Use of digital biomarkers in a Parkinson's Disease open-label extension study for frequent and objective assessment of treatment response

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Introduction

Given the natural fluctuating course of Parkinson's Disease (PD) and the lack of scalability in traditional clinical measures of PD, measuring treatment response in PD can be challenging.

Objective, frequent, and remote measurement of core PD symptomatology using novel technology can facilitate the evaluation of benefits from new therapeutic interventions.

Here, we describe a study design that utilizes smartphones to calculate visual and auditory biomarkers of PD symptomatology and determine symptom severity in response to treatment.

Methods

Video and audio data collection though smartphone tasks

A brief 3-minute interactive task will be deployed using the AiCure smartphone app. Patients will be asked to participate in the task twice a day on three alternating days of the week for the first 16 weeks of the study.

It includes a naturalistic component, which cues open-ended questions about the patient's daily activities. In doing so, it collects data on spontaneous facial expressivity, movement, and free speech and verbal behavior.

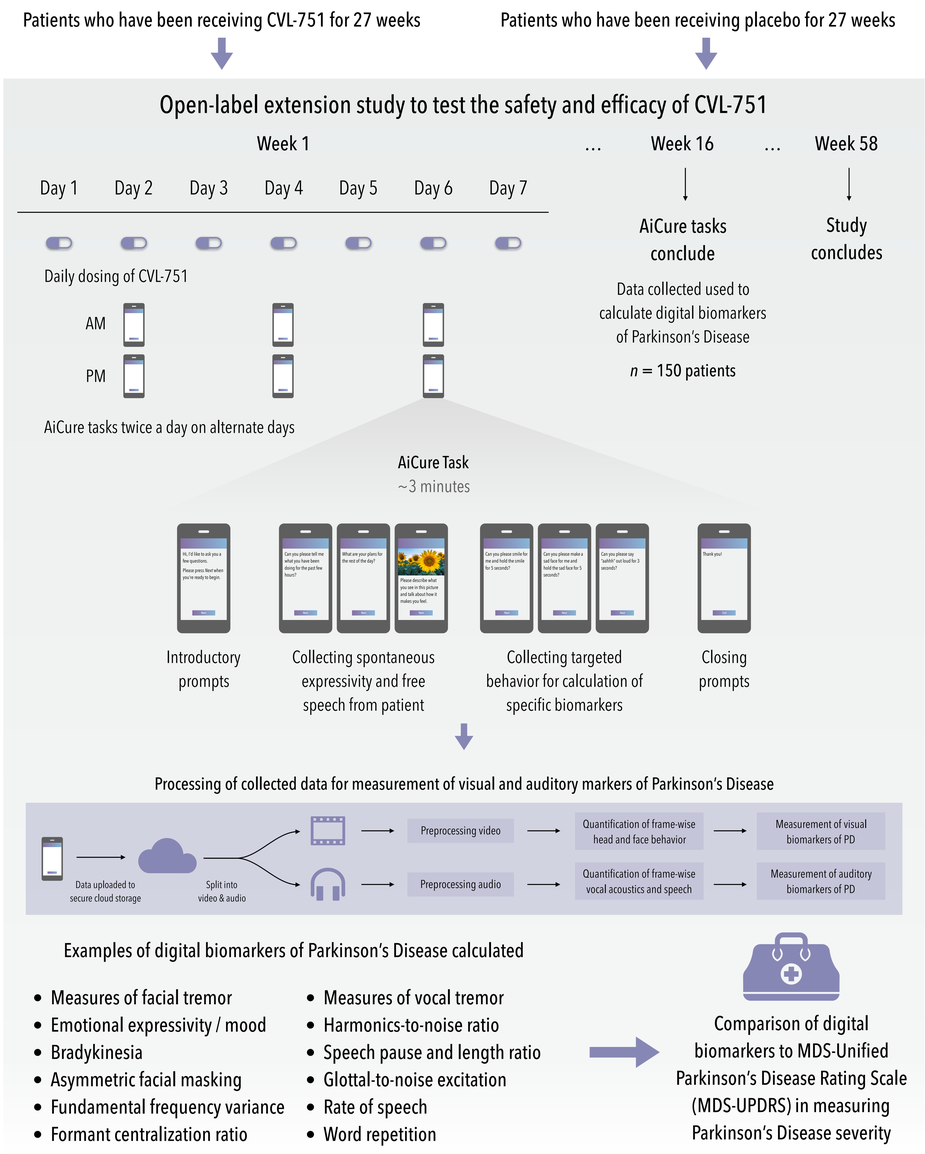
The task also then asks the patients to produce sustained facial expressions and vowel sounds to collect data specifically for the measurement of facial and vocal tremor along with acoustic characteristics of voice indicative of symptom severity.

