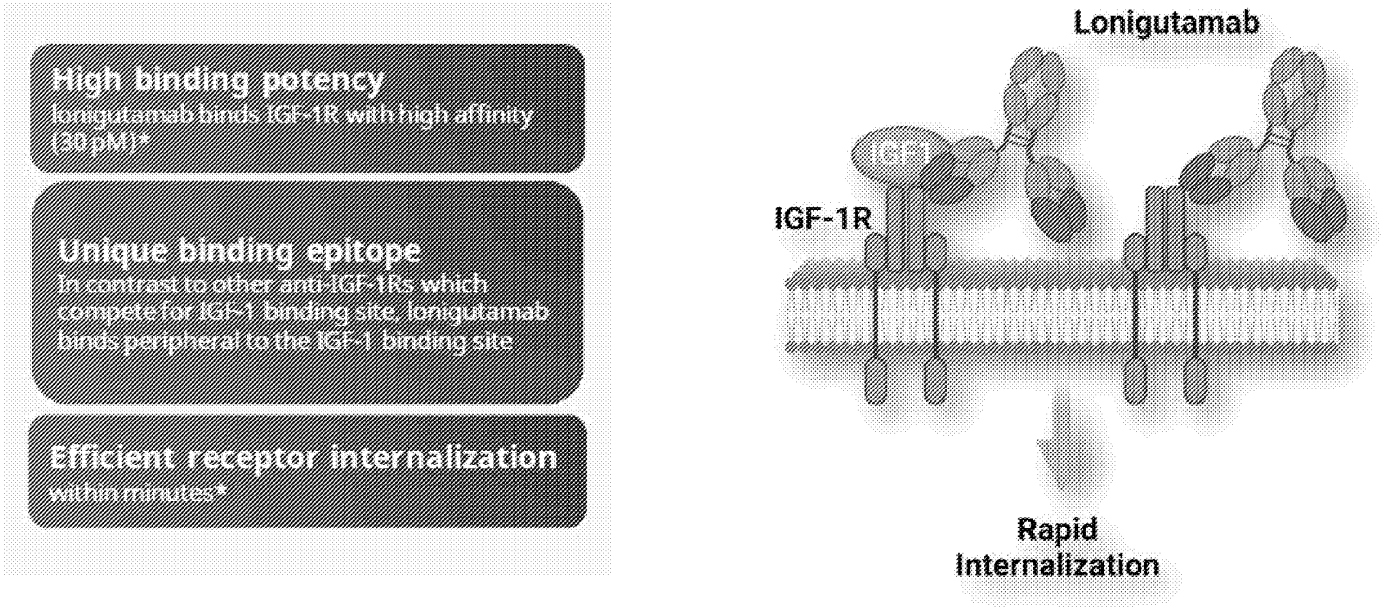
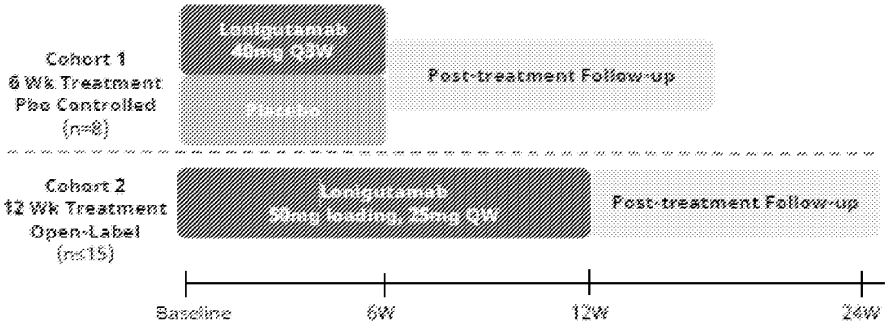


FIG. 8

Phase 1/2 Evaluating Lonigutamab in TED

Screening/ Eligibility

- Proptosis defined in the study eye as ≥3 mm above normal
- Clinical Activity Score (CAS) ≥4 (using a 7-item scale) for the most severely affected eye
- Onset of active TED symptoms within 18 months prior to the baseline



Efficacy Endpoints

- Proptosis (reduction in eye bulging)
- Clinical Activity Score (change in CAS)
- Diplopia (reduction in double vision)

Safety

- Incidence and characterization of nonserious and serious treatment emergent adverse events (TEAEs)

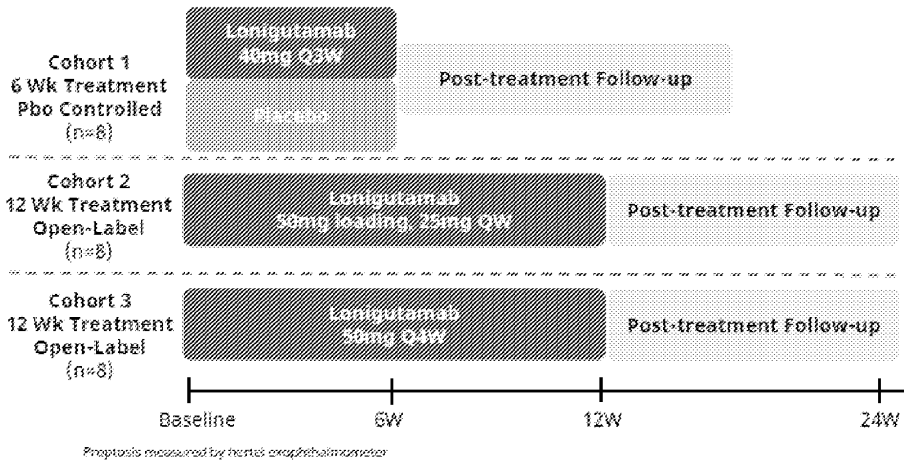
1. Proptosis measured by hertel exophthalmometer
2. Cohort 3 evaluating monthly dosing ongoing
3. Two Dose Healthy Subject PK study completed

FIG. 9A

Phase 1/2 Evaluating Lonigutamab in TED

Screening/ Eligibility

- Proptosis defined in the study eye as ≥3 mm above normal
- Clinical Activity Score (CAS) ≥4 (using a 7-item scale) for the most severely affected eye
- Onset of active TED symptoms within 15 months prior to the baseline



Proptosis measured by hertel exophthalmometer

Efficacy Endpoints

- Proptosis (reduction in eye bulging)
- Clinical Activity Score (change in CAS)
- Diplopia (reduction in double vision)

Safety

- Incidence and characterization of nonserious and serious treatment emergent adverse events (TEAEs)

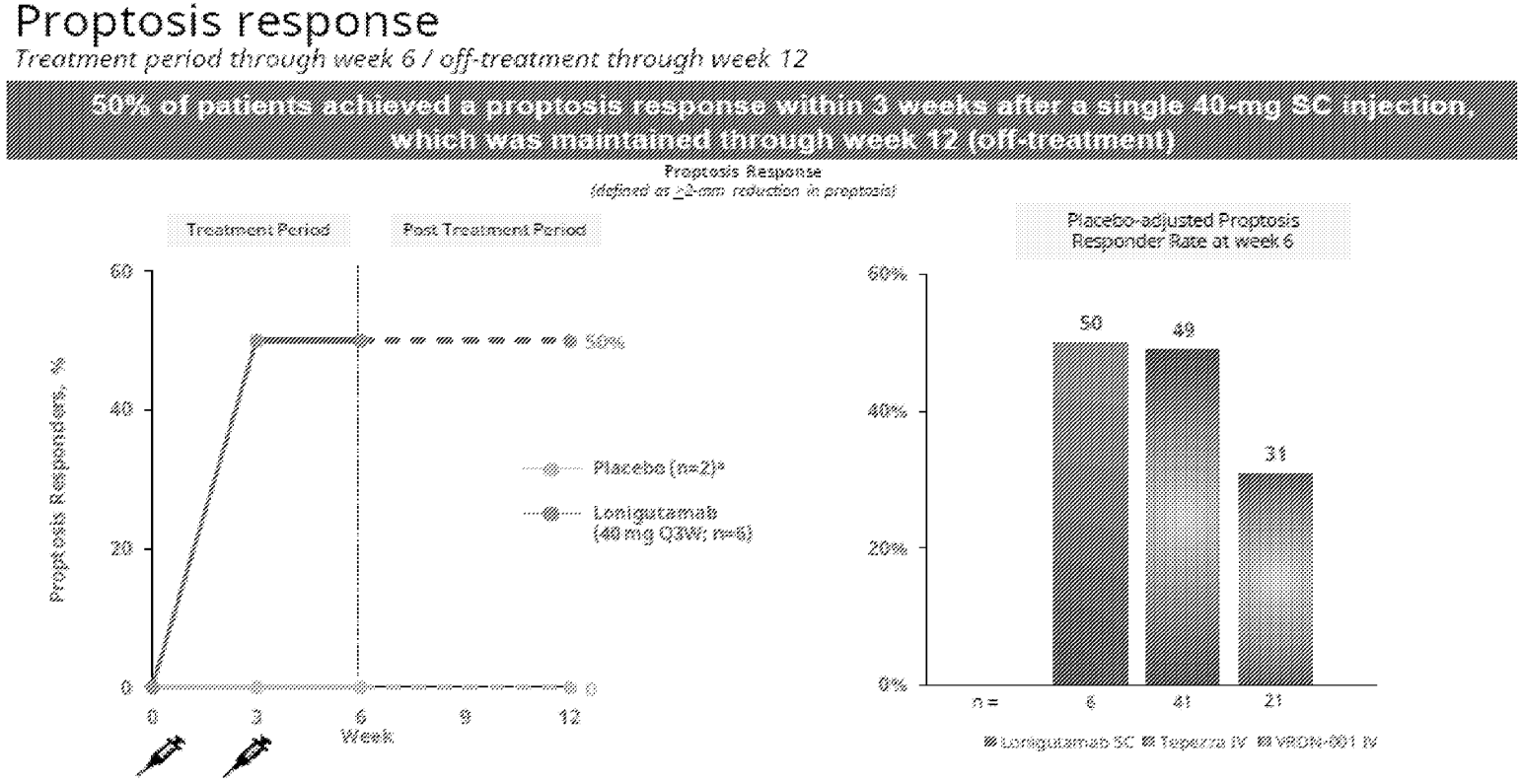
FIG. 9B

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Placebo (Cohort 1) n=2[1]	Lonigutamab (Cohort 1: 48 mg Q3W) n=6
Age, mean (SD), years	49.5 (12.0)	43.8 (13.7)
Female, n (%)	2 (100.0)	5 (83.3)
White, n (%)	1 (50.0)	5 (83.3)
BMI, mean (SD), kg/m²	28.6 (3.5)	26.6 (7.6)
Months to onset of TED, mean (SD),	14.6 (4.6)	10.2 (6.8)
Proptosis for study eye, mean (SD), mm	26.0 (0)	26.2 (2.6)
CAS total score for study eye, mean (SD)	3.5 (2.1)	4.8 (1.0)
Diplopia at baseline, n (%)	2 (100.0)	4 (66.7)

BMI, body mass index; CAS, Clinical Activity Score; Q3W, every 3 weeks; SD, standard deviation * *One subject stopped treatment after the first dose due to AE (dysthyroid optic neuropathy, a complication from thyroid eye disease and exclusion criteria for the study) and terminated the study early due to investigator discretion. Subject was determined to be randomized to placebo following unblinding, which occurred after the final study visit for all Cohort 1 subjects.

FIG. 10



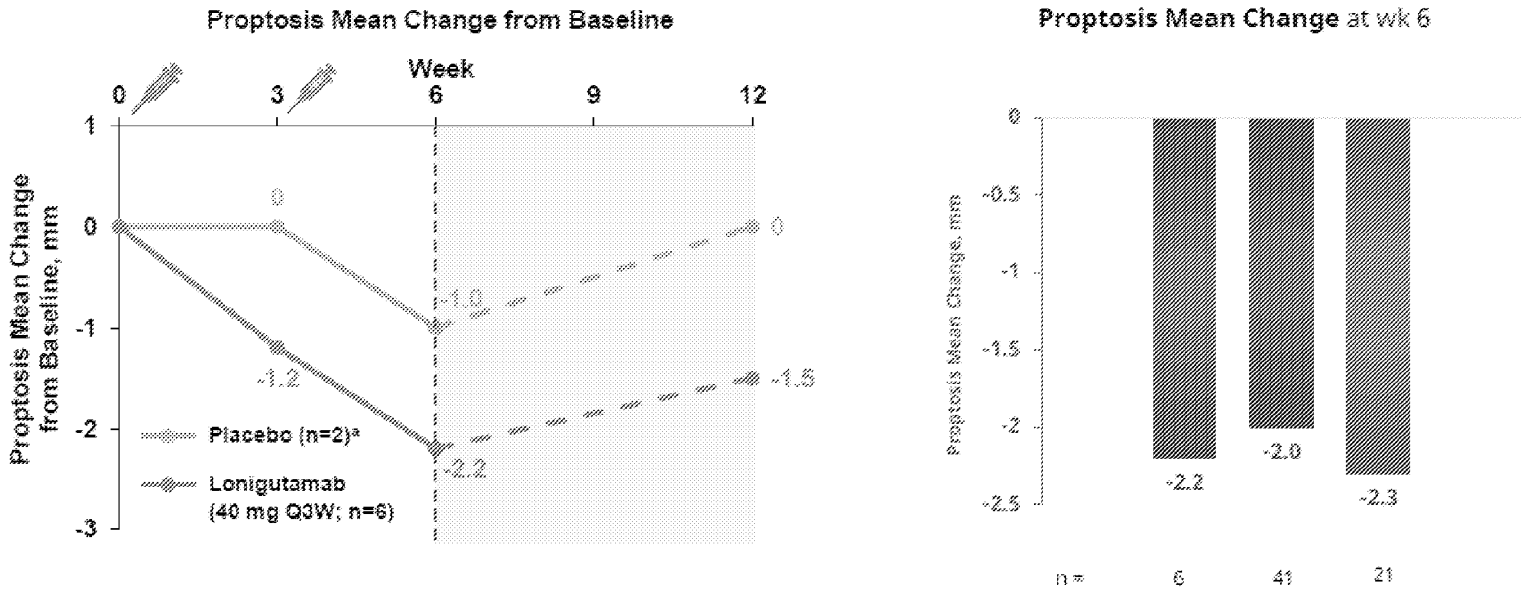
Proptosis was measured via Hertel exophthalmometer. (a) One patient in the placebo group had no post-baseline data and was imputed as a non responder. Q3W, every 3 weeks

Comparisons across trials, with inherent limitations. Not head-to-head trials. Tepezza data from public source: Douglas NEJM 2020 382:341:52. VRDN-001 data from public source: Kossler AAO 2023.

