Full Genomic Analysis of ANAVEX®2-73 Phase 2a Alzheimer's Disease Study Identifies Biomarkers Enabling Targeted Therapy and a Precision Medicine Approach

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Abstract:

Harald Hampel, Prof., MD, PhD[1]; Mohammad Afshar, MD, PhD[2]; Frédéric Parmentier, PhD[2]; Coralie Williams, MSc[2]; Adrien Etcheto, MSc[2]; Federico Goodsaid, PhD[3]; Emmanuel O Fadiran, PhD[4] and Christopher U Missling, PhD[4], (1)Sorbonne University, Paris, France, (2)Ariana Pharma, Paris, France, (3)Regulatory Pathfinders LLC, Pescadero, CA, USA, (4)Anavex Life Sciences Corp., New York, NY, USA

Background: ANAVEX®2-73, a selective sigma-1 receptor agonist was studied in a Phase 2a trial with 32 mild-to-moderate Alzheimer's disease patients for 57 weeks. MMSE baseline range was 16-28. ANAVEX®2-73 demonstrated a favorable safety profile. An ANAVEX®2-73 concentration-response relation was observed using exploratory endpoints MMSE (Mini-Mental State Examination) and ADCS-ADL (Alzheimer's Disease Co-operative Study – Activities of Daily Living). **Methods:** The full exome (DNA) and transcriptome (RNA) of attainable AD patients were sequenced using Illumina HiSeq 2500 with an average sequencing depth of 70x, resulting in the analysis of 33,311 genes and 860 pathways, using non-linear rule based Formal Concept Analysis as implemented in KEM. **Results:** Systematic analysis identifies several genetic variants impacting the response including SIGMAR1(rs1800866), ANAVEX®2-73 putative target, and COMT(rs113895332/rs61143203), a gene involved in memory function. Excluding these variants from the study population, still leaving about 80% of the population, results in improved MMSE and ADCS-ADL scores ($p<0.05$, Cohen's d effect size >0.5 and Specificity=100%). In addition, we observe that high RNA expression levels for SIGMAR1 are associated with improved outcome as measured by MMSE and ADCS-ADL. Including patients with milder disease stage (baseline MMSE ≥20) and the exclusion of AD patients carrying SIGMAR1 mutation results in a score improvement of 1.7 MMSE and 3.9 ADCS-ADL, respectively at week 57. The additional exclusion of the COMT mutation results in a score improvement of 2.0 MMSE and 4.9 ADCS-ADL, respectively for the same period. Both effects would be clinically meaningful. **Conclusions:** This is the first full genomic analysis of ANAVEX®2-73 in AD patients resulting in the identification of actionable genetic variants. Consistent results were found using both DNA and RNA and multiple endpoints and time points. The data provides support to further precision medicine clinical development of ANAVEX®2-73 utilizing genetic biomarkers leading to a pre-specified population, who demonstrated a confirmed response with ANAVEX®2-73. Further larger clinical studies in several indications are planned or underway. Detailed results will be presented at the conference.