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Short communication

Wrist-worn sensor-based measurements for drug effect detection with small samples in people with Lewy Body Dementia

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ABSTRACT

Introduction: Few late-stage clinical trials in Parkinson's disease (PD) have produced evidence on the clinical validity of sensor-based digital measurements of daily life activities to detect responses to treatment. The objective of this study was to assess whether digital measures from patients with mild-to-moderate Lewy Body Dementia demonstrate treatment effects during a randomized Phase 2 trial.
Methods: Substudy within a 12-week trial of mevidalen (placebo vs 10, 30, or 75 mg), where 70/344 patients (comparable to the overall population) wore a wrist-worn multi-sensor device.
Results: Treatment effects were statistically significant by conventional clinical assessments (Movement Disorder Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS] sum of Parts I-III and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change [ADCS-CGIC] scores) in the full study cohort at Week 12, but not in the substudy. However, digital measurements detected significant effects in the substudy cohort at week 6, persisting to week 12.
Conclusions: Digital measurements detected treatment effects in a smaller cohort over a shorter period than conventional clinical assessments.
Trial registration: clinicaltrials.gov, NCT03305809

1. Introduction

Studies of neurodegenerative diseases and movement disorders are starting to incorporate digital technologies in clinical research to measure treatment effects and/or disease status or progression [1,2]. Digital technologies represent a scalable approach to objective data collection that could complement traditional clinical assessments, episodic in nature, with more granular, continuous, and sensitive measures. Digital technology could increase research efficiency by generating relevant insights from smaller patient samples and shorter follow up times, reducing the burden of trial participation and accelerating therapeutic progress for patients in need.

We present a substudy from the randomized phase 2 proof-of-concept PRESENCE trial [3], which evaluated the efficacy of mevidalen in patients with Lewy Body dementia (LBD). Mevidalen is a selective positive allosteric modulator of the dopamine D1 receptor subtype that amplifies dopamine response [4]. Unlike D1 agonists, mevidalen is subject to feedback control and less prone to overstimulation. Based on this mechanism and direct observations from preclinical and phase-1 studies, mevidalen is expected to improve cognition, reduce sleepiness and enhance motor function, and these effects onset within hours to 2 weeks after dosing [5]. This substudy investigated the feasibility of incorporating a battery of digital measurements into a clinical trial protocol, the association between digital and clinical measurements, and their ability to detect treatment effects.

2. Methods

2.1. Patients and main study design

As previously reported [3], PRESENCE enrolled patients with mild-to-moderate LBD (see Suppl.). PRESENCE was a randomized

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proof-of-concept phase 2 study to evaluate the effect of mevidalen to improve the Cognitive Drug Research Continuity of Attention (CoA) composite score (primary endpoint), and scores for the Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-cog13), the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) (secondary endpoints). Patients were randomized to receive placebo, 10 mg, 30 mg, or 75 mg daily doses of mevidalen for 12 weeks (Suppl. Figure 1).

This substudy subcohort ('digital measurement population') consisted of patients who consented, received at least one dose of study treatment, wore a smartwatch (the Verily Study Watch) daily (up to 23 h/day from 2 weeks prior to randomization through end of the follow-up period at 14 weeks), and had sufficient data to compute at least one digital measurement (Suppl. Table 2).

All patients provided informed consent to the substudy before initiation. The trial protocol was approved by relevant ethics committees. See information on assessment schedule and wearable device characteristics in the Supplement.

2.2. Substudy variables

The study included 6 candidate digital measurements across 2 domains, sleep and activity (Suppl. Table 2): daily step count (sum per day); daily ambulatory time (minutes, sum per day); total sleep time per night (minutes, TST), total 'rapid eye movement' (REM) sleep minutes per night, total deep sleep minutes per night, and number of awakenings after sleep onset per night (Suppl. Table 2). We specifically focused on digital measurements for sleep and activity domains because of (a) the early efficacy signals mevidalen demonstrated in these domains (sleep and activity), and (b) the capabilities of the Verily Study Watch to generate relevant measurements in those domains at the time of study planning.

2.3. Analyses

Population characteristics were analyzed using descriptive statistics.

To determine the potential association between digital measurements and clinical assessments, we performed a pairwise correlation analysis adjusting for multiplicity using the Benjamini-Hochberg method (controlling false discovery rate [FDR] at level 20%), that included all candidate digital measurements and the 6 clinical assessments included in the main study (Suppl. Tables 1 and 2). Digital measurements with significant correlations to clinical assessments were selected for subsequent treatment-effect analysis, with analysts blinded to treatment allocation.