FIG. 11A

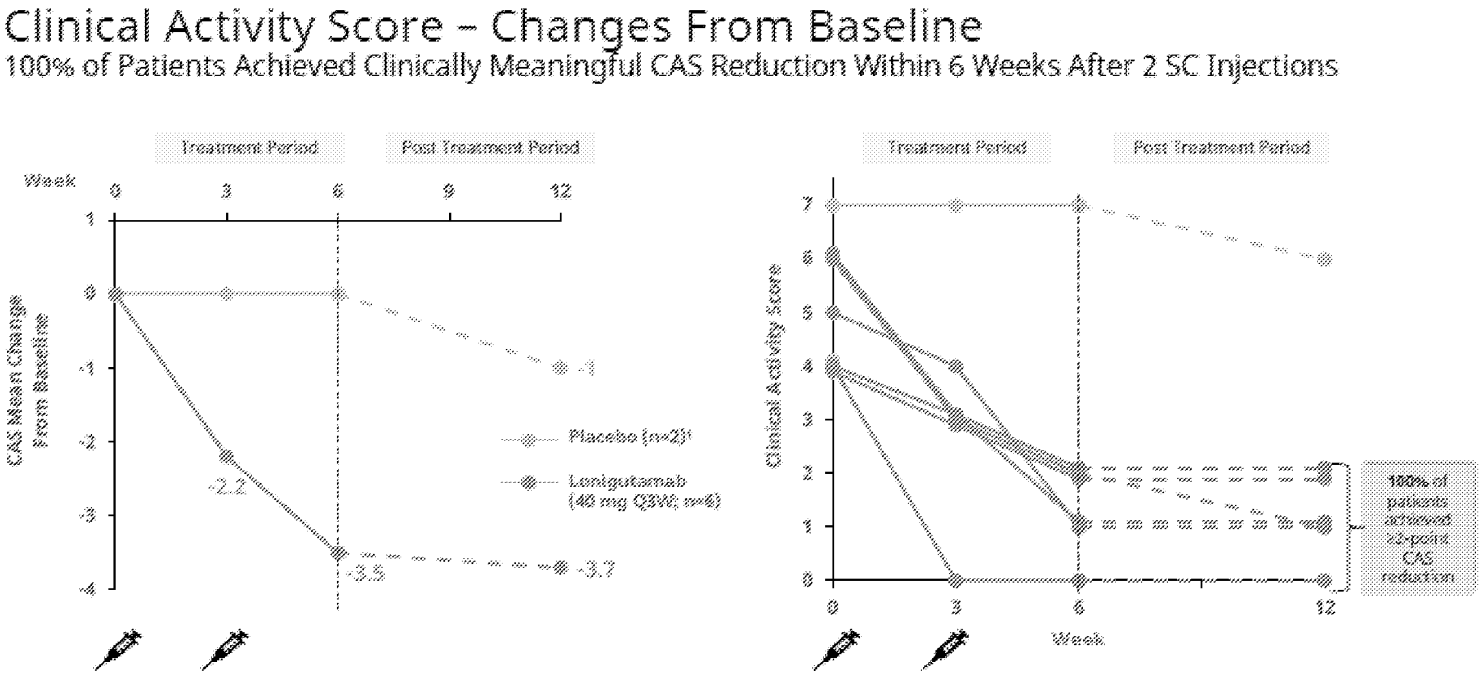
Proptosis Mean Change

Treatment period through week 6 / off-treatment through week 12



1. *Proptosis was measured via Hertel exophthalmometer. aOne patient in the placebo group had no post-baseline data and was imputed as a non responder. Q3W, every 3 weeks*
2. *Comparisons across trials, with inherent limitations. Not head-to-head trials. Teprotumumab data from public source: Douglas NEJM 2020;382:341-52. VRDN-001 data from public source: Kossler AAO 2023, pooled doses*

FIG. 11B

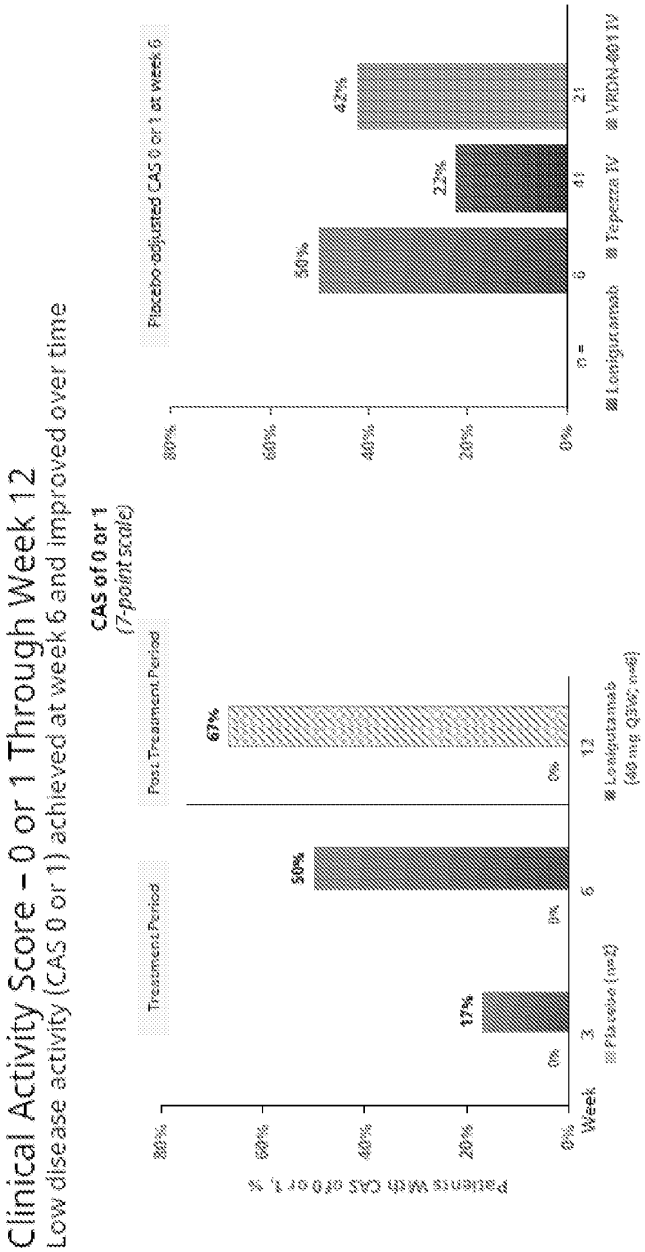


CAS Responders: patients with ≥2 pt CAS reduction considered clinically meaningful

(1) One patient in the placebo group had no post-baseline data.

CAS, Clinical Activity Score; Q3W, every 3 weeks

FIG. 12



Clinically meaningful improvements were seen in patients with evaluable diplopia at baseline. No worsening in diplopia was seen in all patients on treatment
One patient in the placebo group had no post-baseline data and was imputed as a non-responder.
Q3W, every 3 weeks.

FIG. 13

Demographics and Baseline Characteristics

	Placebo (Cohort 1) n=2*	Lonigutamab (Cohort 1: 40 mg Q3W) n=6	Lonigutamab (Cohort 2: 50 mg load, 25 mg QW) n =6
Age, *mean (SD), years*	49.5 (12.0)	49.8 (13.7)	43.3 (13.3)
Female, *n (%)*	2 (100.0)	5 (83.3)	4 (66.7)
White, *n (%)*	1 (50.0)	5 (83.3)	2 (33.3)
BMI, *mean (SD), kg/m²*	28.6 (3.5)	26.6 (7.6)	26.2 (4.1)
Months since onset of TED, *mean (SD)*	14.6 (4.6)	10.2 (6.8)	10.0 (4.5)
Proptosis for study eye, *mean (SD), mm*	26.0 (0)	26.2 (2.6)	23.2 (2.4)
CAS total score for study eye, *mean (SD)*	5.5 (2.1)	4.8 (1.0)	5.2 (0.75)
Diplopia at baseline, *n (%)*	2 (100.0)	4 (66.7)	5 (83.3)

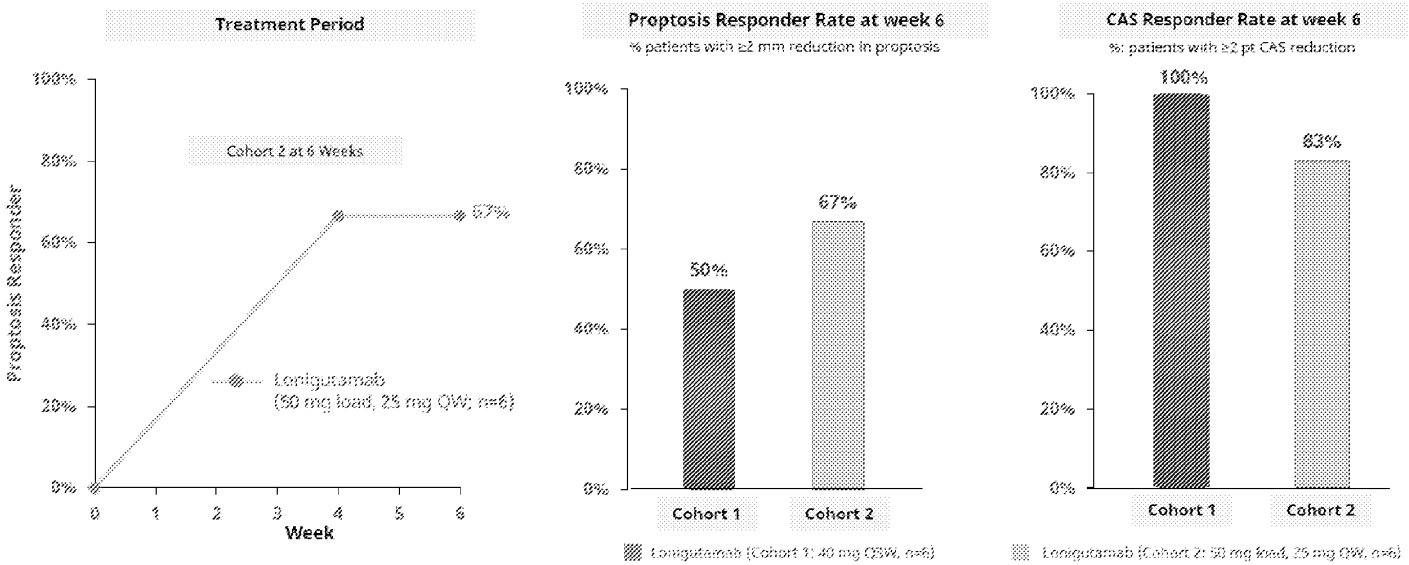
BMI, body mass index; CAS, Clinical Activity Score; Q3W, every 3 weeks; SD, standard deviation

*One subject stopped treatment after the first dose due to AE (dysthyroid optic neuropathy, a complication from thyroid eye disease and exclusion criteria for the study) and terminated the study early due to investigator discretion. Subject was determined to be randomized to placebo following unblinding, which occurred after the final study visit for all Cohort 1 subjects. Cohort 2 demographics and baseline characteristics shown (n = 6).

FIG. 14

Proptosis and CAS Responses Seen at Week 6

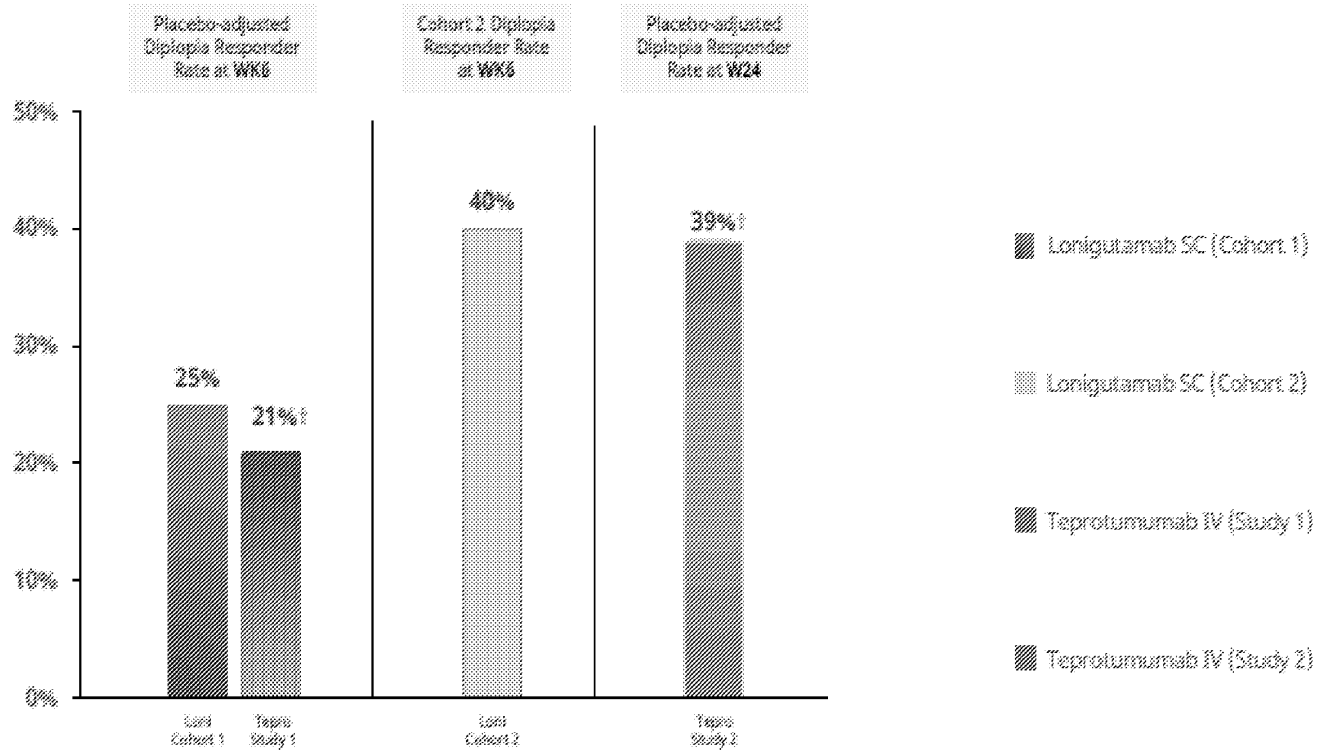
Data Consistent With Cohort 1 and Allows for Regimen Exploration



Proptosis was measured via Hertel exophthalmometer. Proptosis responder rate: % patients with ≥2 mm reduction in proptosis
CAS Responder rate: % patients with ≥2 pt CAS reduction considered clinically meaningful. Q3W, every 3 weeks; QW, weekly.

FIG. 15

Clinically Meaningful Diplopia Responses Observed in Both Cohorts by Week 6[1]



1 Comparisons across trials, with inherent limitations. Diplopia Response defined as improvement in >1 Bahn Gorman grade. † † † †Teprotumumab: Ph2 Smith, et al NEJM 2017 376:1748-61, Ph3 Douglas NEJM 2020 382:341:5

FIG. 16A

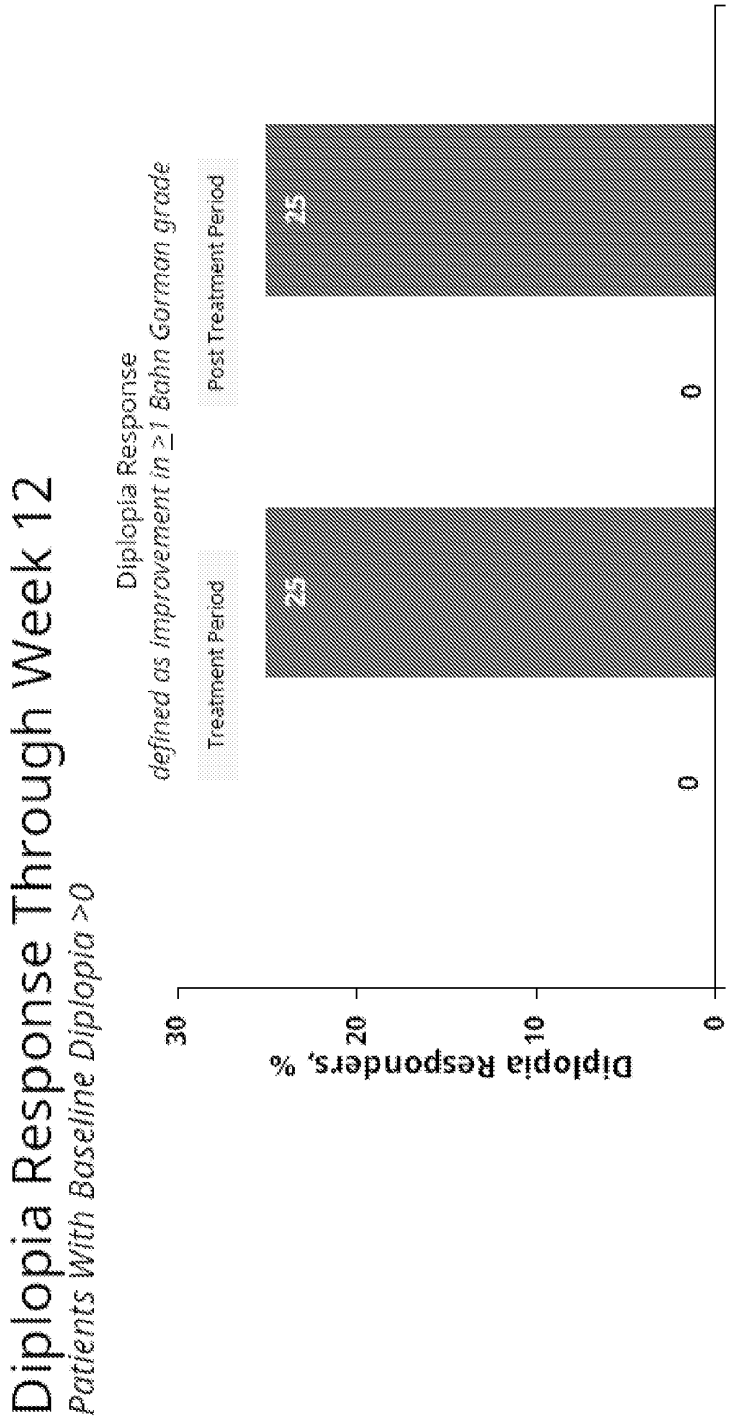
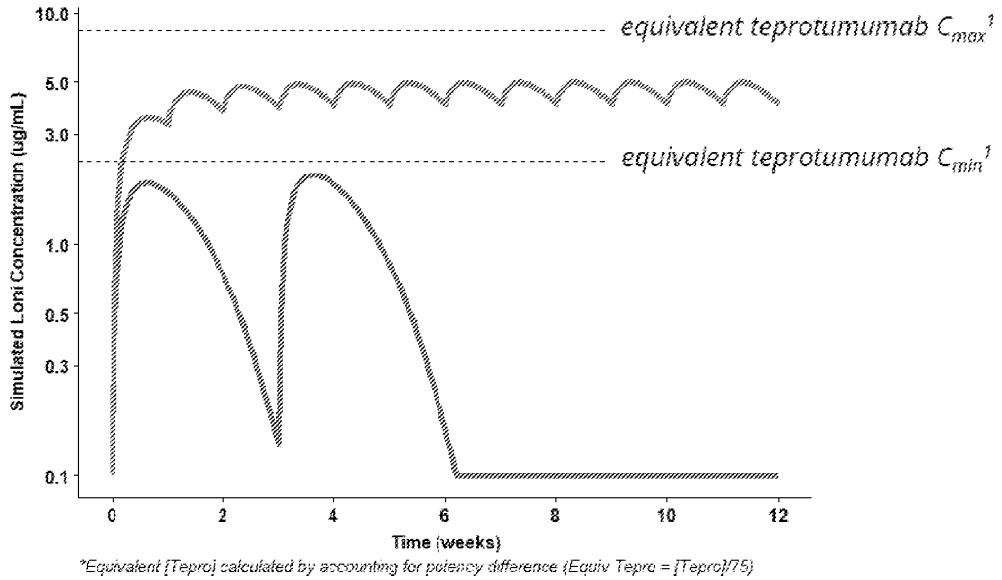