Calculation of digital biomarkers of Parkinson's Disease

All audio and video collected during participation in the smartphone tasks will be securely processed by AiCure's software backend, which will use data to quantify frame-wise behavioral characteristics that will be used to calculate digital biomarkers of Parkinson's Disease.

Videos collected during patient participation in the interactive tasks will be used to quantify behavioral characteristics such as facial expressivity and movement. These will be used to derive measures of PD symptomatology including facial tremor and facial masking.

Audio collected during patient participation in the interactive tasks will be used to quantify acoustic properties of voice and characteristics of speech. These will be used to derive measures of PD symptomatology including vocal tremor, reduced variance in fundamental frequency, and reduction in pause durations during speech.



Study Design

Two patient populations will be enrolled in a 58-week, open-label extension study to evaluate the long term safety of CVL-751, a novel D1/5 dopamine receptor partial agonist. Patients (n ~ 590) will be male and female with an age range of 40 to 80 years and a diagnosis of Parkinson's Disease.

The first population will be patients who have received treatment with CVL-751 for 27 weeks in one of three Phase 3 trials designed to evaluate the efficacy of CVL-751 as a therapy for PD. These patients will continue receiving treatment at their target doses in this study.

The second population will be patients who have received placebo for 27 weeks in one of the Phase 3 trials described above. They will start receiving treatment with CVL-751 in this study, including an initial 10-week dose titration and adjustment phase to reach target dose levels.

Patients will be eligible to participate in naturalistic tasks through the AiCure app for the collection of video and audio data, which will be used to calculate digital biomarkers of Parkinson's Disease.

Results

Measurement of vocal tremor

A 1D convolutional neural network model for prediction of vocal tremor was trained on a dataset of 50 audio files from 25 healthy volunteers (exhibiting no tremor). Half of the audio files had been induced with a synthesized tremor.

Data from a Phase 2 Essential Tremor study (NCT03101241) was used for testing. It consisted of 446 videos from 204 patients with Essential Tremor aged 18-75 performing The Essential Tremor Rating Assessment Scale (TETRAS) Performance Sub-scale assessment. The videos were accompanied by TETRAS scores rated by clinicians and independent raters reviewing the videos, including a vocal tremor discrete score ranging from 0- 4.

The model, trained using the data from the healthy volunteers and the synthesized tremor audio files, was then tested on the videos from the clinical trial for its ability to predict vocal tremor. **Our preliminary results showed the average tremor probabilities were highly correlated with clinical ratings of vocal tremor severity (r = 0.88).**

Post-study analysis

Change in PD symptom severity over the course of treatment and variation in PD severity within each week measured through digital biomarkers will be compared between the two patient populations using a repeated measures ANOVA.

Biomarkers from each patient will be compared against their MDS-UPDRS scores through a Pearson correlation and the relationship of biomarkers with MDS-UPDRS scores across all patients will be assessed via linear regression analysis.

A composite metric of PD severity will be derived by modeling shared variance between individual biomarkers in a random subset of patients and validated in an independent hold-out dataset using principal components analysis (PCA). The largest derived PCs will be validated by examining the inter-correlation between derived PCs and MDS-UPDRS scores.

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