

# Systematic Processing of Full Genomic Analysis of ANAVEX<sup>®</sup> 2-73 Phase 2a Alzheimer's Disease Study Identifies Biomarkers Enabling a Precision Medicine Approach

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## Abstract:

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**Background:** The selective sigma-1 receptor agonist ANAVEX<sup>®</sup> 2-73 was studied in a 57-week Phase 2a with 32 mild-to-moderate AD patients. This study showed favorable safety profile and concentration-response relationship using cognitive(MMSE) and functional(ADCS-ADL) endpoints. Delta MMSE and ADCS-ADL were calculated for the difference between values collected at week 57 and baseline. All 21 patients in a 104-week extension study agreed to full exome(DNA) and transcriptome(RNA) sequencing. **Methods:** Blood samples were collected with Paxgene tubes. Next-generation sequencing was run at Eurofins Genomics. RNA strand-specific libraries were created with commercially available kits (TruSeq Stranded mRNA Library Prep Kit, Illumina). PolyA-RNA was extracted from total RNA (oligo dT-bead based method). First-strand and dUTP-based second strand synthesis was after fragmentation of the mRNA, followed by end-repair, A-tailing, ligation of the indexed Illumina Adapter, and digestion of the dUTP-strand. A bead-based method was used for size selection. After PCR amplification, resulting fragments were processed and used for cluster generation. Library generation was with Agilent SureSelectXT Reagent Kit for 200ng starting material. Enrichment was with Agilent's SureSelect Exome V6+UTR Capture Library Kit. Pooled libraries cluster generation was on the cBot (Illumina). Paired-end sequencing with 100bp read length was on a HiSeq2500 (HiSeq Control Software 2.2.58) with HiSeq Flow Cell v4 and TruSeq SBS Kit v4. Raw data was processed with RTA version 1.18.64. FASTQ-files were generated with CASAVA 1.8.4. Reads were mapped to reference sequence(s) (GRCh37.p13). BAM and BAI files (Binary Sequence Alignment/Map and Index) were generated with mapping statistics. Mapping and variant analysis (BWA/GATK) followed by complete SNP/InDel positions and variant statistics, and variant annotation and comparison, with dbSNP. **Results:** A total of 33,311 genes and 860 pathways were identified in AD patient sequences. Systematic analysis showed several response-linked gene variants, including SIGMAR1(rs1800866), ANAVEX<sup>®</sup> 2-73 putative target, and COMT(rs113895332/rs61143203), a gene involved in memory function. **Conclusions:** This genomic analysis of ANAVEX<sup>®</sup> 2-73-treated AD patients identified actionable genetic variants, and support enrichment with genetic biomarkers in the clinical development of ANAVEX<sup>®</sup> 2-73. These mutations are found at frequencies of approx. 20%. If patients with these are excluded, clinically meaningful effects on cognition and function would be expected on the remaining AD population (approx. 80%).