Diplopia Response Through Week 12
Patients With Baseline Diplopia >0
Diplopia Response
defined as improvement in ≥1 Bahn Gorman grade
Treatment Period
Post Treatment Period
Diplopia Responders, %
30
20
10
0
25
0
25
0

FIG. 16B

SC Exposure Achieves Responses Enabling Optimization of Benefit-Risk Lonigutamab Achieves Robust Responses at Exposures Below teprotumumab C_{max}

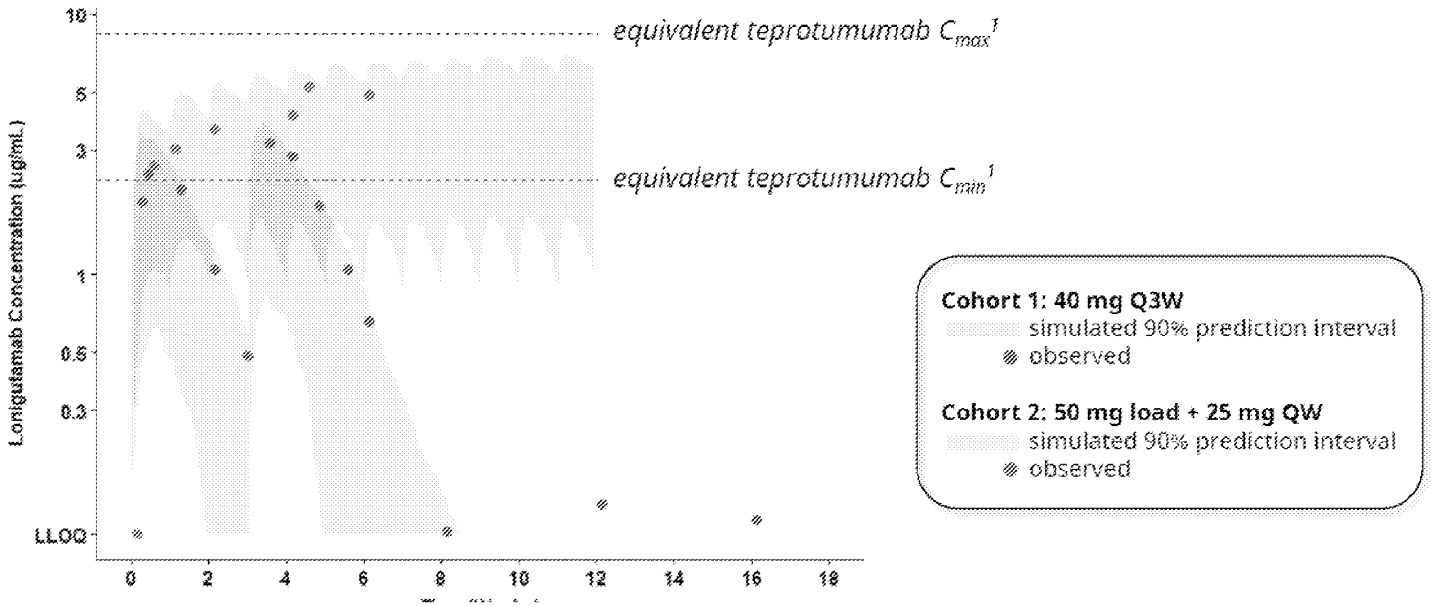


Observed Exposures Consistent With Simulations

[1] Comparisons across trials, with inherent limitations. Not head-to-head trials. Teprotumumab data from public source: FDA Tepezza Clinical Pharmacology review, Teprotumumab Cmax and Cmin from approved dosing regimen (10 mg/kg followed by 20 mg/kg Q3W)

FIG. 17A

SC Exposure Achieves Responses Enabling Optimization of Benefit-Risk
Lonigutamab Achieves Robust Responses at Exposures Below teprotumumab C_{max}



[1]Comparisons across trials, with inherent limitations. Not head-to-head trials. Teprotumumab data from public source: FDA Tepezza Clinical Pharmacology review, Teprotumumab C_{max} and C_{min} from approved dosing regimen (10 mg/kg followed by 20 mg/kg Q3W). Equivalence calculated by ~75x scaled potency. Cohort 1: intensive sampling, Cohort 2: C_{min}, through W6. LLOQ, lower limit of quantitation for the assay. Preliminary PK data from an ongoing study.

FIG. 17B

SUMMARY OF SAFETY

n (%)	Placebo, Cohort 1 n=2	Lonigutumab, Cohort 1 (40 mg Q3W) n=6	Lonigutumab, Cohort 2 (50 mg load, 25 mg QW) n=6
Any TEAEs	2 (100.0)	4 (66.7)	5 (83.3)
Serious	0	0	0
Any grade 2	0	1 (16.7)	2 (33.3)
Any grade 3	0	0	0
TEAEs leading to study drug discontinuation			
Optic neuropathy	1 (50.0)	0	0
TEAEs leading to death	0	0	0

- Majority of events were mild. No interruptions to study drug except the optic neuropathy in the placebo patient
- No hearing impairment, no hyperglycemia events, and no serious adverse events

Most common events (reported in 2 or more subjects on lonigutamab) were headache, injection site reactions, muscle spasms and tinnitus. Tinnitus was reported in 3 subjects all were mild and resolved without intervention. Injection site reactions were all mild. Grade 2 events included headache, joint swelling, and nausea Q3W, every 3 weeks; TEAE, treatment-emergent adverse event; TED, thyroid eye disease.

FIG. 18

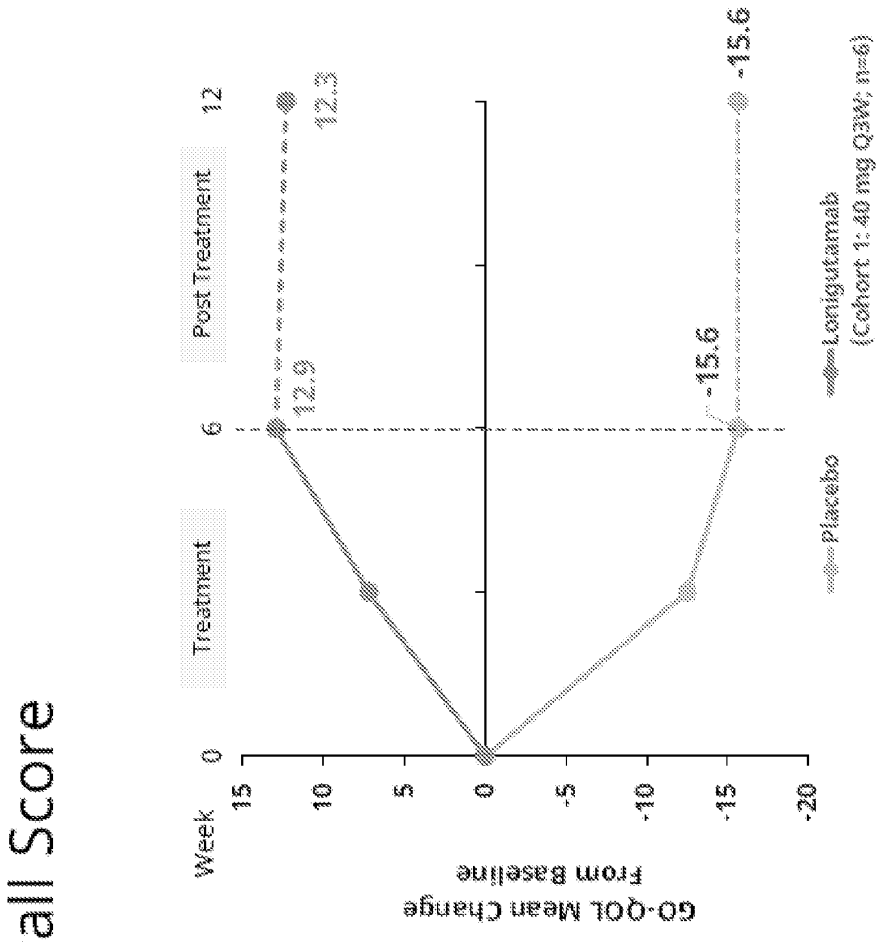

GO-QOL Overall Score
GO-QOL Mean Change From Baseline
Week
0
6
12
Treatment
Post Treatment
15
10
5
0
-5
-10
-15
-20
12.9
12.3
-15.6
-15.6
Placebo
Lonigutamab (Cohort 1: 40 mg Q3W; n=6)

FIG. 19

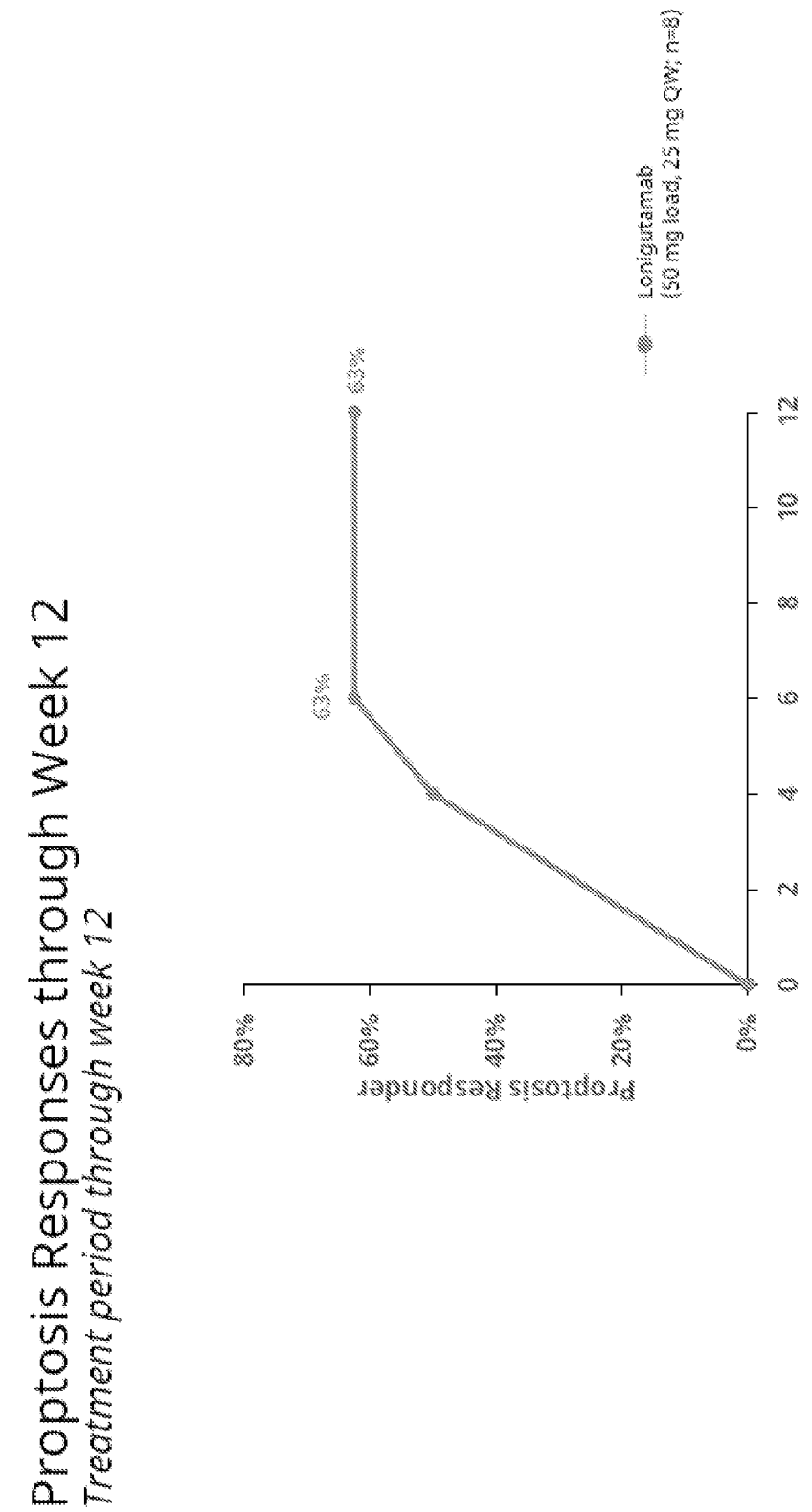

Proptosis Responses through Week 12
Treatment period through week 12
Proptosis Responder
80%
60%
40%
20%
0%
0
2
4
6
8
10
12
Week
63%
63%
Lonigutamab
(50 mg load, 25 mg QW; n=8)

FIG. 20

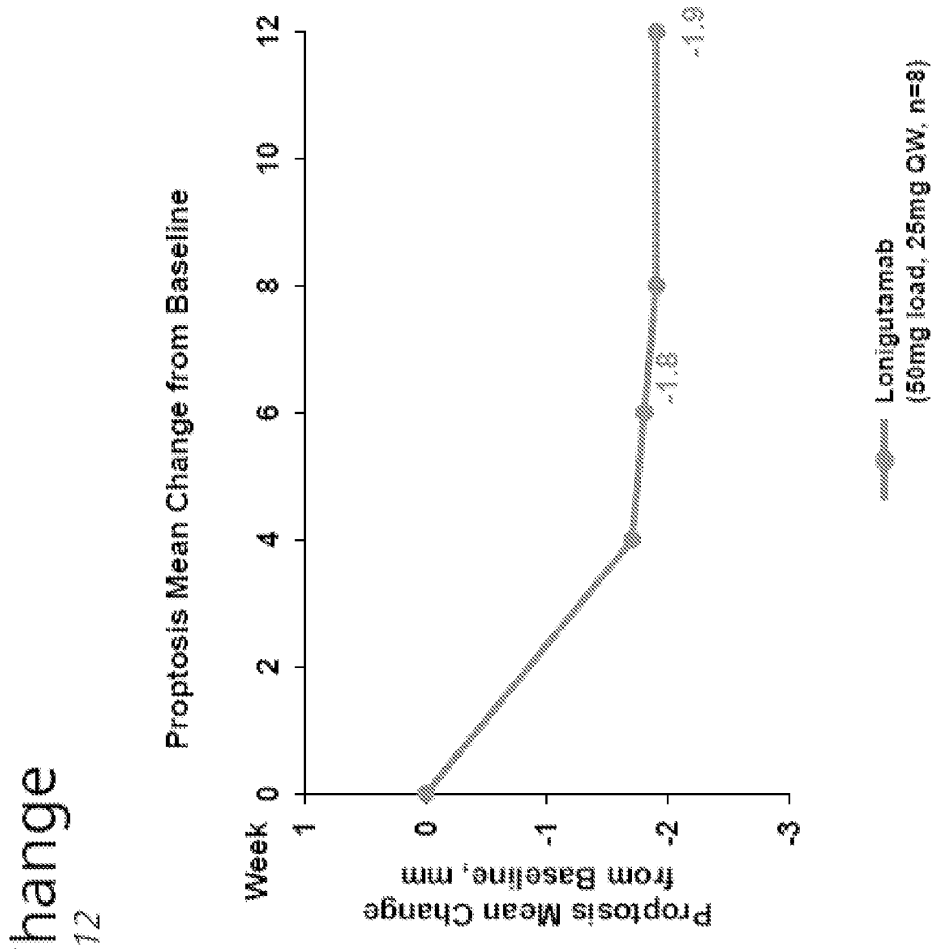
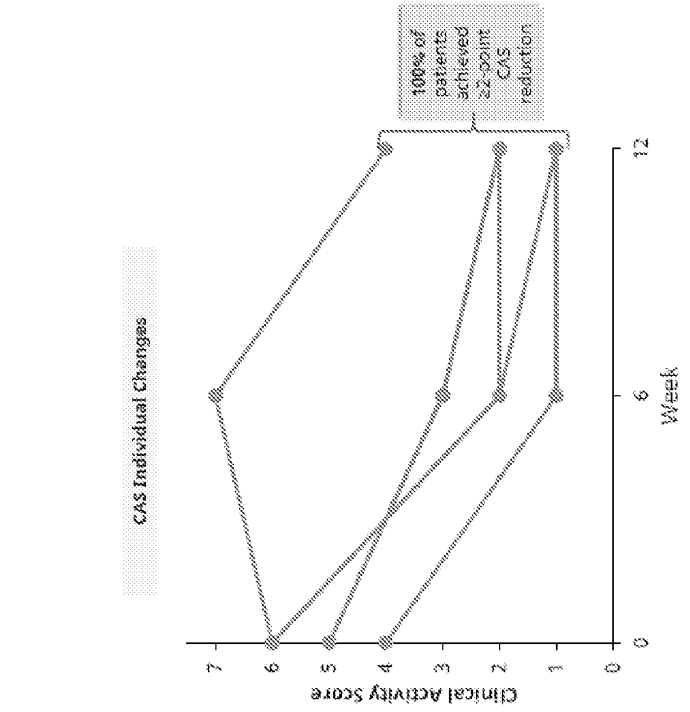

