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NETRAMARK'S AI-BASED TECHNOLOGY IDENTIFIES SIGNIFICANT DRIVERS OF EFFICACY AND PLACEBO RESPONSES AND HAS POTENTIAL TO IMPROVE SUCCESS RATES FOR CLINICAL TRIALS OF PSYCHIATRIC MEDICATIONS

— Results presented in two posters at the International Society for CNS Clinical Trials and Methodology (ISCTM) 20th Annual Meeting demonstrate the potential of NetraAI to enable more efficient clinical development of therapies to treat a variety of mental health disorders —

TORONTO, Feb. 26, 2024 /CNW/ - **NetraMark Holdings Inc. (the "Company" or "NetraMark")** (CSE: AIAI) (OTCQB: AINMF) (Frankfurt: 8TV) a generative AI software leader in clinical trial analytics, announces the presentation of new data demonstrating that the application of its NetraAI clinical solution to data sets of fewer than 400 patients can identify variables that predict efficacy and placebo responses in psychiatric clinical trials with high statistical significance. They also show that application of models based on these variables to independent patient populations correctly predicts efficacy and placebo responses, providing a novel approach to de-risk clinical trials for psychiatric therapies. The data were presented on February 22 at the ISCTM 20th Annual Meeting in Washington DC.

"The presentation and posters presented at ISCTM reveal how the AttractorAI technologies on which NetraAI is based are able to deal with the very complex patient populations found in psychiatric disorders," said Dr. Joseph Geraci, PhD, Founder and Chief Technology Officer of NetraMark. "This approach allows for the generation of insights with the potential to improve the success rates of future trials and, importantly, identify therapies for which efficacy signals are unlikely to be improved and may not warrant continued development in the trial population analyzed. The capabilities of these methods, including the ability to learn from smaller sample sizes, are essential for improving on the 12 percent success rate of clinical trials and enabling the development of novel therapies that can safely and effectively address society's growing mental health crisis."

Poster Presentations

Evaluating drug efficacy: Leveraging machine learning insights from placebo response modeling(Poster #15)

This poster described the results of a study designed to leverage machine learning (ML) algorithms to identify characteristics of drug and placebo response across clinical trials in bipolar disorder, anxiety, and schizophrenia. NetraAI, based on Attractor AI methods, was used to analyze efficacy, demographics, and safety data for predicting placebo responses. Independent variables driving these responses were extracted from initial patient assessments through scales and other variables, while dependent variables were based on trial outcomes. NetraAI has the capability to learn which patients in these trials are explainable and which are unexplainable with the provided variables, and the explainable subsets are used to generate "personas" characterized by 3-12 factors, from which enrichment criteria for a next trial are derived. Applying this approach to the active and placebo arms of the trials distinguishes between drug and placebo effects and identifies the degree of efficacy relative to placebo. Key findings from this study include:

- In a 378-patient bipolar disorder trial in which the study drug did not show separation from placebo, a 115-patient training data set enabled the identification of 71 explainable patients in a placebo response subpopulation. The model was tested on 239 independent participants (i.e., not included in the training data set), and correctly predicted 87% of placebo responders. The model also accurately identified 39/44 drug non-responders.
- Application of NetraAI to a failed, 332-patient Phase 3 anxiety trial identified 8 variables that were drivers of placebo response and 6 variables that were drivers of drug non-response. Importantly, this analysis showed that the drug response was very poor and similar to placebo in all but a small class of patients. Based on these findings, the efficacy of this drug is unlikely to be improved in this patient population.
- Application of NetraAI to a 135-patient Phase 2a schizophrenia trial identified 4 variables driving placebo response and 3 variables driving drug non-response. Use of these variables in determining inclusion/exclusion criteria is expected to greatly improve the statistical significance for future trials of the therapy evaluated in the Phase 2a trial.

Identifying efficacy variables for the use of escitalopram in mild major depression disorder (MDD): Implications for treatment-resistant MDD trials (Poster #24)

This poster described the results of a study designed to determine if NetraAI can identify unique subpopulations in MDD clinical trials with varying responses to escitalopram for the treatment of depression. The study used a 172-patient data set from the exploratory escitalopram arm of a MDD trial. Key findings from this study include:

- NetraAI identified an escitalopram response subpopulation of 110 patients characterized by 7 variables. A model based on these variables and insights gained from the initial analysis showed 94% accuracy for predicting response, non-response, and a no-call subset in cross-validation studies. When the insights weren't included in the model, the cross-validation was only 65% accurate.
- Three of the significant variables form an inclusion/exclusion persona that can be used to enhance the number of escitalopram responders and decrease the number of escitalopram non-responders without excluding a large proportion of patients.
- The same methods used to enrich for escitalopram responders can also be used to mitigate placebo response.

