CY6463 administration in healthy participants was associated with improvements in Alzheimer's disease-relevant biomarkers based on a systematic analysis of multiple Phase 1 clinical trials using KEM® eXplainable AI.

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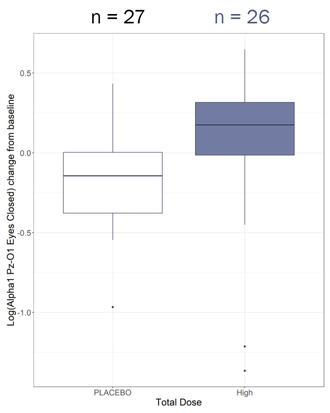
Overview

- CY6463 is a first-in-class, CNS-penetrant, soluble guanylate cyclase (sGC) stimulator that modulates a key node in a fundamental signaling pathway. CY6463 has been evaluated in two Phase 1 studies (NCT03856827, NCT04240158) and is in clinical development for the treatment of CNS diseases including Alzheimer's disease (AD).
- A total of 134 healthy participants were enrolled across 2 randomized, placebo-controlled, Phase 1 studies in which single-ascending doses, multiple-ascending doses, food effect (crossover design), and the pharmacology of CY6463 (crossover design) were evaluated. In each study, safety, pharmacokinetic, and endpoints assessments were collected at baseline and at the end of dosing. Safety assessments included adverse event collection, clinical laboratory values, vital signs, and electrocardiography. Endpoints assessments included electroencephalography (EEG) measures, cognitive performance tests, saccadic eye movement (SEM) evaluations, and cerebrospinal fluid (CSF) biomarkers.
- KEM® (Knowledge Extraction and Management) explainable Artificial Intelligence (xAI) is a tool that systematically extracts and evaluates all associations between all variables in a database. An objective of such an analysis is the identification of potential subgroups with higher chances of treatment response, paving the way to the development of a precision-medicine approach and potentially increasing chances of clinical success.

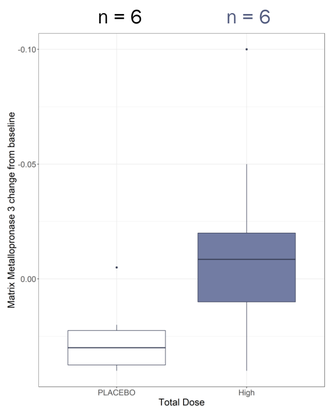
Five endpoints were identified as associated with the treatment at different levels.

AlphaPower was increased in CY6463 treated subjects. [1]



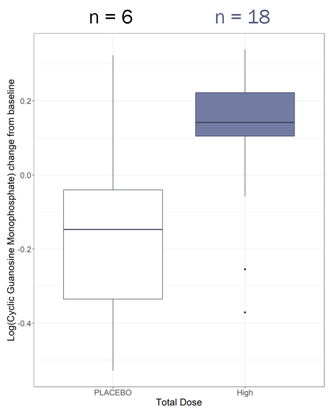
p = 0.003*
d = 0.55

Matrix Metalloproteinase 3 in CSF was decreased in CY6463 treated subjects [2]



p = 0.008*
d = 1.95

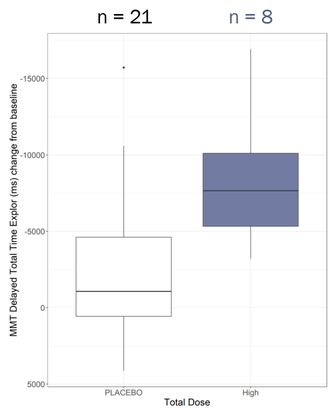
Concentration of cyclic guanosine monophosphate in CSF was increased in CY6463 treated subjects. [3]



p = 0.019*
d = 1.24

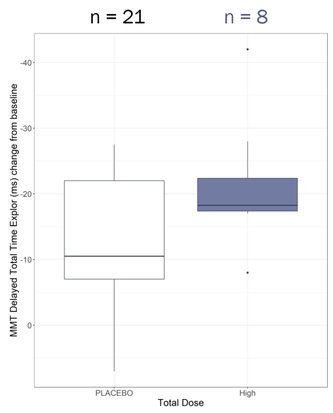
Subjects treated with the highest doses of CY6463 had improved Milner Maze Test results.

