ANAVEX®2-73 (*blarcamesine*): Analysis Of Movement (MDS-UPDRS) And Cognitive (CDR System) Pharmacodynamic-Biomarker Outcome Measures of Placebo-Controlled Phase 2 Trial in 132 Parkinson's Disease Dementia Patients

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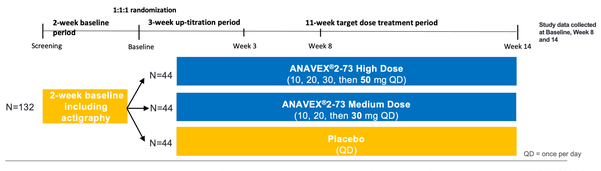
Overview

- ANAVEX®2-73 (*blarcamesine*) is a Sigma-1 receptor (SIGMAR1) agonist and mechanistically focuses on a new target relevant to Parkinson's disease, Alzheimer's disease and other neurological diseases
- SIGMAR1 activation is a compensatory mechanism to chronic CNS diseases
- The direct occupancy of ANAVEX®2-73 at SIGMAR1 has been established previously using quantitative PET scan
- Full genomic analysis of ANAVEX®2-73-PDD-001 Phase 2 study in patients with Parkinson's Disease Dementia (PDD) assessed biomarkers of response exploring potential for a Precision Medicine approach

ANAVEX®2-73 PoC Phase 2 PDD Study Design

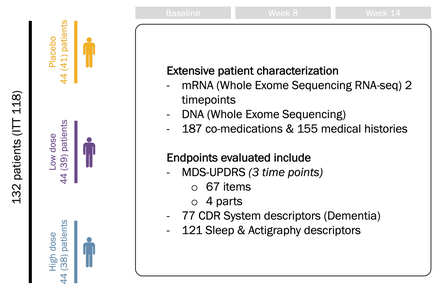
A Phase 2 trial to Assess the Safety, Tolerability and Efficacy of ANAVEX®2-73 (*blarcamesine*) Oral Capsules in the Treatment of Parkinson's Disease Dementia



- **PDD Patient Population**
  - Diagnosis of probable Parkinson's disease dementia
  - Diagnosis of idiopathic Parkinson's disease
  - Patients aged ≥ 50 years
  - MoCA score 13-23
- **Key Primary and Secondary Endpoints**
  - Safety and tolerability
  - CDR Cognitive Domain of Attention
  - Sleep function
  - MDS-UPDRS
  - Actigraphy (24-hour monitoring)
  - Entire DNA and RNA sequencing
- **Pre-specified Endpoints**
  - Genetic variants SIGMAR1 (rs1800866),
  - COMT(rs113895332/rs611432 03) with influence on treatment effect

ANAVEX®2-73-PDD-001 is a Proof of Concept (PoC) Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-arm, 14-week study

Data rich cohort of 132 patients with data collected at 3 different timepoints



ANAVEX®2-73-PDD-001 Phase 2 Baseline Characteristics

ANAVEX2-73-PDD-001 Baseline Demographics and Clinical Characteristics	
Baseline demographics	Overall (n=132)
Male, %	76.5%
Age, mean (years)	74.56
White, %	98.5%
AChEI use, %	47.0%
PDD, %	100.0%
Concomitant PD therapy use, %	99.2%
MDS-UPDRS	**Baseline scores (SD)**
Total score	69.5 (24.6)
Part I	12.5 (5.8)
Part II	16.1 (8.0)
Part III	38.3 (15.2)
Part IV	2.6 (3.3)
Other scores	
MoCA. total	18.2 (3.0)
Modified H&Y	2.3 (0.7)

Movement Disorder Society (MDS) - Unified Parkinson's Disease Rating Scale (UPDRS) Total Score used in clinical trials for assessment of efficacy

MDS-UPDRS Total Score is defined by:

- Part I: Non-motor Experiences of Daily Living
- Part II: Motor Experiences of Daily Living
- Part III: Motor Examination
- Part IV: Motor Complications

Key cognitive domains addressed by ANAVEX®2-73 using CDR System

Addressed in ANAVEX2-73-PDD-001 Phase 2 Study

(a) Episodic memory
(b) Attention
(c) Language
(d) Visuospatial skills
(e) Executive functions

Related CDR System domains

- Episodic memory ✅
- Choice reaction time ✅
- Word recognition ✅
- Picture recognition ✅
- Numeric working memory ✅

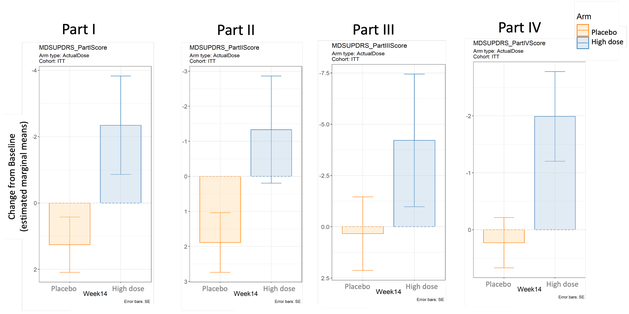
ANAVEX®2-73 improved MDS-UPDRS Total Score in placebo-controlled Parkinson's Disease Dementia Phase 2 study

MDS-UPDRS Total score -14.51 improvement is clinically relevant and corresponds to a relative improvement of 18.9 % over 14 weeks

	Estimated Difference between Active and Placebo: -14.51 points (p = 0.034)
	MDS-UPDRS Total Score
ANAVEX2-73 high dose	-10.98
Placebo	3.53

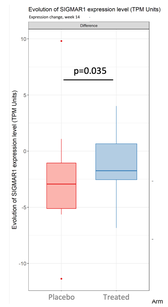
- Randomized, double-blind, placebo-controlled Phase 2 trial that randomized 132 patients with Parkinson's disease dementia equally (ratio of 1:1:1) to target doses of 30mg (medium), 50mg (high) ANAVEX®2-73 or placebo

MDS-UPDRS Score for Parts I through IV show improvement from baseline in patients on high dose compared to placebo



Effects of ANAVEX®2-73 (blarcamesine) treatment. Scores are estimated marginal means from the analysis of mixed-effect models for repeated measures of the change from baseline scores over 14 weeks by Visit and Treatment Group. Error bars are standard errors.

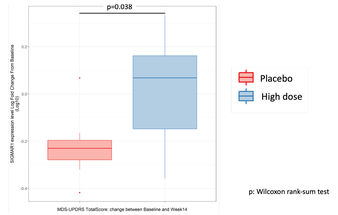
Pharmacodynamic biomarker for patients exposed to ANAVEX®2-73: SIGMAR1 mRNA expression significantly increased in Treated Patients vs Placebo (p=0.035)



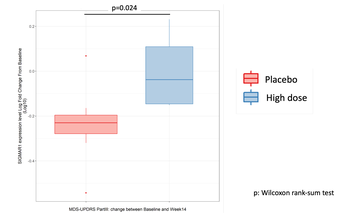
Patients treated with ANAVEX®2-73 demonstrated a higher median difference in mRNA expression of SIGMAR1 compared to patients in the placebo arm

mRNA Integrity Number (RIN) quality threshold ≥ 4.0 *applied to all patient samples*

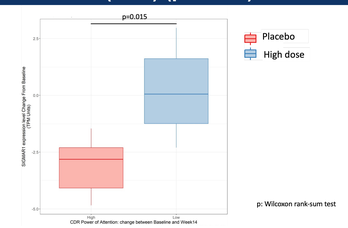
MDS-UPDRS Total Score was significantly associated with an increase in SIGMAR1 expression for treated, improving patients, compared to non treated patients who experienced decline (p=0.038)