Proptosis Mean Change
Treatment period through week 12
Proptosis Mean Change from Baseline
Week 0 2 4 6 8 10 12
1 0 -1 -2 -3
Proptosis Mean Change from Baseline, mm
-1.8
-1.9
Lonigutamab
(50mg load, 25mg QW, n=8)

FIG. 21


CAS Individual Changes
100% of patients achieved ≥2-point CAS reduction
Clinical Activity Score
Week
0
1
2
3
4
5
6
7
0
6
12

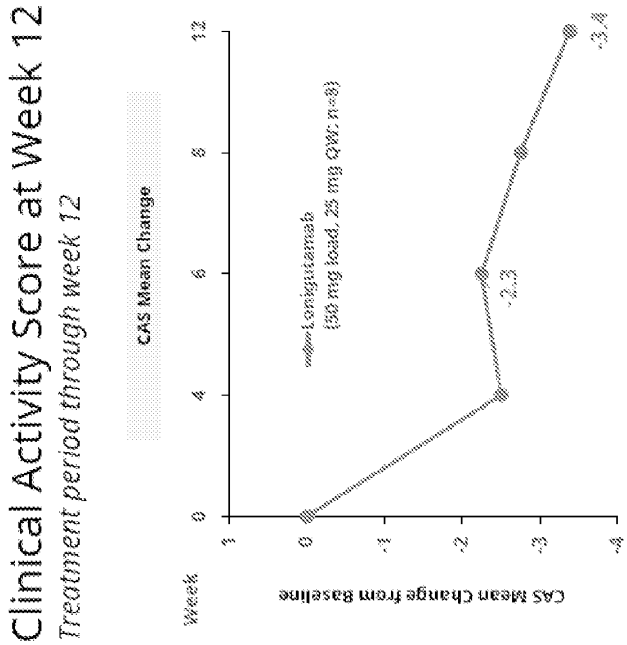

Clinical Activity Score at Week 12
Treatment period through week 12
CAS Mean Change
Week
CAS Mean Change from Baseline
Lonigutamab
(50 mg load, 25 mg QW; n=8)
-2.3
-3.4
0
-1
-2
-3
-4
0
4
6
8
12

FIG. 22

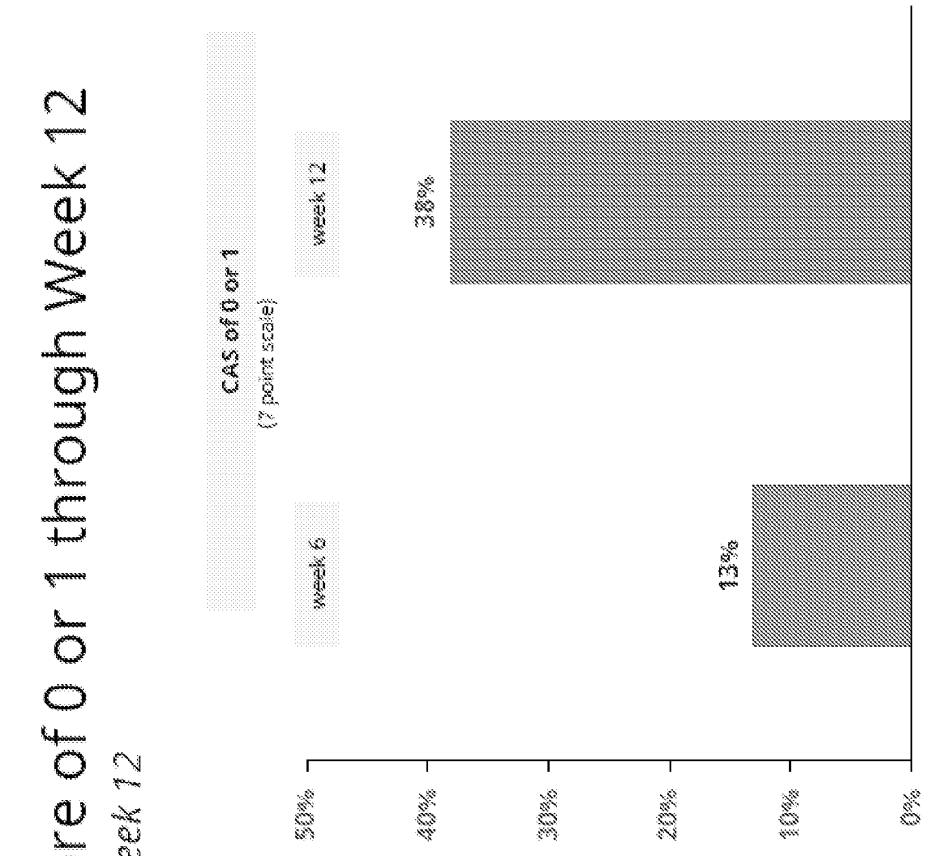

Clinical Activity Score of 0 or 1 through Week 12
Treatment period through week 12
CAS of 0 or 1
(7 point scale)
week 6
week 12
13%
38%
50%
40%
30%
20%
10%
0%

FIG. 23

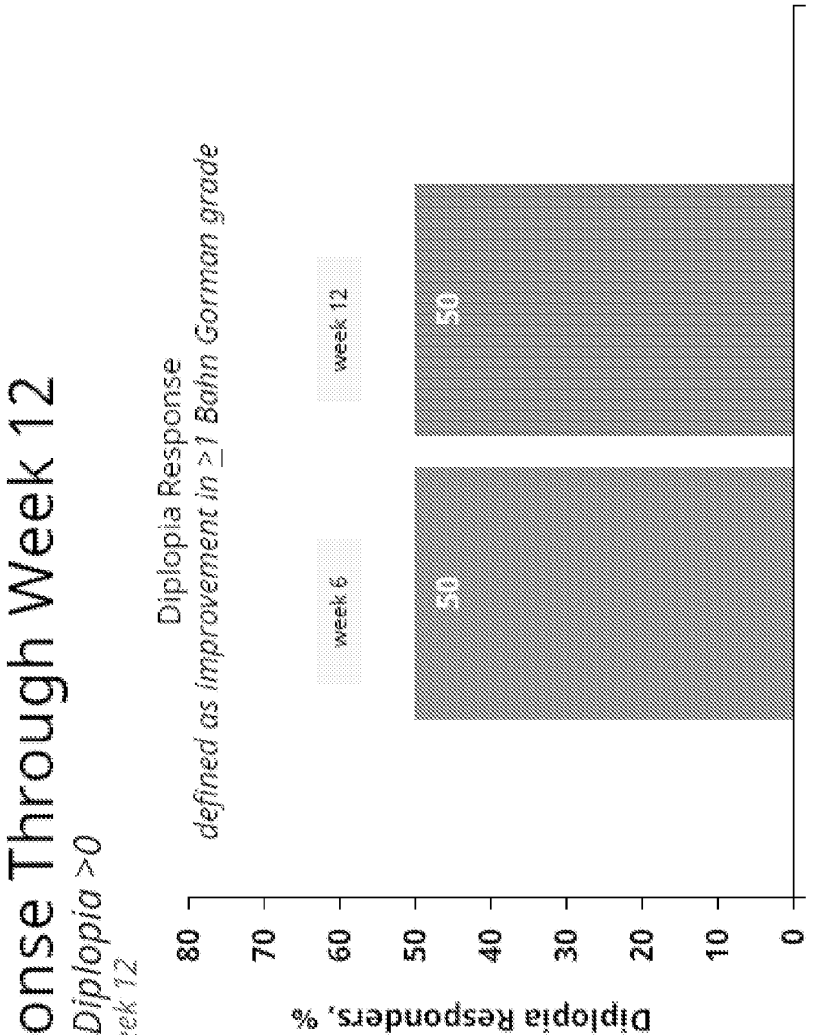

Diplopia Response Through Week 12
Patients With Baseline Diplopia >0
Treatment period through week 12
Diplopia Response
defined as improvement in ≥1 Bahn Gorman grade
Diplopia Responders, %
80
70
60
50
40
30
20
10
0
week 6
week 12
50
50

FIG. 24

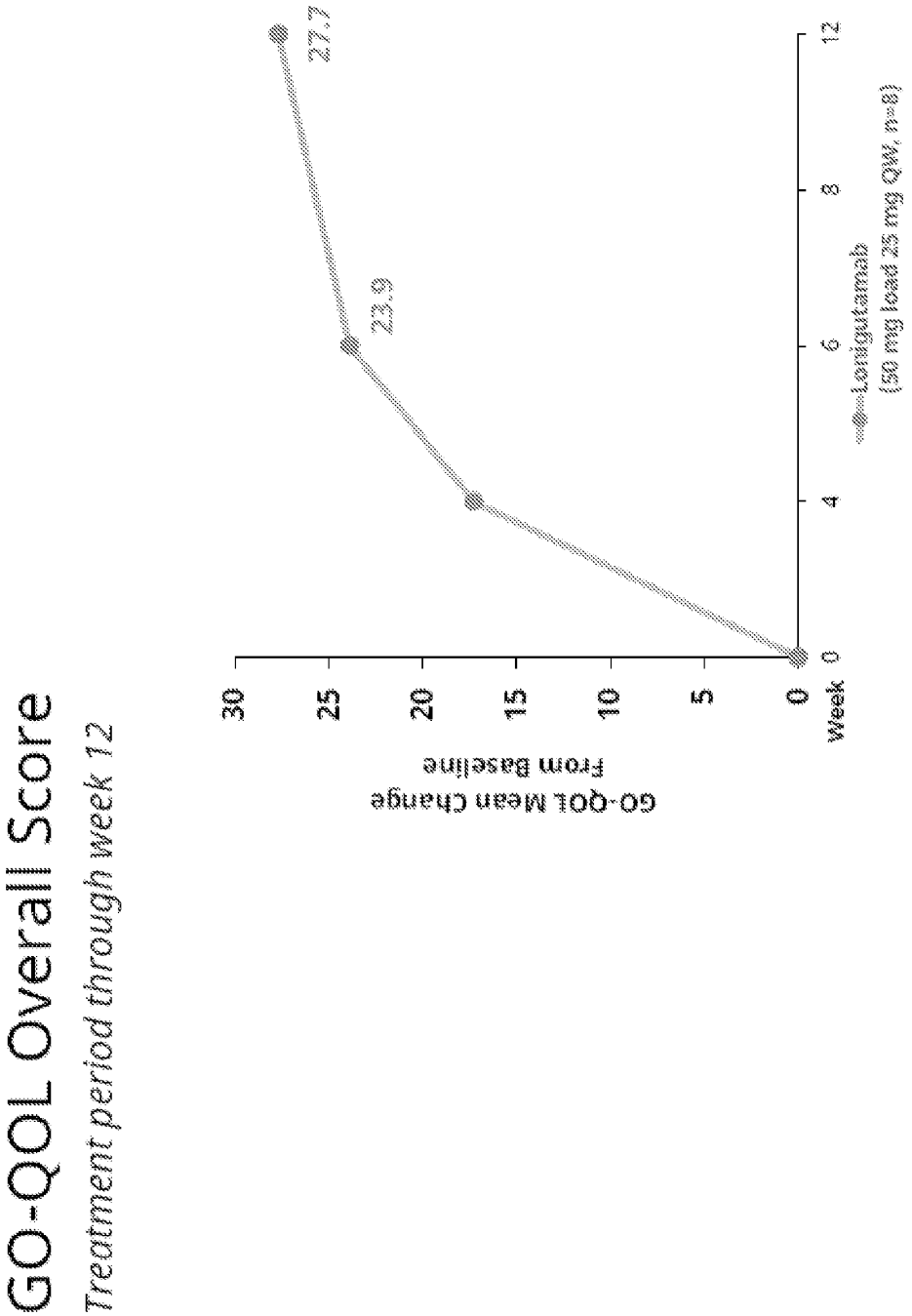

GO-QOL Overall Score
Treatment period through week 12
GO-QOL Mean Change From Baseline
30
25
20
15
10
5
0
Week
0
4
6
8
12
27.7
23.9
Lonigutamab
(50 mg load 25 mg QW, n=8)

FIG. 25

Epitope Availability Data Shows Clear Dose/PK and PD Relationship

Epitope availability assay measures IGF-1R unbound by lonigutamab

Healthy Volunteer (HV) Single Ascending Dose Study

- 40 mg allowed max receptor occupancy for ~ 3 wks→ confers efficacy in Cohort 1

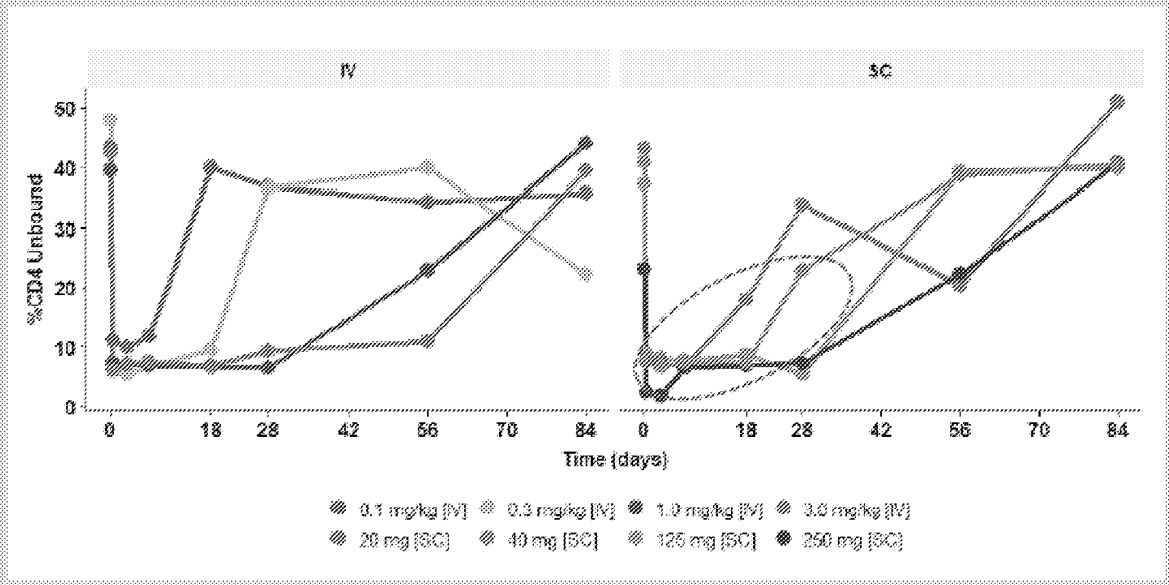


FIG. 26A

Epitope Availability Data Shows Clear Dose/PK and PD Relationship

Epitope availability assay measures IGF-1R unbound by lonigutamab

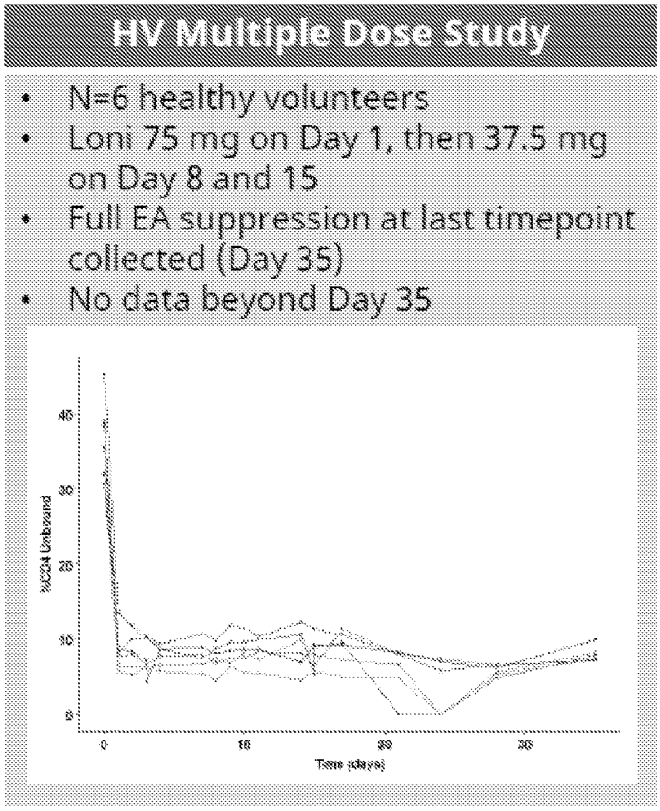


FIG. 26B

Cohorts Designed to Test Minimally Effective Dose

- Cohort 3 dose, 50 mg Q4W, tests "Cohort 1-like" average exposure for 12-week treatment duration
  - Corroborates and confirms Cohort 1 results with longer treatment duration
  - Explores if lower C_{min} impacts response

