

Sensitivity of Digital Clinical Biomarker Endpoints to Detect Disease Progression during the 8-week Pretreatment Run-In Period in Proof-of-Concept ALS Study VGCS-50635-002

Authors: Diego Cadavid¹, Dina Katabi², Ines Hoffmann¹, Payal Nanavati¹, Anil Tarachandani¹, Irene Choi¹, Robert H. Scannevin¹, Ashwin Swami¹, Joanna Haas¹, Martin Schmidt¹, William Tracewell¹, Paula Sandler¹, Brian Shook¹, Shane Raines³, Rumen Hristov², Pranav Krishna², Rachel Levy², Hariharan Rahul², Shichao Yue², Hardik Kothare⁴, Michael Neumann⁴, Meredith Bartlett⁴, Vikram Ramanarayanan⁴, Philip Van Damme⁵, Pentti Tienari⁶, Eino Solje⁷, Manu Jokela⁸, Angela Genge⁹, Colleen O'Connell¹⁰, Ruben van Eijk^{11,12}, Leonard van den Berg^{11,12}

Affiliations: ¹ Verge Genomics South San Francisco, CA, USA; ² Emerald Innovations, Cambridge, MA, USA; ³ 2b Analytics, Wallingford, PA, USA; ⁴ Modality,AI, San Francisco, CA, USA; ⁵ Universitar Ziekenhuis Leuven, Leuven, BE; ⁶ Helsinki University Hospital, Helsinki, FI; ⁷ University of Eastern Finland, Brain Research Unit, Kuopio, FI; ⁸ Turku University Hospital, Turku, FI; ⁹ The Neuro – Montreal Neurological Institute Hospital, Montreal, CA; ¹⁰ Stan Cassidy Centre for Rehabilitation (Horizon NB), Fredericton, CA; ¹¹ Utrecht University medical Center, Utrecht, NL; ¹² TRICALS, Utrecht, NL.

Background



- The ALS-FRS-R is the primary efficacy endpoint for proof of concept and registrational ALS trials.
- It is challenging to perform early efficacy (Proof of Concept) and dose ranging studies in ALS with the ALS-FRS-R as large sample size and long study duration is needed.
- Digital clinical biomarkers could provide a better option for Proof of Concept, dose-ranging studies than the ALS-FRS-R due to better precision, lower variability, and better measurement properties.
- However, there has been minimal use of digital clinical biomarkers in therapeutic ALS drug trials to this day.
- The Proof of Concept, Dose-Ranging Study of the PIKfyve small molecule inhibitor VRG50635 is testing several digital clinical biomarker endpoints to study whether

Study Design



Phase 1b, open-label, within-participant multiple ascending dose escalation, multicenter study of VRG50635 in participants with sALS and fALS



Change during the Part 1 Run-In period with the traditional ALS endpoints:

- ALS Functional Rating Scale-Revised (ALS-FRS-R) total score mean [SD] (N=50): 37.4 [4.0] at Week 0 and 35.6 [5.5] at Week 8 (p<0.001)
- Slow vital capacity (SVC) percent predicted mean [SD] (N=50); 86.7% [14.3] at Week 0 and 82.2% [14.2] at Week 8 (p=0.001)

Plasma neurofilament light (NfL) median [range] (N=20): 75 [18-160] at Week 0 and 70 [20-102] ng/mL at Week 8 (n<0.001) A critical need exists for novel ALS clinical endpoints to measure disease progression over shorter periods of time

Clinical Digital Biomarkers for the ALS POC Study



Mobility (Home)



Touchless sensors: EMERALD

- Gait, movement in bed, sleep and respiration at home
- Minimal patient burden

Liu, et al., *Sci Transl Med*. 2022;14(663). DOI: 10.1126/scitranslmed.adc9669

Activity & Mobility



- Accelerometry: ACTIGRAPH Key metrics: Gait, activity, upper and lower extremities
- ALS datasets available
- Some patient burden Van Unnik, et al. *eBioMedicine*. 2024;103:105104. DOI:

1016/j.ebiom..2024.105104

Speech

Speaking: MODALITY.AI Key metrics: Speaking duration,

toy motiloo. opouning up

Speaking rate

Recognized as sensitive to

change in bulbar onset ALS

- Low patient burden
- ALS data available

Neumann, et al. *Comput Biol Med*. 2024; 180:108949. DOI: 10.1016/j.combiomed.2024.108949

EMERALD Touchless Sensors: State of the Art technologies to measure mobility 24/7 while at home



Al-powered Touchless Digital Home Devices

Dramatically increase power to detect changes in diseases of movement



Digital devices placed in each study participant's home capture thousands of 24/7 measurements of mobility, sleep, and breathing to precisely and sensitively detect changes over

EMERALD: Gait speed and turns in bed decrease over 8 weeks of continuously monitoring at home





Green Box shows the 25-75 percentile range; solid black line shows the mean across all included participants; dotted red line shows 0.