Subjects treated with the highest doses are faster



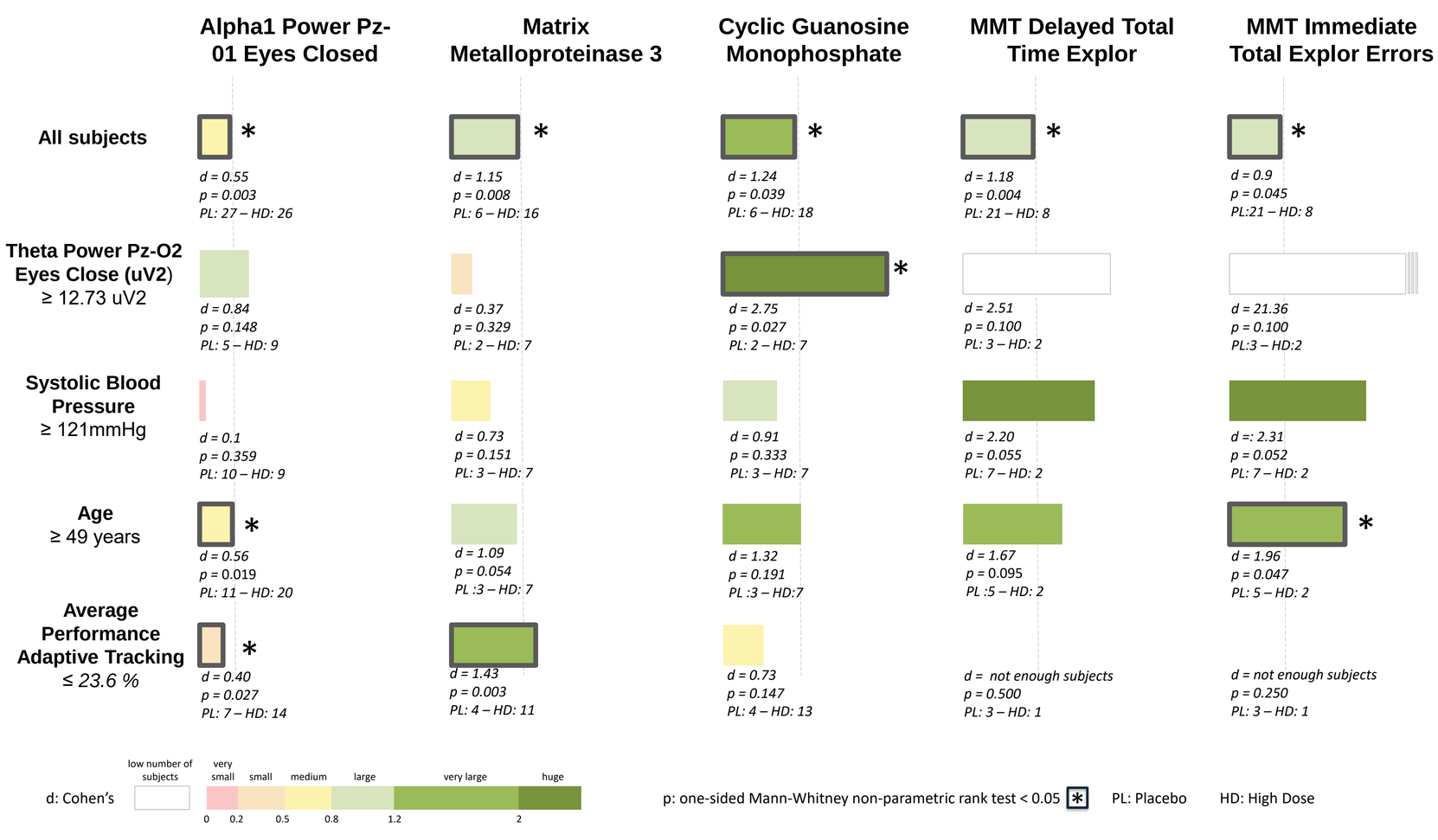
p = 0.004*
d = 1.18

Subjects treated with the highest doses make the less errors



p = 0.045*
d = 0.90

Age, certain neurophysiological measures, and high systolic blood pressure at baseline were identified with an increased response for the endpoints.