- **Previously-reviewed decision tree:**
  - IF similar efficacy and safety in Cohorts 1-3
    → ph3 dose = **50 mg Q4W** (= *Cohort 1 C_{ave}*)
  - IF Cohort 3 efficacy suboptimal to Cohort 2
    → ph3 dose > **50 mg Q4W** (eg, *Cohort 1 C_{min}*)

- Emerging data suggests low C_{min} may be suboptimal for early response

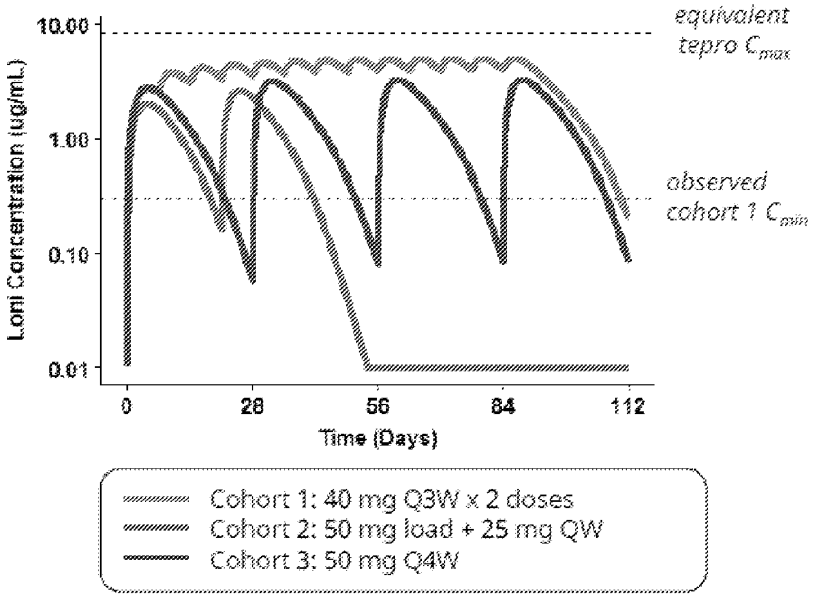


FIG. 27

P1/2 Demographics and Baseline Characteristics

	Placebo (Cohort 1) n=2	Lonigutamab (Cohort 1: 40 mg Q3W) n=6	Lonigutamab (Cohort 2: 50 mg load; 25 mg Q1W) n=8	Lonigutamab (Cohort 3: 50 mg Q4W) n=8
Age, mean (SD), years	49.5 (12.0)	43.8 (13.7)	42.1 (13.2)	45.6 (11.4)
Female, n (%)	2 (100.0)	5 (83.3)	5 (62.5)	3 (37.5)
White, n (%)	1 (50.0)	5 (83.3)	4 (50.0)	4 (50.0)
BMI, mean (SD), kg/m2	28.6 (3.5)	26.6 (7.6)	26.6 (4.0)	28.0 (3.4)
Months since onset of TED, mean (SD)	14.6 (4.6)	10.2 (6.8)	10.0 (4.0)	11.8 (5.9)
Proptosis for study eye, mean (SD), mm	26.0 (0)	26.2 (2.6)	22.5 (2.5)	24.4 (3.5)
CAS for study eye, mean (SD)	5.5 (2.1)	4.8 (1.0)	5.1 (0.8)	5 (1.1)
Diplopia at baseline, n (%)	2 (100.0)	4 (66.7)	6 (75.0)	5 (62.5)

*preliminary

FIG. 28

Proptosis Responses through Week 12

Preliminary data – Cohort 3 ongoing

Proptosis was measured via Hertel exophthalmometer. Proptosis responder rate: % patients with ≥2 mm reduction in proptosis

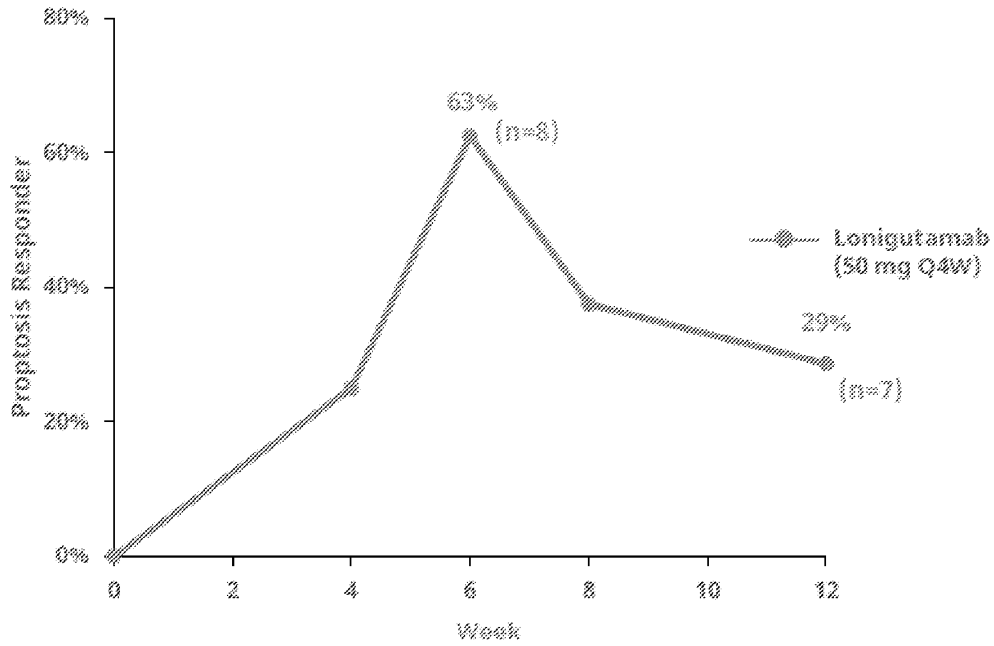


FIG. 29

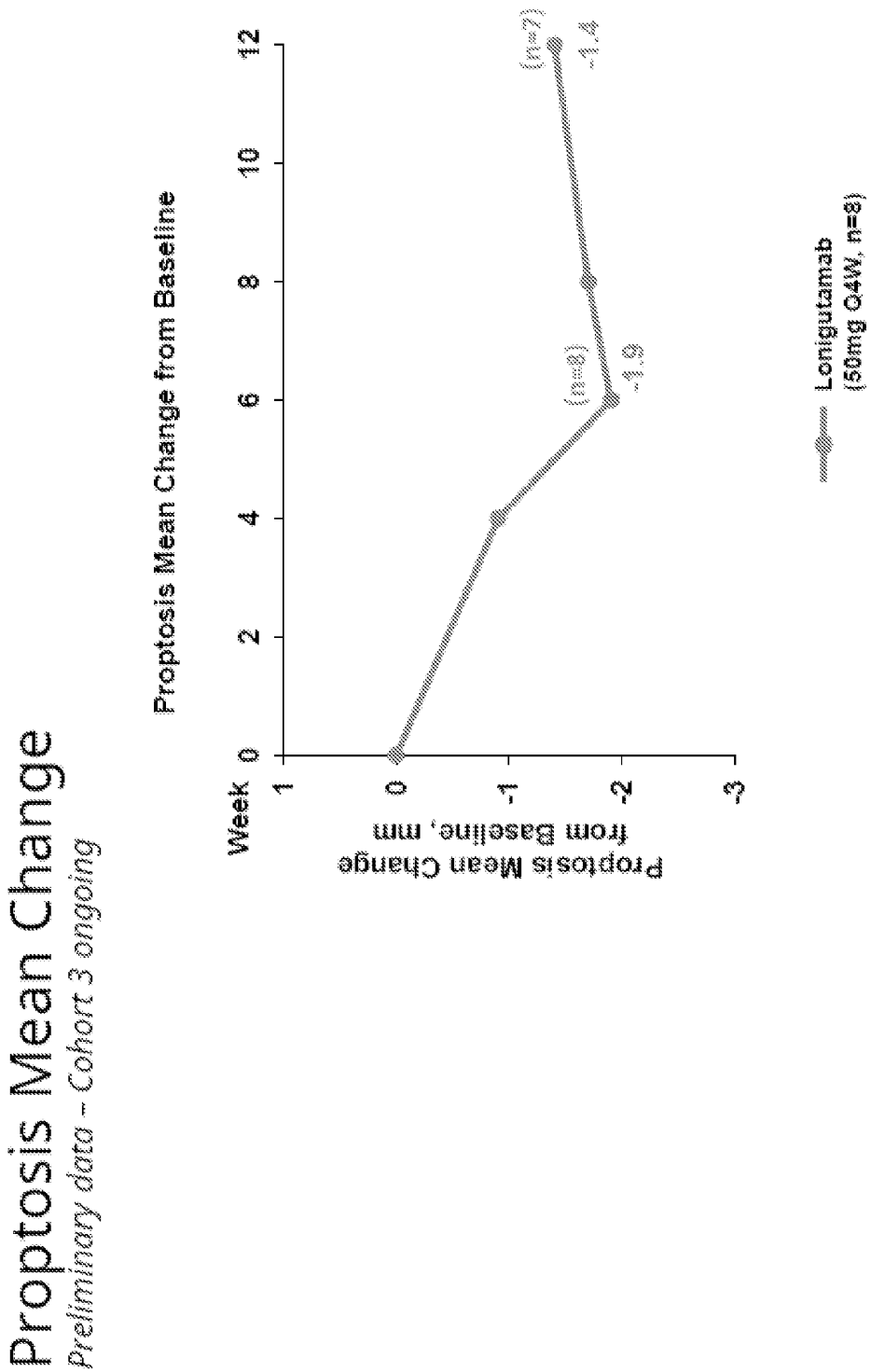

Proptosis Mean Change
Preliminary data – Cohort 3 ongoing
Proptosis Mean Change from Baseline
Week
0
2
4
6
8
10
12
1
0
-1
-2
-3
Proptosis Mean Change from Baseline, mm
(n=8)
-1.9
(n=7)
-1.4
Lonigutamab
(50mg Q4W, n=8)

FIG. 30

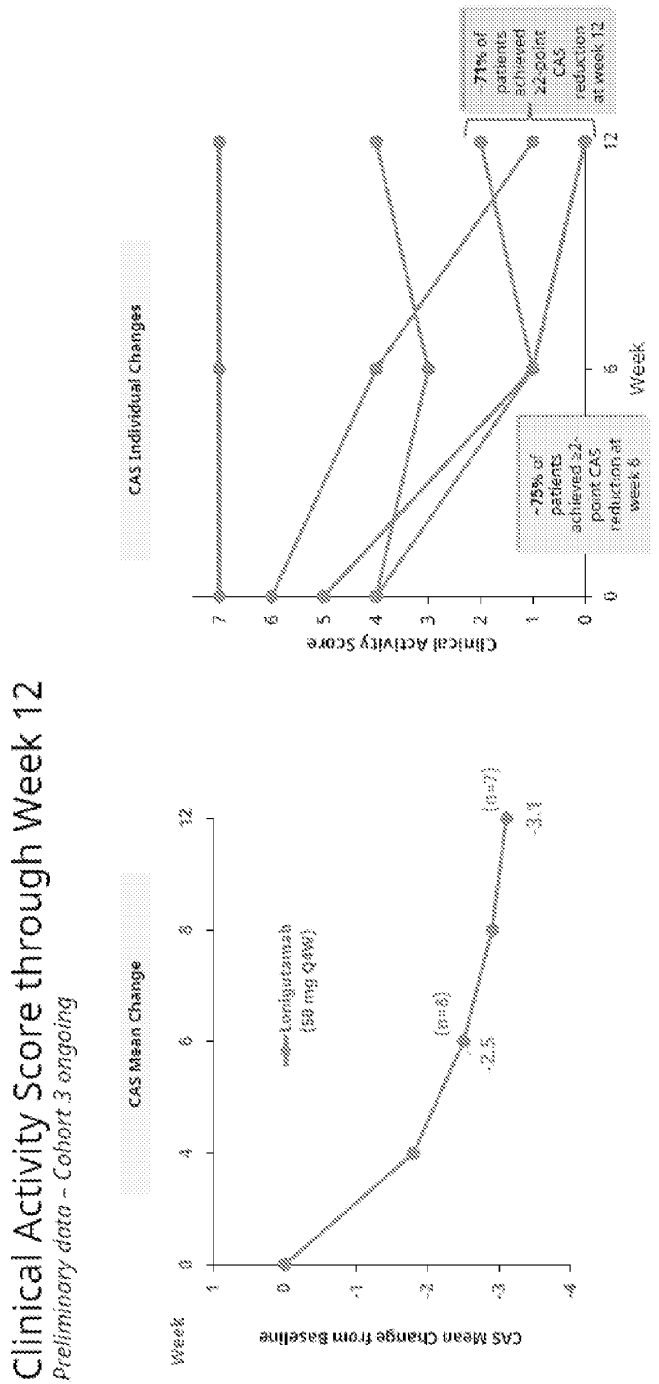

Clinical Activity Score through Week 12
Preliminary data - Cohort 3 ongoing
CAS Mean Change
CAS Mean Change from Baseline
Week
Lonigutamab (50 mg Q4W)
(n=8)
(n=7)
-2.5
-3.1
CAS Individual Changes
Clinical Activity Score
Week
~75% of patients achieved ≥2 point CAS reduction at week 8
71% of patients achieved ≥2 point CAS reduction at week 12

FIG. 31

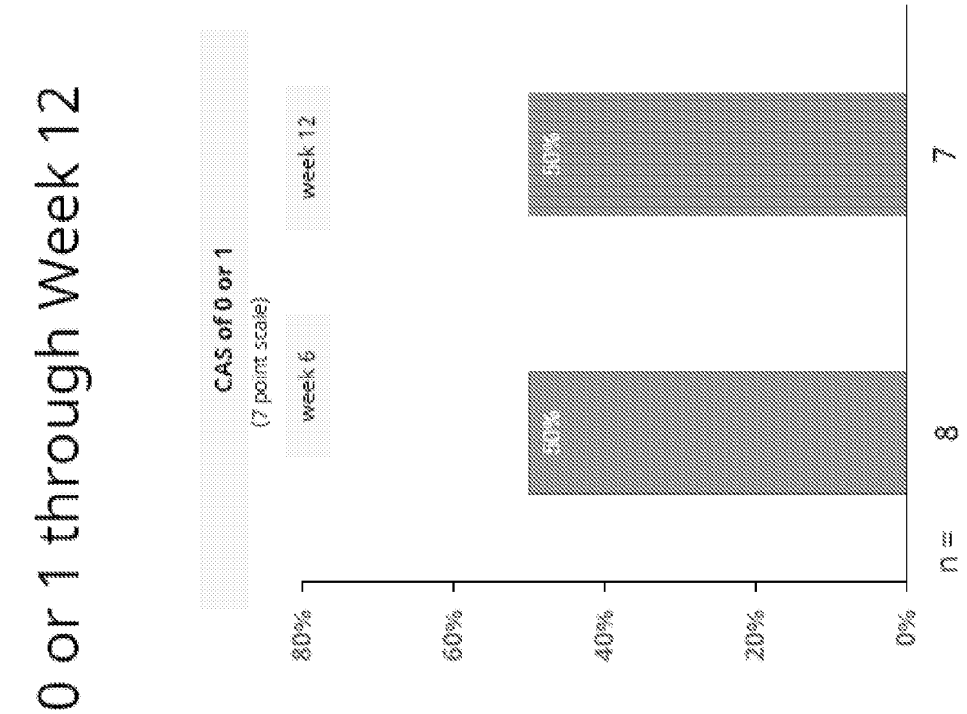

Clinical Activity Score of 0 or 1 through Week 12
Preliminary data – Cohort 3 ongoing
CAS of 0 or 1
(7 point scale)
week 6
week 12
80%
60%
40%
20%
0%
n =
8
7