The primary analysis tested whether digital measurements selected pre-unblinding captured a treatment effect of mevidalen compared with placebo. This was addressed in 2-stages:

Stage 1: To maximize both usage of continuously collected data and statistical power, we used random slope models to test for treatment effect among the pre-selected digital measurements. Time was modeled as a continuous variable (to identify change trends and time-by-treatment interactions); both the patient intercept and slope were modeled as random effects. Baseline values of the given digital measurement, demographic information (age and sex), and baseline levodopa equivalent dose were also included, to take into consideration any potential confounding brought by baseline differences in disease severity, behavior and demographics.

Stage 2: Subsequently, we evaluated the magnitude of the treatment effect detected by digital measurements versus traditional clinical assessments selected a priori using two methods:

1) Random slope models applied to traditional clinical assessments that were key secondary endpoints of the main study, ADAS-Cog Total, Epworth Sleepiness Scale (ESS), MDS-UPDRS composite (I + II + III), and MDS-UPDRS Part III. Treatment effect test results obtained from traditional clinical assessments were compared with those from digital measurements.
2) Mixed models for repeated measures (MMRMs) applied to the digital measurements with the strongest signal from Stage 1. Weekly change from baseline was analyzed by fitting treatment, week, baseline, baseline-by-week interaction, and treatment-by-week interaction as fixed effects, and week as a repeated effect within individual patients' data. Demographic information (age and sex) and baseline levodopa equivalent dose were also included.

Hypothesis testing in the primary analysis for treatment effects was not adjusted for type I error. Analyses were performed using SAS 9.4. Statistical tests were conducted with an alpha level of 0.05. We used daily data in random slope models and weekly average in MMRMs. Missing data were not imputed in the analysis.

3. Results

3.1. Substudy population

Of 344 participants enrolled in PRESENCE, a total of 98 (28.5%) consented to the substudy; of them, 70 had digital measurements evaluable (Suppl. Figure 2). This subpopulation was comparable to the overall population in the main PRESENCE study in age and UPDRS scores (Suppl. Table 3). All had underlying Parkinson's Disease (PD) with dementia or Dementia with Lewy Bodies [3].

3.2. Association between digital measurements and clinical measures

Of the 6 digital measurements and 6 clinical assessments analyzed pairwise, we found statistically significant associations for the following digital measurements: daily step count (with UPDRS 2.12), daily ambulatory time (with UPDRS 2.12), and TST (with UPDRS 1.7); see Suppl. Tables 2 and 4 We used these measurements in subsequent treatment effect analyses

3.3. Treatment effect as detected by digital measurements

For the daily step count (n = 59; 3595 daily and 563 weekly observations), the 75 mg treatment group showed statistically significant differences in change from baseline vs placebo for (P = 0.02 in the random slope model; P = 0.0017 and effect size = 0.640 in MMRM; Fig. 1A; Suppl. Table 5). There was an apparent difference in baseline step counts between the placebo and the 75-mg groups. But 'change from baseline' was modeled with baseline values included as a covariate, therefore the impact of baseline group differences would be minimized in this analysis.

For TST (n = 58; 2324 daily and 456 weekly observations), neither the random slope model nor the MMRM showed statistically significant differences in changes from baseline between treatment groups and placebo (Fig. 1B; Suppl. Table 5).

For the daily ambulatory time (n = 59; 3595 daily observations), the random slope model showed statistically significant differences between the 75 mg and placebo groups in change from baseline (P = 0.0234 in the random slope model; P = 0.0020 and effect size = 0.571 in MMRM; Fig. 1C; Suppl. Table 5).

3.4. Magnitude of the digital measurement signal and comparison with clinical assessments

Using daily step count, we interrogated how early digital measurements detected treatment effects. In the digital measurement population, the MMRM detected statistically significant treatment effects on daily step counts for the 75 mg group at week 6 (P = 0.0313, effect size = 1.052), earlier than the 12-week follow-up specified for clinical

Fig. 1. Treatment effect analyses for the digital measurements. Top tables present the least square mean estimate of pairwise treatment group differences in changes from baseline across week 1–12 from random slope (left) and MMRM (right) models. Bottom graphs plot changes from baseline throughout the time course of the study. **A.** Daily step count. **B.** Total sleep time (minutes). **C.** Ambulatory time (minutes).
(For full detailed results, Suppl. Table 5).
Abbreviations: LS = Least Squares; SE = standard error. In bold, significant results.

measures (Fig. 1A; Suppl. Table 5). In contrast, clinical assessment results within a similar domain (UPDRS Total, UPDRS III, ESS) were not statistically significant in the digital measurement population, even though results for those clinical assessments had been statistically significant in the larger sample of the main study (Fig. 2) [3].