Key results

- **Safety**: our analysis showed that headache was the only adverse event associated with CY6463 treatment, with transient headache occurring more often in subjects with high total dose of CY6463. Headaches were generally mild and did not lead to discontinuation. No other associations among safety variables were identified.
- **Endpoints**: our analysis showed that a high total dose of CY6463 was associated with faster speed and better accuracy in the Milner Maze Test (MMT) (nominal p=0.004 for speed and nominal p=0.045 for accuracy). High total dose was also associated with increase in alpha power (Pz-O1) as measured by EEG during eyes closed resting state (nominal p=0.003). Additionally, exposure to CY6463 treatment was associated with a decrease in CSF levels of matrix metalloproteinase 3 (MMP3; nominal p=0.008) and increase in CSF levels of cyclic guanosine monophosphate (cGMP; nominal p=0.019).
- **Baseline age, blood pressure, and certain neurophysiological measures were found to be associated with greater response as measured by relevant endpoints**. Greater CY6463 treatment-associated improvement in MMT (Cohen's d increase by respectively 86% and 157% for respectively the speed and the accuracy) was observed in participants with high baseline systolic blood pressure (≥121mmHg). Similarly, greater CY6463 treatment-associated improvements in MMT were observed in older patients (≥49y). Cohen's d increased by respectively 40% and 120%. Focusing on subjects with higher age also enabled the identification of additional signals such as the decrease in EEG theta power Pz-O2 eyes closed (nominal p = 0.005).

Conclusion

- Results for safety endpoint associations were consistent with the favorable safety profile of CY6463 as reported previously.
- Endpoints: this analysis identified CY6463 treatment-associated positive effects on endpoints that have been linked with AD including theta and alpha power by EEG as well as MMP3 and cGMP levels. The initial demonstration of improvement of these AD-associated endpoints as well as the systematic identification of candidate patient selection criteria may enable the design of next-phase studies with higher probability of success.
- This analysis of Phase 1 data in healthy participants demonstrates the ability of eXplainable AI tools, such as KEM®, to integrate and analyze broad and heterogeneous sources of data from different trials, to provide insight into a drug's mechanism of action, to generate testable hypotheses, and to guide the optimal design of the next steps in clinical development.

Data description

- All data were integrated into a single, consolidated meta-database totaling 134 subjects and 48,300 variables
- Data across the 4 different study designs were integrated into a common data-driven framework with doses and plasma concentrations binned into three different levels – low, medium, and high.

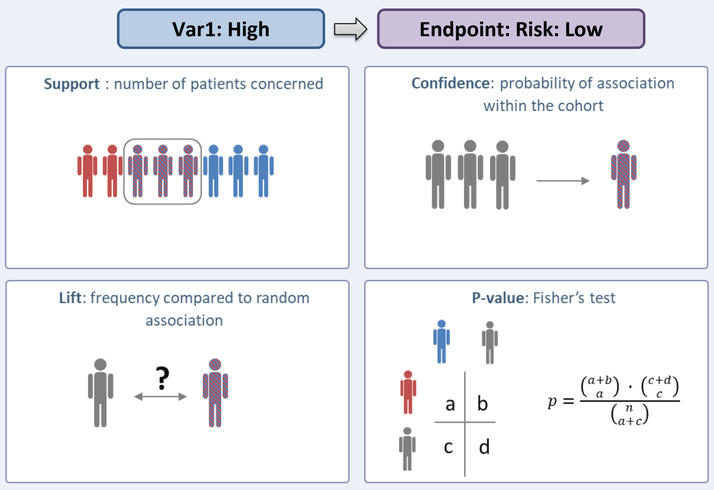
References

1. Gattaz, Wagner F., H. Cramer, and Helmut Beckmann. "Low CSF concentrations of cyclic GMP in schizophrenia." *The British Journal of Psychiatry* 142.3 (1983): 288-291
2. Ordak, M., Libman-Sokolowska, M., Nasierowski, T., Badyra, B., Kaczmarek, L., Muszynska, E., & Bujalska-Zadrozny, M. (2022). Matrix metalloproteinase-3 serum levels in schizophrenic patients. *International journal of psychiatry in clinical practice*, 1–7. Advance online publication.
3. Jelic, Vesna, et al. "Quantitative electroencephalography power and coherence in Alzheimer's disease and mild cognitive impairment." *Dementia and Geriatric Cognitive Disorders* 7.6 (1996): 314-323.

Methods

KEM® Framework

KEM® generates association rules $Var_1 \rightarrow Var_2$, in an exhaustive manner. These rules are characterized by 4 metrics that help rank them.



Does my rules correspond to a frequent event? Or a rare one?
Is the association due to chance? Or statistically significant?

KEM® Clinical Endpoints

KEM® explored the associations between pharmacokinetic and endpoints variables in the meta-database. Filtering the associations using metrics such as Support (number of examples), Confidence (conditional probability), Lift (relative probability) and Fisher's p-value (unadjusted for multiplicity), identified the associations with the greatest support for future hypothesis testing. In total, 1015 theoretical associations between all variables were explored by KEM®, extracting a subset of 20,860,826 associations that were further reduced to a subset of 67 using the filtering metrics.

Biomarker Stratification

KEM® was used to identify biomarkers that stratified the patients within the identified associations.