FIG. 32

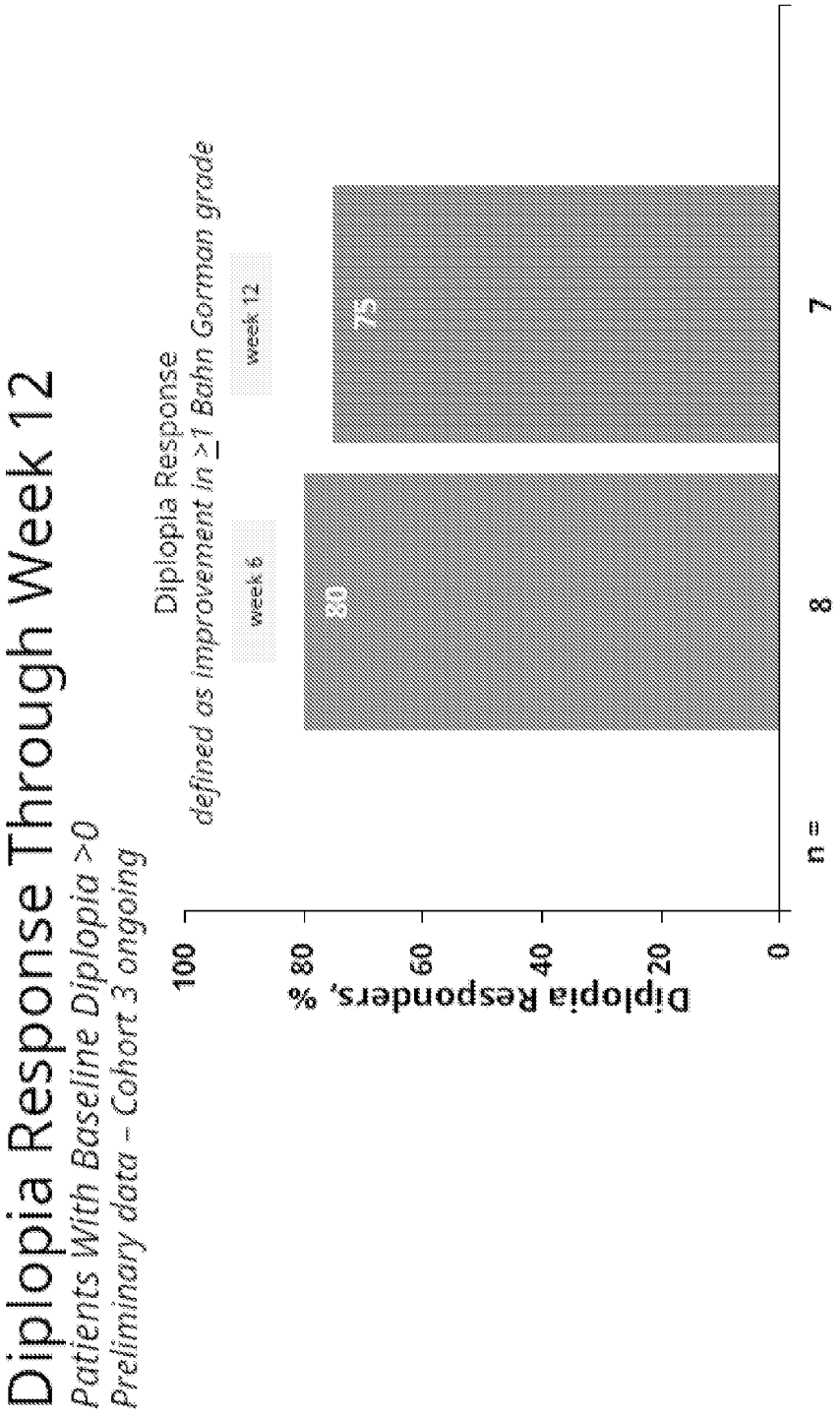

Diplopia Response Through Week 12
Patients With Baseline Diplopia >0
Preliminary data – Cohort 3 ongoing
Diplopia Response
defined as improvement in ≥1 Bahn Gorman grade
week 6
week 12
Diplopia Responders, %
100
80
60
40
20
0
30
75
n =
8
7

FIG. 33

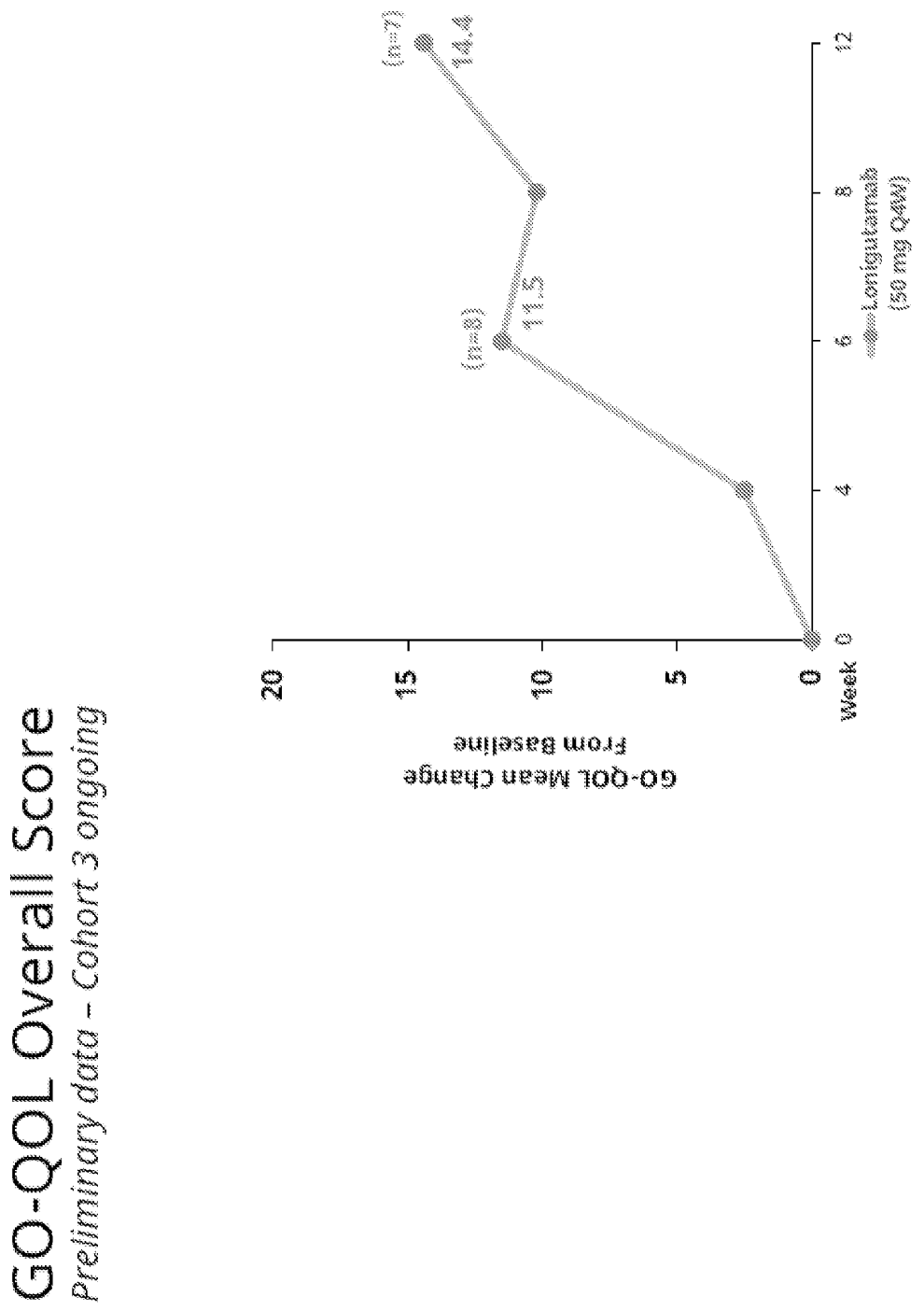

GO-QOL Overall Score
Preliminary data – Cohort 3 ongoing
GO-QOL Mean change from Baseline
20
15
10
5
0
Week 0
4
6
8
12
(n=8)
11.3
(n=7)
14.4
Lonigutamab (50 mg Q4W)

FIG. 34

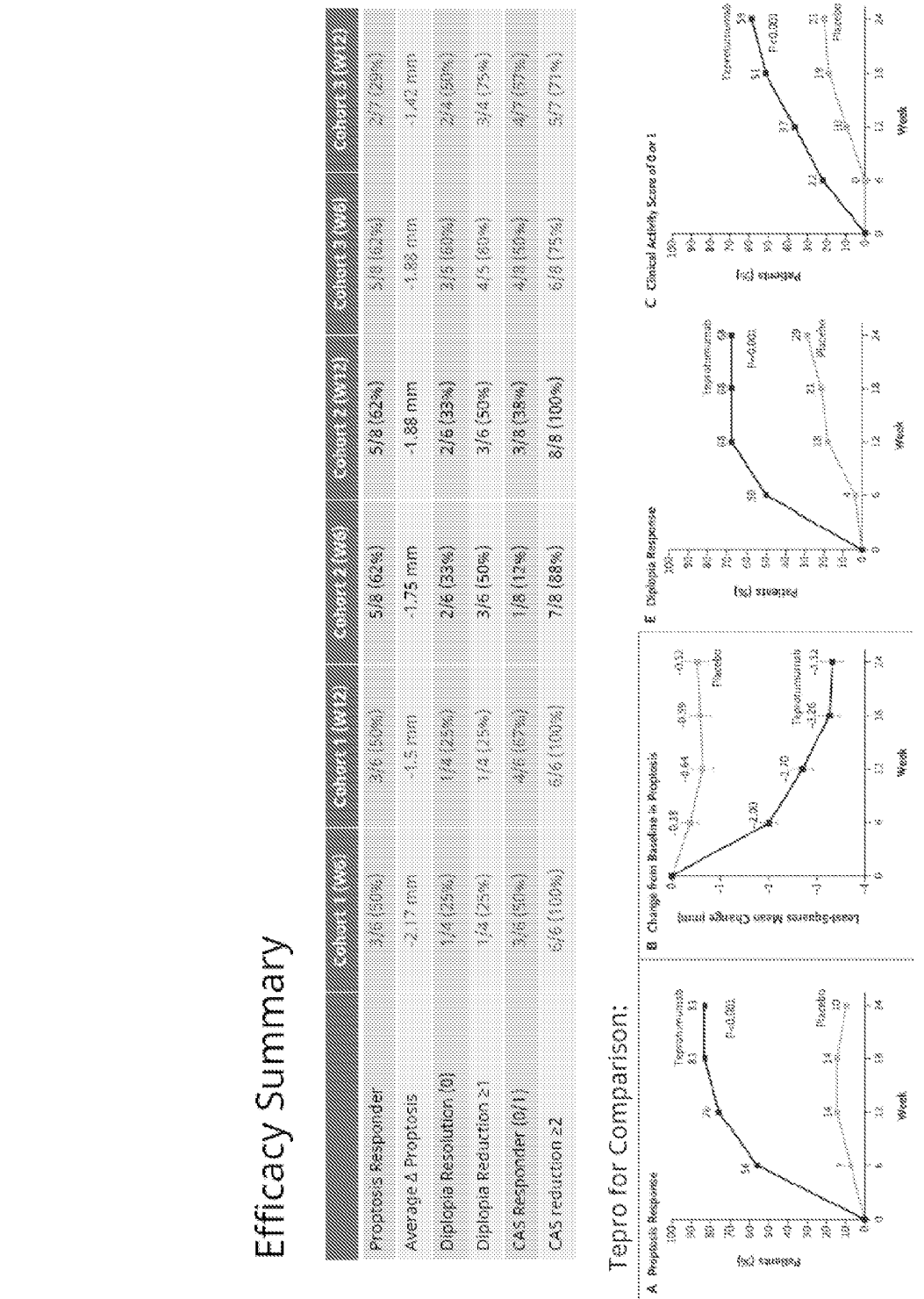
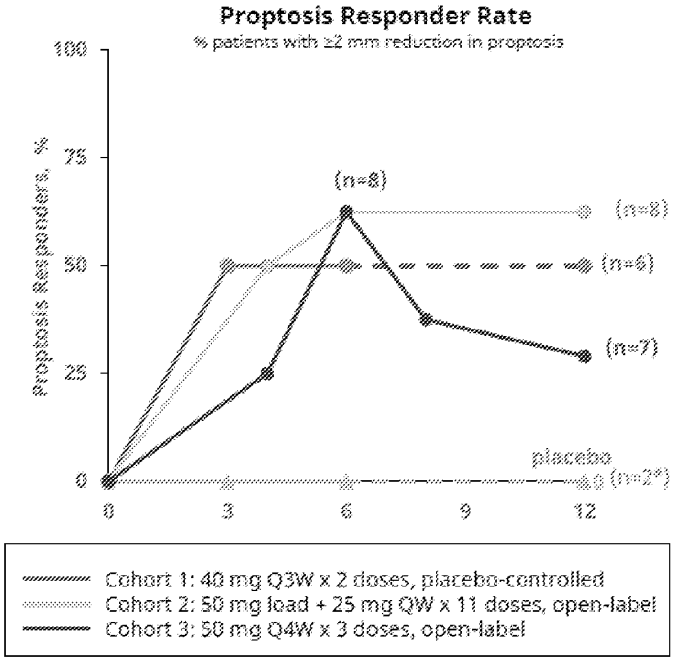
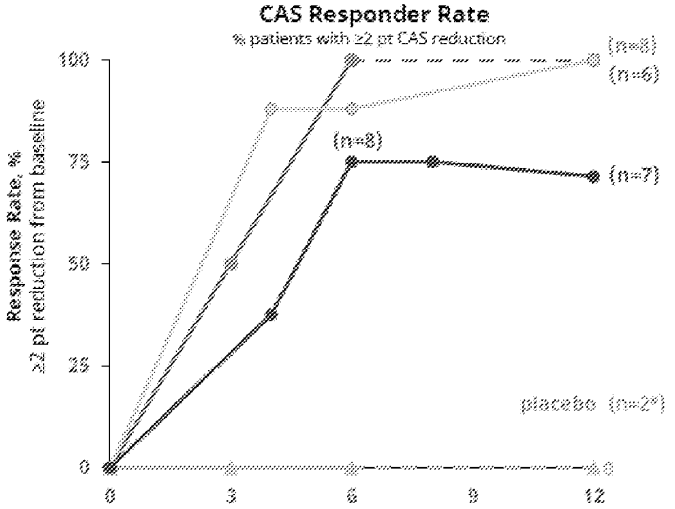

Efficacy Summary
Cohort 1 (W1)
Cohort 2 (W12)
Cohort 2 (W16)
Cohort 3 (W12)
Cohort 3 (W16)
Cohort 4 (W12)
Cohort 4 (W16)
Proptosis Responder
3/8 (38%)
3/8 (38%)
5/8 (62%)
5/8 (62%)
5/8 (62%)
5/8 (62%)
2/7 (28%)
Average Δ Proptosis
-2.17 mm
-1.5 mm
-1.75 mm
-1.88 mm
-1.88 mm
-1.38 mm
-1.42 mm
Diplopia Resolution (0)
1/4 (25%)
1/4 (25%)
2/6 (33%)
2/6 (33%)
2/6 (33%)
3/6 (50%)
2/4 (50%)
Diplopia Reduction ≥1
1/4 (25%)
1/4 (25%)
3/6 (50%)
3/6 (50%)
3/6 (50%)
4/5 (80%)
3/4 (75%)
CAS Responder (0/1)
7/8 (88%)
4/8 (50%)
1/8 (13%)
3/8 (38%)
4/8 (50%)
4/8 (50%)
4/7 (57%)
CAS reduction ≥2
6/6 (100%)
6/6 (100%)
7/8 (88%)
8/8 (100%)
6/8 (75%)
5/7 (71%)
Tepro for Comparison:
A Proptosis Response
Responders (%)
Week
Teprotumumab
Placebo
P=0.001
B Change from Baseline in Proptosis
Least-Squares Mean Change (mm)
Week
Teprotumumab
Placebo
E Diplopia Response
Patients (%)
Week
Teprotumumab
Placebo
P=0.001
C Clinical Activity Score of 0 or 1
Patients (%)
Week
Teprotumumab
Placebo
P=0.003

FIG. 35

Efficacy Responses Mimics PK Modeling

W6 (peak), W4, 8 and 12 (trough)





Cohort 1: 40 mg Q3W x 2 doses, placebo-controlled
Cohort 2: 50 mg load + 25 mg QW x 11 doses, open-label
Cohort 3: 50 mg Q4W x 3 doses, open-label

- Cohort 2 diplopia response consistent W4 through W12 (50%)
- Cohort 3 diplopia response consistent W4 through W8 (80%)

