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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

Clinical trials: results

Biographies (1 for poster/oral communications & 4 for the symposium) / 200 words per bio

Mohammad Afshar is the founder and CEO of Ariana® Pharma, a leading Artificial Intelligence drug development company. Using its KEM® Artificial Intelligence (xAI) technology, Ariana helps its partners introduce personalized medicine clinical trial design into their protocols and optimize clinical endpoints, identify biomarkers of therapeutic response and potential novel indications. Prior to joining Ariana, Mohammad was a founder and the Director of Drug Design at RiboTargets, Cambridge, UK. He set up and managed the structure-based discovery platform which successfully licensed novel therapeutic molecules. Before joining RiboTargets Mohammad held several positions in academic institutions including the Department of Chemistry of the University of York, UK, and the CRBM of the CNRS in France. Mohammad is member of the board of Genomic Vision, an innovative single DNA molecule analysis company. He holds a Medical Degree (DCEM), MPhil in Computer Science (DEA), a PhD in structural biochemistry and a "Habilitation doctorate" (HDR) from the Faculty of Medicine of the University of Montpellier, France

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Abstract:

BACKGROUND:
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 pharmacodynamic assessments were collected at baseline and at the end of dosing. Safety assessments included adverse event collection, clinical laboratory values, vital signs, and electrocardiography. Pharmacodynamic 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.

OBJECTIVES:
The goal of this post hoc analysis was to use KEM xAI to characterize CY6463 impact on a range of endpoints and to identify characteristics of subgroups that had a greater pharmacodynamic response.

METHODS:
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.
The analysis was divided into two steps: first, the impact of CY6463 on all pharmacodynamic outcomes was assessed to identify changes associated with CY6463 treatment; second, subgroups of subjects with a further improved response were characterized.
In the first step, KEM explored the associations between pharmacokinetic and pharmacodynamic 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. In a second step, KEM was used to identify biomarkers that stratified the patients within the identified associations.

RESULTS:
On 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.
On pharmacodynamics, our analysis showed that faster speed and better accuracy in the Milner Maze Test (MMT) was associated with a high total dose of CY6463 (nominal p=0.004 for speed and nominal p=0.045 for accuracy). Increase in alpha power (Pz-O1) as measured by EEG during eyes closed resting state was also associated with high total CY6463 dose (nominal p=0.003). Additionally, 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=0.013) were associated with CY6463 treatment.
In the second step of the analysis, baseline age, blood pressure, and certain neurophysiological measures were found to be associated with greater pharmacodynamic response on some endpoints. For example, greater CY6463 treatment-associated improvement in MMT (Cohen's d increase by respectively 39% and 157% for respectively the speed and the accuracy) was seen in participants with high baseline systolic blood pressure (≥121mmHg). Similarly, greater CY6463 treatment-associated improvements in MMT were seen in those with higher age (≥49y): Cohen's increase by respectively 40% and 120%. Focusing on subjects with higher age also enables 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 previously reported. On pharmacodynamics, this analysis identified CY6463 treatment-associated, positive effects on endpoints that have been linked with AD. For example, AD patients have been described in previous studies as showing increased theta and decreased alpha power by EEG as well as increased MMP3 and decreased cGMP levels. Demonstration of improvement on these AD-associated endpoints as well as identification of candidate patient-selection criteria lay a promising foundation for the design of hypothesis-testing, next-phase studies.
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 optimal design of clinical development next steps.