- **Gait speed** is measured for ALS participants who are ambulatory. Metric is measured across walking intervals that are determined to be of sufficient length and straightness. Results are reported in meters/second for such walking intervals.
- **Turns in Bed** are measured for participants who do not sleep with pets in bed. Metric is measured during the sleep opportunity period and normalized by the duration of the sleep opportunity period.

Emerald metrics of mobility, sleep and respiration sensitively track disease progression in ALS over 8 weeks.

EMERALD: Sleep decreases and breathing variability increase with ALS progression over 8 weeks





Green Box shows the 25-75 percentile range; solid black line shows the mean across all included participants; dotted red line shows 0.

- Sleep Efficiency is computed as the ratio of the time spent sleeping (i.e. in light, deep, and REM sleep) to the duration of the total sleep opportunity period.
- Wake After Sleep Onset (WASO) is computed as the time in minutes spent in the awake stage during the period between falling asleep and waking up for the last time at the end of the sleep opportunity period.
- **Breathing Variability** is computed as the mean change per night in breathing rate (measured in breaths/minute) between successive 5 second intervals.

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Emerald metrics of mobility, sleep, and respiration sensitively track disease progression in ALS over 8 weeks.

EMERALD: Gait speed and turns in bed correlate with ALSFRS-R total score





Each point represents one participant in the pre-treatment period; shaded blue region shows the 95% confidence interval for the regression line.

Emerald metrics show moderate-to-high correlation with the ALSFRS-R total score

EMERALD: A composite of Gait speed and turns in bed predicts the ALSFRS-R total score





Predicted ALSFRS = 36.54 + 2.31 x Z-Score (Turns In Bed) + 0.85 x Z-Score (Gait Speed) Each point represents one participant in the pre-treatment period; Z-Score of Turns In Bed and Gait Speed are computed and regressed against the ALSFRS-R; shaded blue region shows the 95% confidence interval for the regression line.

Composite metric from linear combination of turns in bed and gait speed shows high correlation with the ALSFRS-R score

ACTIGRAPH: Iotal steps decrease in ALS over 4 weeks







Average steps for individuals = 5000^a P-value for paired t-test for change in total number of steps on week 2 versus week 6 = 0.0186 ^aAlthoff, et al. *Nature*. 2017 Jul 10;547(7663):336-339. DOI: 10.1038/nature23018 Week

Change

ACTIGRAPH: Moderate to vigorous activity (MVPA) decreases with disease progression over 4 weeks





P-value for paired t-test for change in MVPA on week 2 versus week 6 = 0.0225 Abbreviations: MVPA, minutes per day spent in moderate to vigorous physical activity

MODALITY.AI: Single breath capacity is reduced in bulbar-affected ALS participants over 8 weeks





Sustained Phonation Duration

- Total duration between start and end of phonation of sustained vowel /i/ on a single breath
- Growth curve models track disease progress and accounts for individual variability
- Measures single breath capacity
- Normative mean values (English language): healthy controls, 22.08 +/- 5.56^a; all patients, 17.8 +/- 8.6^b

^aMaslan, et al. *J Voice*. 2011 Mar 25;25(6):709-713. DOI: 10.1016/j.voice.2010.10.002. ^bGray, et al. J Speech Lang Hear Res. 2023 Mar 6;66(4):1165-1172. DOI:

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MODALITY.AI: Bulbar-affected participants take longer to read a passage over 8 weeks as ALS progresses



Reading Passage speaking duration (s): Baseline Values and Changes by Disease



Speaking Duration

- Indicator of motor and respiratory function
- Measures how long a participant takes to read a passage
- Normative mean values (English language): healthy controls, 32.07 +/- 4.78; all patients, 42.52 +/- 18.09, non-bulbar patients, 39.6 +/- 16.87; bulbar patients, 57.02 +/- 16.94

Conclusions and summary



- The Phase 1b proof-of-concept study of VRG50635 for the treatment of sporadic and familial forms of ALS in underway
- Various Digital Clinical Endpoints for measuring short term functional decline were evaluated during the 8-week pre-treatment period

EMERALD Touchless Sensors

- Gait speed, turns in bed, sleep efficiency, and breathing variability showed significant deterioration over 8 weeks.
- EMERALD metrics of mobility significantly correlate with ASLFRS-R on cross-sectional evaluation (convergent validity)

ACTIGRAPH

· Total step count and MVPA significantly declined over four weeks in ALS participants.

MODALITY.AI

· Sustained phonation duration and reading speed decrease in ALS participants with bulbar involvement.

Summary

- This ALS PoC Study was designed to use each participant as their own control.
- · Here we present the results of change over the 8-week pre-treatment period.
- Several digital clinical biomarkers tested detected statistically significant functional decline in ALS over 8-weeks despite a modest sample size
- · Continuous monitoring through touchless sensors at home markedly decrease evaluation burden and increase data collection
- Efficacy Results of VRG50635's proof of concept study in ALS comparing the treatment and pre-treatment periods are anticipated for Q3 this year.

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