Clinical data from 54 subjects from the Phase 1 and the Phase 2a dose adjustment design of the Phase 2a study protocol to-moderate Alzheimer’s disease. ANAVEX-273 demonstrated a muscarinic receptor ligand properties was tested in a Phase 1 study in healthy volunteers and in a Phase 2a study in patients with mild-to-moderate AD. The primary objective of this study was to translate to man is unknown as the effects of plasma on cognitive function have not yet been studied in aged humans or in patients with Alzheimer’s disease subjects. ANAVEX-273 administration does not prolong QTc interval, while ANAVEX19-144 was found to be anti-arrhythmic. A strong relation was observed between ANAVEX-273 apparent dose and MMSE (Mini-Mental State Examination) response. Drug doses in the upper tertile increase the probability of improved MMSE score 2.1-fold (110%) during 57 weeks. Similarly, higher drug doses increase the probability of improved ADCS-ADL (Alzheimer’s Disease Co-operative Study Activities of Daily Living) score 1.6-fold (67%) during the same period. Conclusions: The clinical data from the completed studies enabled a detailed and robust dose-response analysis and the identification of optimal dosing for future studies. The data provides support to further clinical development of ANAVEX-273 and further clinical studies in several indications are planned or underway. A more complete set of results will be available at the time of the conference.

LBP33: CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS CHARACTERIZATION OF ANAVEX™-273 FOR DESIGNING A PHASE 2/3 STUDY IN MILD-TO-MODERATE ALZHEIMER’S DISEASE. Mohammad Afshar1, Frédéric Parmentier1, Ene I Ette2, Emmanuel O Fadiran3, Christopher U Missling1 (1) Ariana Pharma, Paris, France; (2) Anoixis Corp., Natick, MA; (3) Avanex Life Sciences Corp., New York, NY, USA)

Background: ANAVEX-273, a selective sigma-1 agonist with muscarinic receptor ligand properties was tested in a Phase 1 study in healthy volunteers and in a Phase 2a study in patients with mild-to-moderate Alzheimer’s disease. ANAVEX-273 demonstrated a favorable safety profile in both studies. The most common side effects across all AE categories tended to be of mild severity, and were resolved with dose reductions that were anticipated within the adaptive dose adjustment design of the Phase 2a study protocol. Methods: Clinical data from 54 subjects from the Phase 1 and the Phase 2a was analyzed with non-linear mixed effect (NLME) modeling and non-compartmental analysis approach. The QT/QTc data was analyzed according to ICH E14 guidelines. Relationship between dose and response was investigated using non-linear rule based Formal Concept Analysis (FCA, implemented in Ariana’s KEM® software). Results: ANAVEX-273 is metabolized into a pharmacologically active metabolite, ANAVEX19-144. Its pharmacokinetics is linear in the dose range studied and exhibits moderate pharmacokinetics variability. The apparent elimination half-life of the metabolite (21.45 hr) is approximately twice that of the parent drug (10.71 hr). No sex difference in the pharmacokinetics of ANAVEX-273 was observed. The clearance of the drug is not a function of renal function, and younger subjects clear the drug twice as fast as elderly Alzheimer’s disease subjects. ANAVEX-273 administration does not prolong QTc interval, while ANAVEX19-144 was found to be anti-arrhythmic. A strong relation was observed between ANAVEX-273 apparent dose and MMSE (Mini-Mental State Examination) response. Drug doses in the upper tertile increase the probability of improved MMSE score 2.1-fold (110%) during 57 weeks. Similarly, higher drug doses increase the probability of improved ADCS-ADL (Alzheimer’s Disease Co-operative Study Activities of Daily Living) score 1.6-fold (67%) during the same period. Conclusions: The clinical data from the completed studies enabled a detailed and robust dose-response analysis and the identification of optimal dosing for future studies. The data provides support to further clinical development of ANAVEX-273 and further clinical studies in several indications are planned or underway. A more complete set of results will be available at the time of the conference.