Panel Discussion

Towards precision medicine in CNS disorders: Progress and challenges
In addition to the new results presented in the posters, Dr. Geraci also presented previously reported results demonstrating the power of AttractorAI in a presentation, titled "Biomarker identification for patient enrichment strategies in CNS clinical trials: Alternative approaches and challenges," that underscored NetraAI's ability to discover subpopulations of clinical trial participants for which causal factors for response are present in combination, and to transform insights from these participants into tunable parameters that can be used to improve clinical trial outcomes. This included data from a schizophrenia clinical trial use case showing that NetraAI delivered insights regarding variables driving placebo and drug responses. Notably, while only 30% of the subpopulation identified by these variables was explainable, the application of these variables to a model of a larger trial is predicted to have a substantial impact on statistical significance — a reduction in p-value from 0.04 to 0.0019.

"Traditional ML methods can be effective when they can be trained on large amounts of data and when the objects they are trained to recognize are clearly distinct from one another," added Dr. Geraci. "However, psychiatric patient populations are highly heterogeneous, which leads to ambiguity when data from these populations are labeled for ML training. NetraAI overcomes this limitation because it has the ability to recognize and set aside aspects of the data that it cannot explain. As shown in the schizophrenia use case described in the presentation, models based on variables with high statistical significance in a subset of the total population can be extremely powerful and can drive the significant improvements in p-values that the biopharmaceutical industry needs to improve its clinical trial success rate."

About NetraAI

In contrast with other AI-based methods, NetraAI is uniquely engineered to include focus mechanisms that separate small datasets into explainable and unexplainable subsets. Unexplainable subsets are collections of patients that can lead to suboptimal overfit models and inaccurate insights due to poor correlations with the variables involved. The NetraAI uses the explainable subsets to derive insights and hypotheses (including factors that influence treatment and placebo responses, as well as adverse events) that can significantly increase the chances of a clinical trial success. Other AI methods lack these focus mechanisms and assign every patient to a class, even when this leads to "overfitting" which drowns out critical information that could have been used to improve a trial's chance of success.

About NetraMark

NetraMark is a company focused on being a leader in the development of Generative Artificial Intelligence (Gen AI)/Machine Learning (ML) solutions targeted at the Pharmaceutical industry. Its product offering uses a novel topology-based algorithm that has the ability to parse patient data sets into subsets of people that are strongly related according to several variables simultaneously. This allows NetraMark to use a variety of ML methods, depending on the character and size of the data, to transform the data into powerfully intelligent data that activates traditional AI/ML methods. The result is that NetraMark can work with much smaller datasets and accurately segment diseases into different types, as well as accurately classify patients for sensitivity to drugs and/or efficacy of treatment.

For further details on the Company please see the Company's publicly available documents filed on the System for Electronic Document Analysis and Retrieval (SEDAR).

Forward-Looking Statements

This press release contains "forward-looking information" within the meaning of applicable Canadian securities legislation including statements regarding the potential improvements and success arising from NetraAI and the Company's position to empower pharmaceutical companies, provide them with critical insights and the possible improvement of patient outcomes and operational results, which are based upon NetraMark's current internal expectations, estimates, projections, assumptions and beliefs, and views of future events. Forward-looking information can be identified by the use of forward-looking terminology such as "expect", "likely", "may", "will", "should", "intend", "anticipate", "potential", "proposed", "estimate" and other similar words, including negative and grammatical variations thereof, or statements that certain events or conditions "may", "would" or "will" happen, or by discussions of strategy. Forward-looking information includes estimates, plans, expectations, opinions, forecasts, projections, targets, guidance, or other statements that are not statements of fact. The forward-looking statements are expectations only and are subject to known and unknown risks, uncertainties and other important factors that could cause actual results of the Company or industry results to differ materially from future results, performance or achievements. Any forward-looking information speaks only as of the date on which it is made, and, except as required by law, NetraMark does not undertake any obligation to update or revise any forward-looking information, whether as a result of new information, future events, or otherwise. New factors emerge from time to time, and it is not possible for NetraMark to predict all such factors.

When considering these forward-looking statements, readers should keep in mind the risk factors and other cautionary statements as set out in the materials we file with applicable Canadian securities regulatory authorities on SEDAR at www.sedarplus.ca including our Management's Discussion and Analysis for the year ended September 30, 2023. These risk factors and other factors could cause actual events or results to differ materially from those described in any forward-looking information.

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CNW 08:45e 26-FEB-24