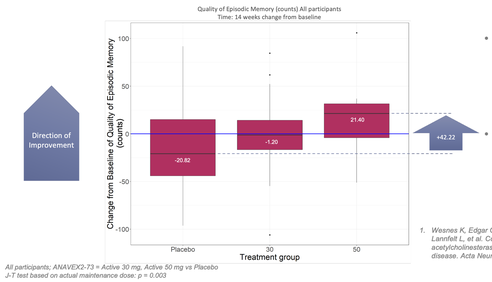
MDS-UPDRS Part III was significantly associated with an increase in SIGMAR1 expression for treated, improving patients, compared to non-treated patients who experienced decline (p=0.024)



SIGMAR1 expression correlated with clinical efficacy as measured by efficacy endpoint, CDR system Power of Attention (PoA) (p=0.015)



Dose-dependent, statistically significant improvement of Quality of Episodic Memory with ANAVEX®2-73



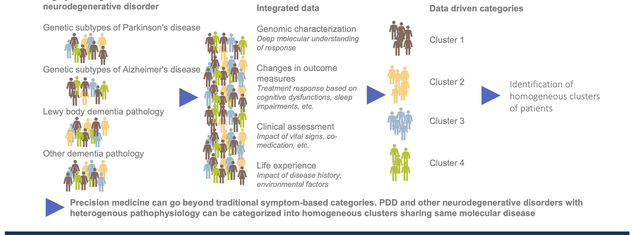
All participants; ANAVEX2-73 = Active 30 mg, Active 50 mg vs Placebo
J-T test based on actual maintenance dose; p = 0.003

- A high score reflects ability to store, hold and retrieve information of an episodic nature (e.g., an event or name)
- CDR system Quality of Episodic Memory highly correlated (70%) with ADAS-Cog (r = 0.7)[1]

1. *Wesnes K, Edgar C, Andreasen N, Annas P, Basun H, Lamfelt L, et al. Computerized cognition assessment during acetylcholinesterase inhibitor treatment in Alzheimer's disease. Acta Neurol Scand 2010; 122:270–7*

Ongoing analysis of DNA and RNA and AI-informed analysis: Application of Artificial Intelligence Methodologies to ANAVEX®2-73-PDD-001 Study

Unbiased, data-driven analysis of the heterogenous PD/PDD patient population using DNA and RNA Whole Exome Genomic Sequencing



Summary

- Randomized, placebo-controlled clinical trial in 132 patients with PDD including prespecified biomarkers of response as well as Whole Exome Sequencing DNA data and full RNA exome expression data collected for all patients during 14-week study
- MDS-UPDRS Total score significantly improved by -14.51 points (p = 0.034) for patients treated with ANAVEX®2-73 high oral dose once daily. This improvement is clinically relevant and corresponds to a relative improvement of 18.9% over 14 weeks
- Balanced and global improvements were observed within all MDS-UPDRS sub-scores Part I-IV:
- MDS-UPDRS Part I: 92.23% items improved (12 items out of 13)
- MDS-UPDRS Part II: 76.92% items improved (10 items out of 13)
- MDS-UPDRS Part III: 88.23% items improved (30 items out of 34)
- MDS-UPDRS Part IV: 71.42% items improved (5 items out of 7)
- SIGMAR1 mRNA expression significantly increased in ANAVEX®2-73 treated patients vs placebo (p = 0.035)
- The increase of SIGMAR1 mRNA expression was significantly associated with the improvement of MDS-UPDRS Total Score (p = 0.038) and MDS-UPDRS Part III (p = 0.024)

Next Steps

- Design and implementation of ANAVEX®2-73 Phase 3 study in Parkinson's Disease with suggested Primary Endpoint MDS-UPDRS Total score
- Design and implementation of ANAVEX®2-73 Phase 3 study in Parkinson's Disease Dementia with suggested Primary Endpoint CDR system