* first timepoint assessed; # NRI for one early term;
▲placebo ● active

FIG. 36

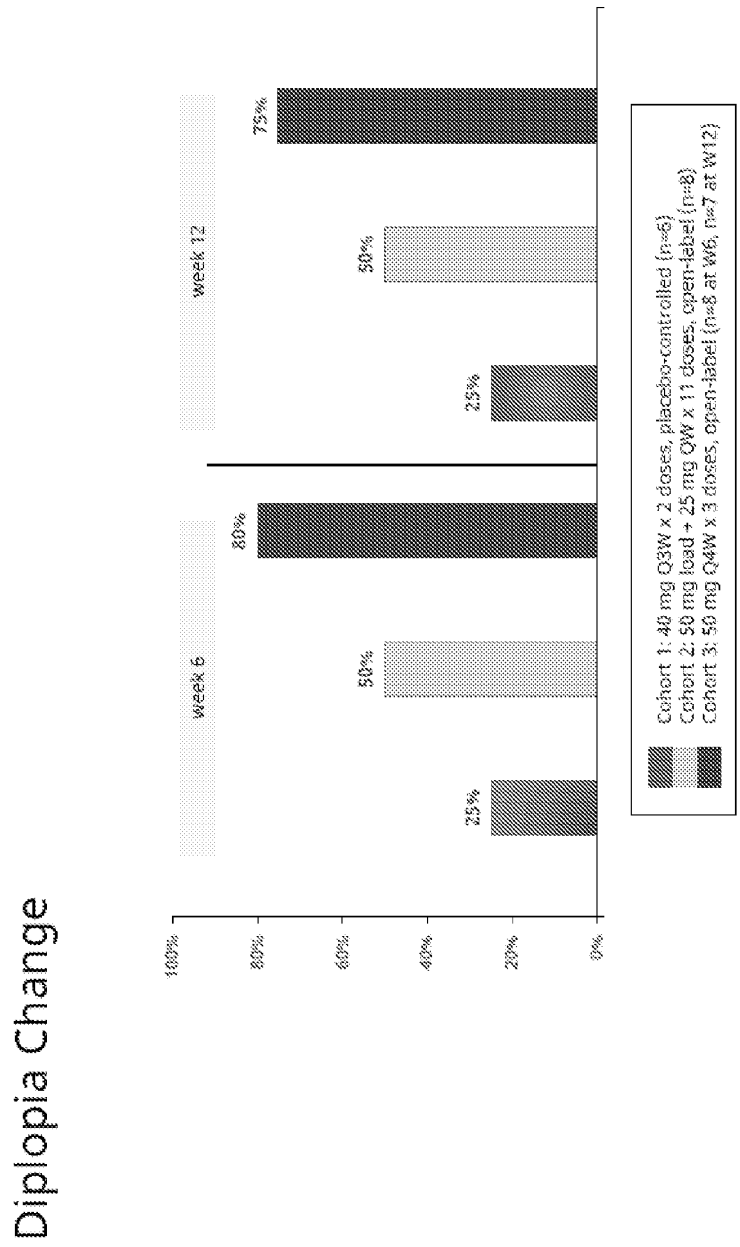

Diplopia Change
100%
80%
60%
40%
20%
0%
week 6
25%
50%
80%
week 12
25%
50%
75%
Cohort 1: 48 mg Q3W x 2 doses, placebo-controlled (n=6)
Cohort 2: 50 mg load + 25 mg QW x 11 doses, open-label (n=8)
Cohort 3: 50 mg Q4W x 3 doses, open-label (n=8 at W6, n=7 at W12)

FIG. 37

Summary of Safety

Muscle spasm, diarrhea, vs Tepro common AEs

n (%)	Placebo, Cohort 1 n=2	Lonigutumab, Cohort 1 (50 mg Q3W) n=6	Lonigutumab, Cohort 2 (50 mg load, 25 mg Q3W) n=8	Lonigutumab, Cohort 3 (50 mg Q4W) n=8
Any TEAEs	2 (100.0)	4 (66.7)	7 (87.5)	4 (50)
Serious	0	0	0	0
Any grade 2	0	1 (16.7)	3 (37.5)	0 (0)
Any grade 3	0	0	0	0
TEAEs leading to study drug discontinuation				
Optic neuropathy	1 (50.0)	0	0	0
TEAEs leading to death	0	0	0	0

- Majority of events were mild. No discontinuation of study drug except pbo subject with optic neuropathy
- No audiology changes, no hyperglycemia events, and no serious adverse events
- Total of 3 subjects with mild tinnitus in Cohort 1; all events were resolved or resolving
- 421-01-01: no notable safety findings; no dose-related trends; no TEAEs related to hearing changes
- 23109 HV: no notable safety findings, no TEAEs related to hearing changes

Most common events (reported in 2 or more subjects on lonigutamab) were headache, tinnitus, injection site erythema, injection site swelling, fatigue, muscle spasms, hypoaesthesia teeth. Injection site reactions were all mild. Grade 2 events included headache, fatigue, and nausea.

Q3W, every 3 weeks; TEAE, treatment-emergent adverse event; TED, thyroid eye disease.

FIG. 38

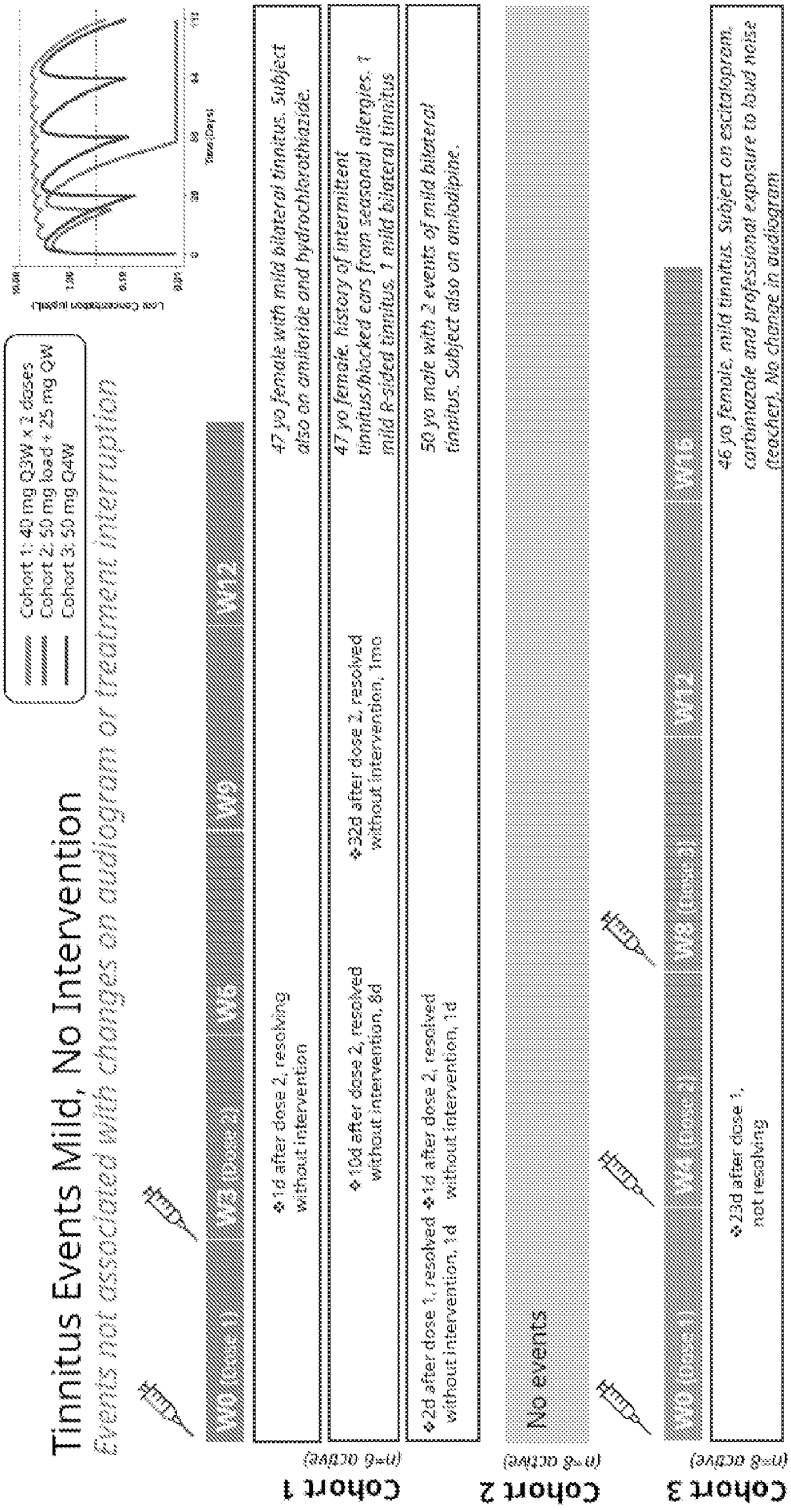

Tinnitus Events Mild, No Intervention
Events not associated with changes on audiogram or treatment interruption
Cohort 1: 40 mg Q3W x 3 doses
Cohort 2: 50 mg load + 25 mg QW
Cohort 3: 50 mg Q4W
W0 (Day 1)
W1
W2
W3
Cohort 1
(n=6 active)
❖1d after dose 2, resolving without intervention
47 yo female with mild bilateral tinnitus. Subject also on amiloride and hydrochlorothiazide.
❖10d after dose 2, resolved without intervention, 8d
❖32d after dose 2, resolved without intervention, 1mo
47 yo female, history of intermittent tinnitus/blocked ears from seasonal allergies. 1 mild R-sided tinnitus, 1 mild bilateral tinnitus
❖2d after dose 1, resolved without intervention, 1d
❖1d after dose 2, resolved without intervention, 1d
50 yo male with 2 events of mild bilateral tinnitus. Subject also on amlodipine.
Cohort 2
(n=6 active)
No events
Cohort 3
(n=6 active)
W4 (Day 29)
W8 (Day 57)
❖23d after dose 1, not resolving
46 yo female, mild tinnitus. Subject on escitalopram, carbamazole and professional exposure to loud noise (teacher). No change in audiogram

FIG. 39

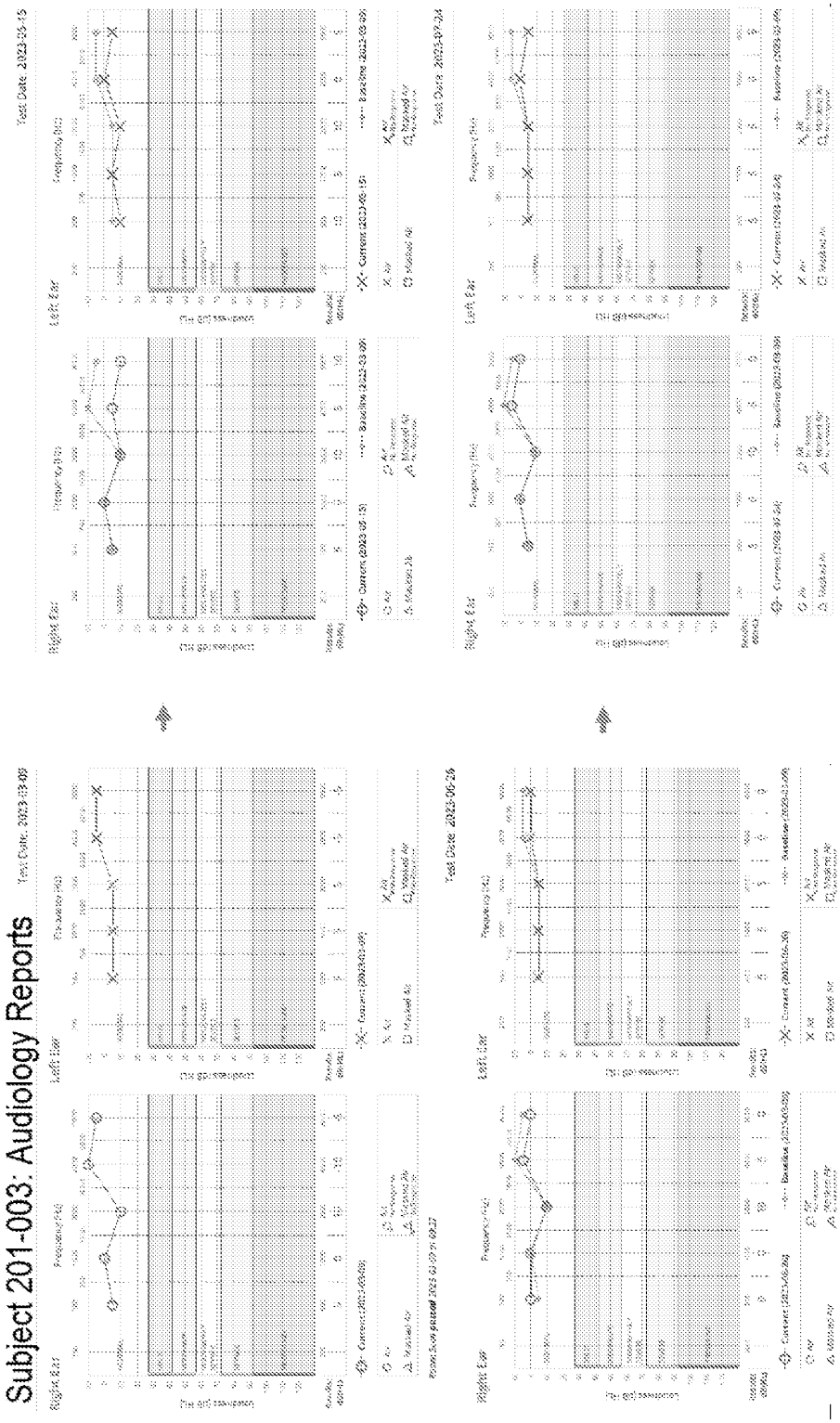

Subject 201-003: Audiology Reports
Right Ear
Left Ear
Test Date: 2023-06-26
Test Date: 2023-09-15
Test Date: 2023-09-24