4. Discussion

In this substudy, we detected a statistically significant treatment effect in an interventional trial in patients with LBD via digital measurements. We obtained this result in a smaller sample size and at an earlier time point (by several weeks) than the main study based on traditional clinical assessments. The significant results for key secondary endpoints in the main study [3] provided a unique analytic backdrop: we could test whether digital measures could detect significant treatment effects with sample sizes too small (in the substudy) to generate significant results based on traditional clinical measurements. We also observed statistically significant associations between digital measurements and traditional clinical assessments at each time point from baseline onward and no placebo effect upon visual examination in the digital measurements, a promising finding regarding their objectivity. In addition, we were able to collect wearable-device data, even in a population with reduced cognitive and motor capacity.

Numerous observational studies of digital technology in movement disorders have contributed to the emerging development of biomarkers of disease progression [6]. Multiple technologies capable of monitoring physical symptoms in movement disorders have been evaluated side-to-side with clinical assessments (reviewed in Refs. [7,8]), including wearables such as the Kinesia systems (Great Lakes NeuroTechnologies) [9], those developed by APDM [10], and the stride velocity 95th centile (SV95C) [11], or smartphone-based, such as the Mon4t systems [12]. Furthermore, several interventional clinical studies have incorporated digital markers in their protocols, but to our knowledge, this is one of the first randomized, controlled studies of a therapeutic intervention for a movement disorder that both showed a treatment effect in key secondary endpoints and used digital measurements [13–16].

The observed difference in daily step count changes (75 mg vs placebo) was in the range of 1000 steps on average. While this is comparable to minimal clinically important changes (MCIDs) proposed in other studies in neurodegenerative diseases [17], there is a dearth of published data appropriate for contextualization, and defining 'meaningful change' remains an open question to standardize endpoints based on digital measurements. .

While these results suggest that digital measurements such as ambulatory time and daily steps are *sensitive* to treatment effect, we acknowledge that this study doesn't demonstrate that these changes are *specific* to disease status changes in LBD. However, mobility and walking

Clinical Assessment	n/K	Treatment Arm (*P*-value)	Treatment by Time Interaction (*P*-value)
ADAS- Cog Total (13 items)	61 / 111	0.8802	0.4937
ESS	69 / 193	0.9124	0.7297
UPDRS Total	56 / 99	0.6581	0.6524
UPDRS Part 3 Total	56 / 98	0.4384	0.4956

