effects with titrated aducanumab in the second year of the LTE were generally consistent with findings in the 10 mg/kg fixed-dose cohort. The safety profile of aducanumab remains unchanged. These data support further investigation of aducanumab in patients with early AD in the ENGAGE and EMERGE Phase 3 trials. 1. Sevigny J, et al. Nature. 2016;537:50-56; 2. Budd Haeberlein S, et al. J Prev Alz Dis. 2017;4:313; 3. Joshi AD, et al. J Nucl Med. 2015;56:1736-1741.

LB9: LONGITUDINAL 148-WEEK EXTENSION STUDY FOR ANAVEX®2-73 PHASE 2A ALZHEIMER'S DISEASE DEMONSTRATES MAINTAINED ACTIVITIES OF DAILY LIVING SCORE (ADCS-ADL) AND REDUCED COGNITIVE DECLINE (MMSE) FOR PATIENT COHORT ON HIGHER DRUG CONCENTRATION AND CONFIRMS ROLE OF PATIENT SELECTION BIOMARKERS. Harald Hampel[1], Mohammad Afshar[2], Frédéric Parmentier[2], Coralie Williams[2], Adrien Etcheto[2], Federico Goodsaid[3], Christopher U Missling[4] *((1) Department of Neurology, Sorbonne University, Paris, France; (2) Ariana Pharma, Paris, France; (3) Regulatory Pathfinders LLC, San Francisco, CA; (4) Anavex Life Sciences Corp., New York, NY)*

Backgrounds: ANAVEX®2-73, a selective sigma-1 receptor (SIGMAR1) agonist was investigated in a 57-week Phase 2a study with 32 mild-to-moderate Alzheimer's disease dementia patients showing a favorable safety profile. An ANAVEX®2-73 concentration-dependent response was observed using exploratory functional (ADCS-ADL) and cognitive (MMSE) endpoints. According to the precision medicine concept, data-driven unbiased genomic analysis was used to identify biomarkers. Status of a single genetic variant on the ANAVEX®2-73 target SIGMAR1 was shown to significantly impact the drug effect. Here we report the current results of the extension study (148 weeks). **Methods:** Relationship between all biomarkers and efficacy outcome measures were investigated using a non-linear rule based Formal Concept Analysis (FCA, implemented in Ariana's KEM® software). This approach identifies all biomarkers in an unbiased data-driven mode. In order to model functional and cognitive progression over time, Mixed Model Repeated Measures (MMRM), with a linear time effect hypothesis, and Linear Mixed Effect (LME) modeling, was performed. The outcome for patient cohort with the highest tertile drug concentrations was compared to the patient cohort with medium and low tertile concentrations. Standard covariate adjustments were based on age, sex, APOE ε4 allele carrier status, concomitant treatment with donepezil, and the interaction between APOE ε4 allele, time and ANAVEX®2-73 concentration. Three further parameters previously identified with KEM were included into the model: baseline MMSE score, polymorphisms of both SIGMAR1-Q2P (rs1800866) and COMT-L146FS (rs113895332/ rs61143203), as well as their interaction with time and ANAVEX®2-73 concentration. **Results:** The significant association between ANAVEX®2-73 concentration and both MMSE and ADCS-ADL changes was confirmed over the extended 148-week period using the MMRM-LME method. The analysis shows that the cohort of patients treated with higher ANAVEX®2-73 concentration maintains ADCS-ADL performance compared to the lower concentration cohort ($p<0.0001$), with a significant impact of SIGMAR1 ($p<0.0080$) and COMT ($p<0.0014$) biomarkers on the drug response. Higher delta MMSE is also maintained for the higher drug concentration cohort compared to lower concentration cohort ($p<0.0008$). The observed impact of the APOE ε4 allele was statistically significant for both ADCS-ADL ($p<0.0001$) and MMSE ($p<0.0001$) irrespective of ANAVEX®2-73 concentration. Notably, APOE ε4 allele carriers were 2.4x more frequent in the higher concentration cohort. **Conclusions:** The longitudinal 148-week data show that patient cohort with the higher concentration of ANAVEX®2-73 maintains the ADCS-ADL score and better perform at MMSE, along the trial duration, when compared to the lower concentration cohort. A significant impact of SIGMAR1 and COMT biomarkers on the drug response level was confirmed over the 148-week period, irrespective of the fact that APOE ε4 carriers were more frequent in the higher concentration cohort. Taken together, these findings are consistent with the hypothesis that ANAVEX®2-73 induces an improved clinical outcome with adequate effect size. Results demonstrate robustness by using both DNA- and RNA-based biomarkers, multiple endpoints and time points. Excluding the patients with the two identified biomarker variants (approximately 20% of the population), the resulting 80% of the enrolled population would lead to further clinically significant improved functional and cognitive scores. The combination of KEM FCA and MMRM-LME data analysis methodologies shows the innovative ability to identify early biomarkers in clinical trials with small size-population recruited. Our data support the clinical development of ANAVEX®2-73 by using genetic biomarkers identified within the study population itself. Indeed, this innovative approach allowed to select pre-specified population (SIGMAR1 and COMT) in forthcoming larger studies, with the expectation to confirm the observed response to ANAVEX®2-73. Further clinical studies in several indications are underway, including a Phase 2b/3 study in 450 patients with early Alzheimer's disease. This approach may expand the access to precision medicine and precision pharmacology for a wide range of neurodegenerative diseases, thus, identifying the right patients that can benefit from the right drug(s), at the right moment. Detailed methodology and results will be presented at the conference.

LB10: PREDICTIVE PERFORMANCE OF CSF AND IMAGING AD BIOMARKERS IN ADNI1/GO/2 MCI PARTICIPANTS USING THE NIA-AA RESEARCH FRAMEWORK. Leslie M Shaw[1], Michal Figurski[1], Susan Landau[2], William Jagust[2], Clifford R Jack[3], Paul S Aisen[4], Ronald C Petersen[3], Michael W Weiner[5], John Q Trojanowski[1] *((1) University of Pennsylvania, Philadelphia, USA; (2) University of California, Berkeley, Berkeley, USA; (3) Mayo Clinic, Rochester, USA; (4) University of Southern California, San Diego, USA; (5) University of California, San Francisco – San Francisco, USA)*

Backgrounds: A key characteristic of Alzheimer's disease is its multifactorial nature. Important developments in this field include the standardization of biomarker measures that detect different aspects of the underlying pathologic processes of the disease. The recently described National Institute on Aging-Alzheimer's Association research framework on Alzheimer's disease provides a systematic approach to defining the state of Alzheimer's pathologic change in patients using a combination of amyloid (A), tau(T) and neurodegeneration (N) biomarkers. **Objectives:** To assess the combination of 3 biomarkers, A-CSF Aβ1-42, T-CSF p-tau181 and N-FDG PET, measured at baseline, for their prediction of progression from MCI to AD dementia and for decline in memory (MMSE), cognition (CDRsob) and function (FAQ). All ADNI1/GO/2 MCI participants who provided CSF and who underwent FDG PET at baseline