FIG. 40A

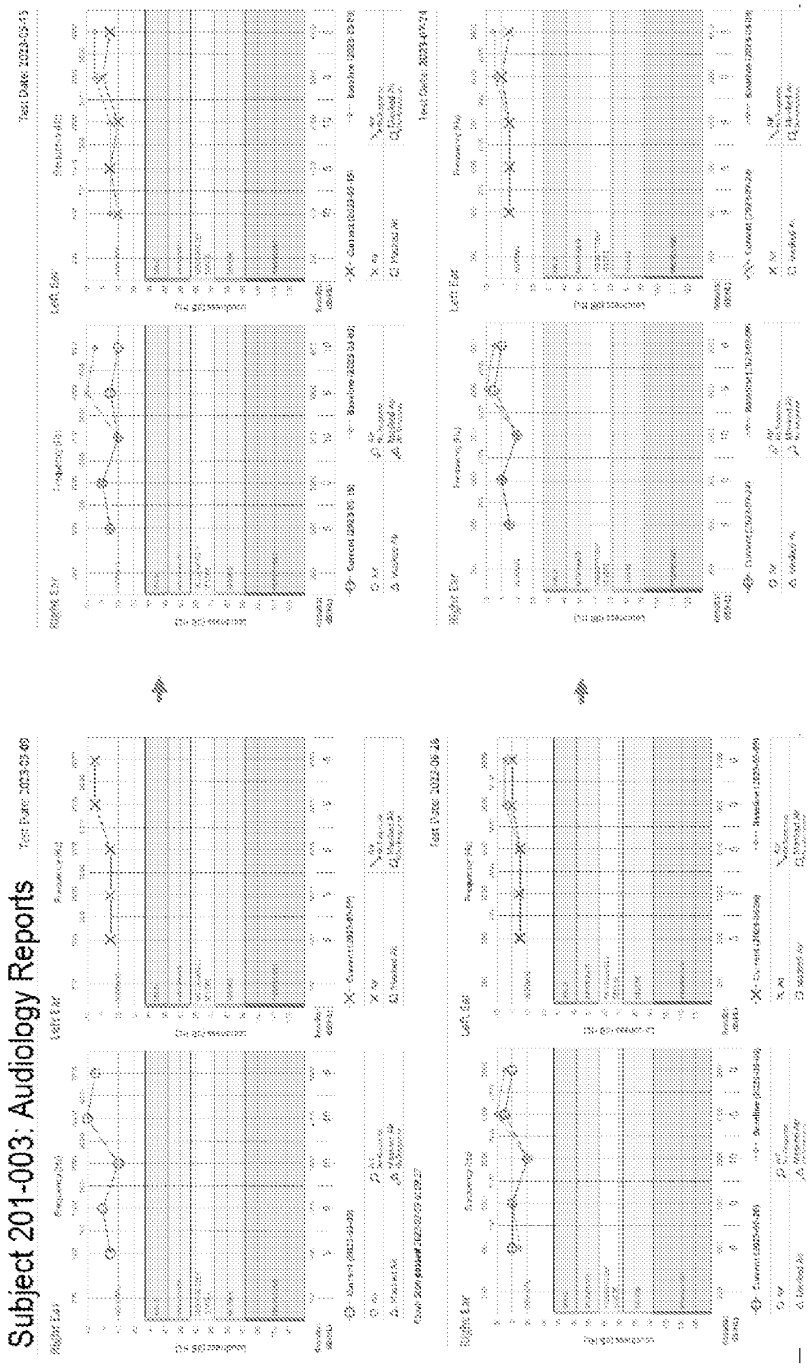


FIG. 40B

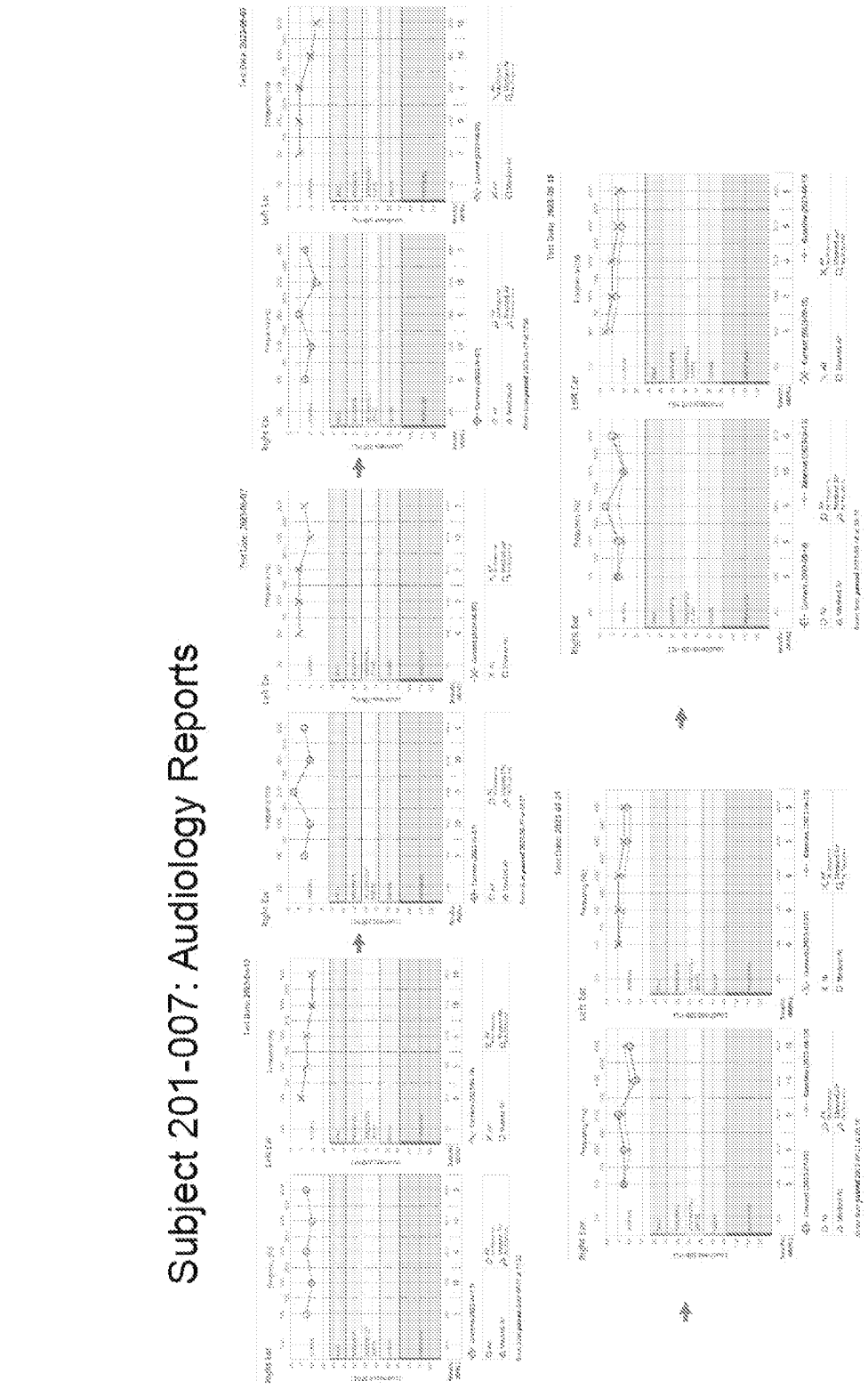


FIG. 40C

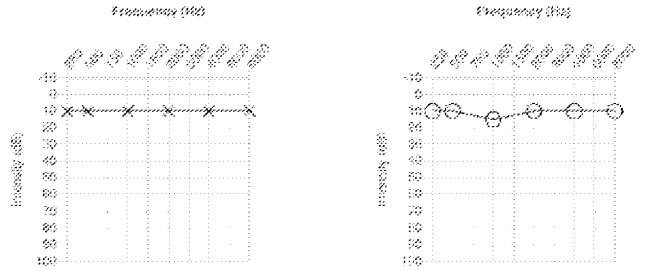
Subject 204-034- Audiology Reports

Test Date: 14-Feb-2024

THRESHOLDS

Hz	500	600	700	1000	1500	2000	3000	4000	6000	8000
Left Ear (dB)	10	10	-	10	-	10	-	10	-	10
Masked (dB)	38	32	-	31	-	30	-	30	-	30
Right Ear (dB)	10	10	-	10	-	10	-	10	-	10
Masked (dB)	39	33	-	31	-	30	-	30	-	30

*Noise is measured at -5 dB or at minimum testing intensity if patient responded at that level.



PTA LEFT 10.0 dB Normal

PTA RIGHT 11.2 dB Normal

FIG. 40D

Subject 204-034- Audiology Reports
Test Date: 04-Apr-2024
THRESHOLDS
Frequency (Hz)
Frequency (Hz)
PTA LEFT
PTA RIGHT

FIG. 40E

Subject 204-034- Audiology Reports
Test Date: 16-Apr-2024
THRESHOLDS
Left Ear (dB)
Normal (dB)
Right Ear (dB)
Normal (dB)
Frequency (Hz)
Frequency (Hz)
PTA LEFT 10.0 dB Normal
PTA RIGHT 10.0 dB Normal

FIG. 40F

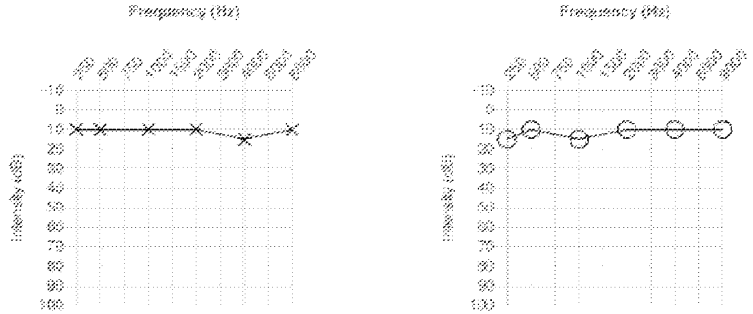
Subject 204-034- Audiology Reports

Test Date: 30-Apr-2024

THRESHOLDS

Hz	250	500	750	1000	1500	2000	3000	4000	6000	8000
Left Ear (dB)	10	10	-	10	-	10	-	15	-	10
Noise (dB)	35	30	-	30	-	30	-	30	-	30
Right Ear (dB)	15	10	-	15	-	10	-	10	-	10
Noise (dB)	37	30	-	30	-	30	-	30	-	30

*Noise is measured at -5 dB of all minimum masking intensity. If patient responded at that level



PTA LEFT 11.2 dB Normal

PTA RIGHT 11.2 dB Normal

Left		Right	
×	×	○	⌀
No Conduction	No Response	No Conduction	No Response

FIG. 40G

Subject 204-034- Audiology Reports

Test Date: 30-May-2024

THRESHOLDS

Hz	250	500	750	1000	1500	2000	3000	4000	6000	8000
Left Ear (dB)	10	15	-	15	-	10	-	15	-	10
Noise* (dB)	25	30	-	30	-	30	-	30	-	30
Right Ear (dB)	10	10		15	-	10	-	10		10
Noise* (dB)	25	30	-	30	-	30	-	30	-	30

*Noise is measured at -5 dB or at maximum testing intensity, if patient responded at that level.

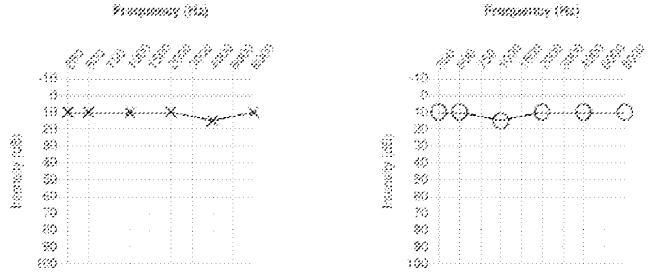
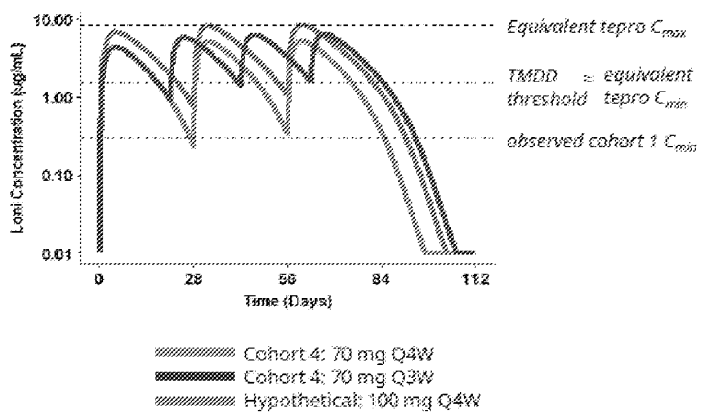
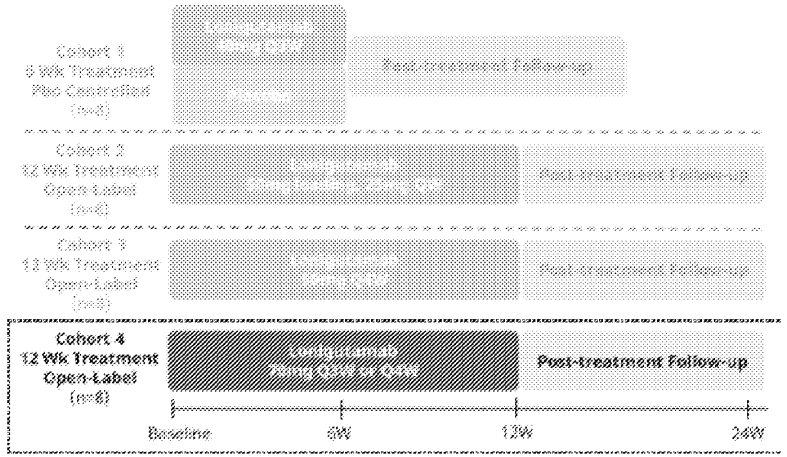


FIG. 40H

70 mg Q3W Best Maintains Drug Levels Within Equivalent (Potency Adjusted) Tepro C_{max} and Tepro C_{min} ≈ TMDD Thresholds

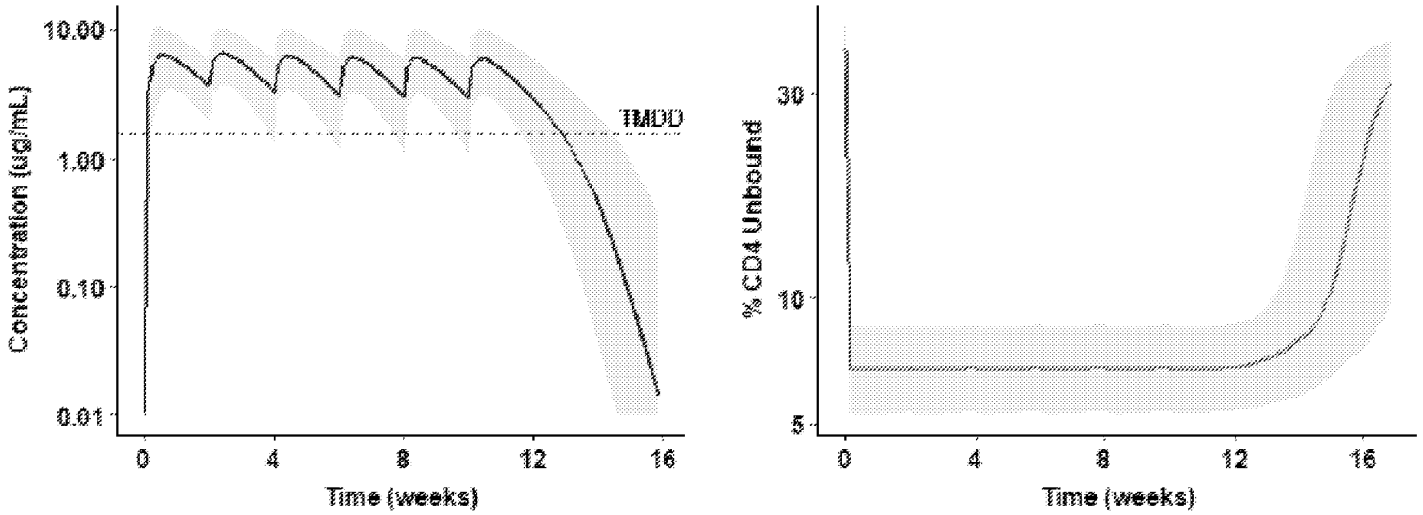




- Population PK model estimated IGF1-R concentration of 1.5 ug/mL.
  - Maintaining Loni levels > 1.5 ug/mL will allow the receptor to be fully saturated and reduce the risk of target-mediated drug disposition (fast clearance)
- 70 mg Q3W maintains Loni concentration above TMDD threshold at steady-state

FIG. 41

Model-simulated Lonigutamab Concentrations and Receptor Occupancy for 100 mg loading dose and 50 mg Q2W



Abbreviations: Q2W = every 2 weeks; TMDD=target-mediated drug disposition.
Solid line denotes median and shaded area represents 10th – 90th percentiles. Dashed lines denote the TMDD threshold of 1.5 ug/mL.

FIG. 42

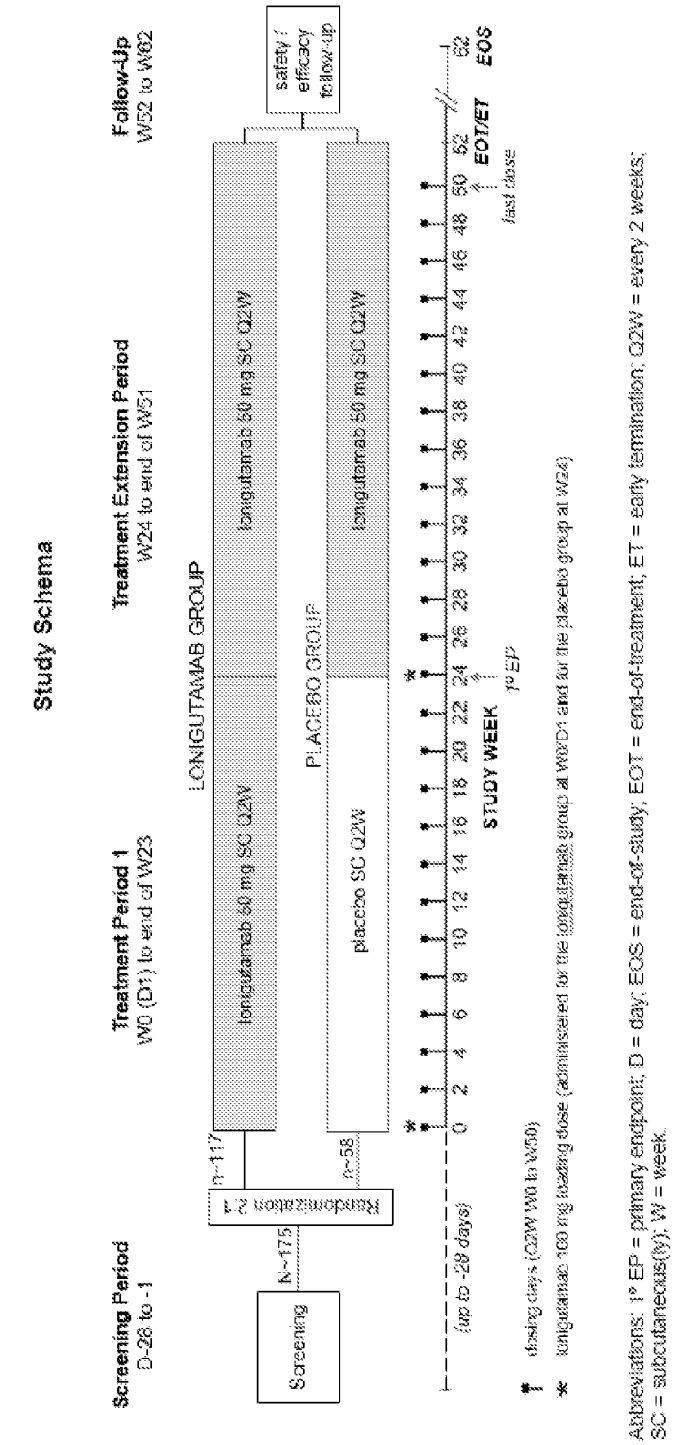

Study Schema
Screening Period
D-28 to -1
Treatment Period 1
W0 (D1) to end of W23
Treatment Extension Period
W24 to end of W51
Follow-Up
W52 to W62
Screening
N~175
Randomization 2:1
n~117
n~58
LONIGUTAMAB GROUP
PLACEBO GROUP
lonigutamab 50 mg SC Q2W
placebo SC Q2W
lonigutamab 50 mg SC Q2W
safety / efficacy follow-up
(up to -28 days)
STUDY WEEK
1° EP
last dose
EOT/ET
EOS
dosing days (Q2W W0 to W50)
lonigutamab 100 mg loading dose (administered to the lonigutamab group at W0D1 and to the placebo group at W24)
Abbreviations: 1° EP = primary endpoint; D = day; EOS = end-of-study; EOT = end-of-treatment; ET = early termination; Q2W = every 2 weeks; SC = subcutaneous(ly); W = week.

FIG. 43