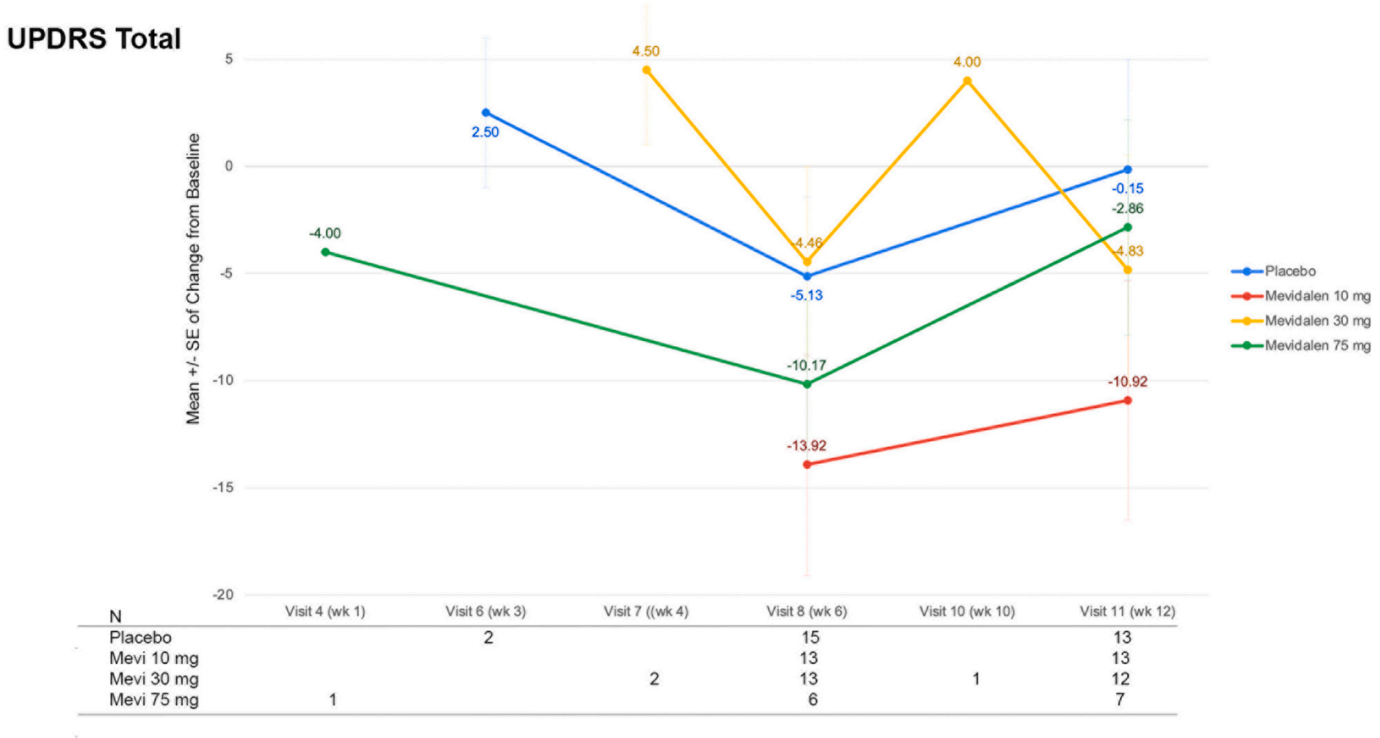

Fig. 2. Analyses, in the digital measurement population, of clinical assessments with statistically significant results in the main study. Top table, results from global treatment effect tests on differences (in changes from baseline) across the 4 treatment groups for the clinical measures listed; lack of significance at the global test level indicated lack of differences among any treatment groups, precluding the conduct of pairwise tests. The bottom graph presents a detailed view of one such analysis for UPDRS Total, as example (additional example for UPDRS III, see Suppl. Fig. 3).
Abbreviations: ADAS-cog13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; ESS = Epworth Sleepiness Scale; UPDRS=Unified Parkinson's Disease Rating Scale.

ability are meaningful aspects of a person's general health, specifically for people with neurological or chronic conditions. Furthermore, absence of mobility (i.e., sedentary state) has been associated with negative health outcomes [18,19], including reduced cognitive function [20]. Therefore, it is reasonable to consider that these measures do not need to be LBD-specific for improvements to be clinically meaningful in this disease. Conversely, while this substudy anchored to the population of interest to investigate a drug intervention (within a main phase II trial for mevidalen in LBD), further efforts are ongoing to understand the interrelation between meaningful aspects of health and the clinical relevance of physical activity across therapeutic areas, parkinsonism and others, and could include more encompassing metrics such as timed pre-defined activity tasks (for instance walking a given distance).

Ours may be one of the few studies where a positive treatment effect demonstrated via clinical assessments was confirmed by digital measurements from a smaller sub-cohort (70 out of 344 patients), where the signal based on traditional clinical assessments was lost. These results indicate that digital measurements can deliver on the premises for their development, which include detecting missed efficacy signals and making clinical trials less burdensome and more efficient. The observed associations with traditional clinical assessments support the use of digital measurements as basis for potential surrogate endpoints, though frameworks for evidentiary criteria required by regulators are still being established.

In sum, we found that digital measurements could detect treatment responses with a substantially reduced sample size and several weeks earlier than required when using traditional clinical assessments. We believe that digital measurements can contribute to efficiency gains in clinical trials, thus facilitating the development of much needed therapies for neurodegenerative diseases.

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EliLilly and Company

Role of the sponsor

EliLilly and Company is the funding source for this study. EliLilly and Company and Verily Life Sciences were responsible for data collection. Authors were fully responsible for the data analysis and interpretation presented herein and for the writing of this article. The following individuals: CB, JW, had access to the raw data. Authors had access to the full dataset for the study, reviewed and approved the final manuscript for submission.

Authors' disclosures concerning this research

CC, NRK, ER, MB, WJM and RK report employment and equity ownership in Verily Life Sciences.

LM, CB, JW, KB report full-time employment and minor stock ownership at Eli Lilly and Company

Authors' contributions

Study concept and design: WJM, RK, KB
Data collection: Verily Life Sciences, Eli Lilly and Company
Data analysis and interpretation: WJM, RK, KB, LMM, CC, NRK
Draft writing and review: All
Draft approval for submission: All

Data sharing statement

Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105355.

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