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

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BACKGROUND

Advancing ALS Trial Design Through Novel Clinical Endpoints

- ALSFRS-R, the traditional primary endpoint in proof-of-concept and registrational ALS trials, requires large sample sizes and long study durations and lacks good measurement properties.
- Digital clinical biomarkers
  - » offer greater precision and sensitivity
  - » can perform more frequent measurements
  - » likely have lower variability
  - » yield improved measurement properties
  - » are better suited for early-phase, dose-ranging, proof of concept studies
- Despite their promise, digital clinical biomarkers have seen limited use in ALS therapeutic clinical trials.

Proof-of-Concept ALS Study VGCS-50635-002

- CONVERGE® AI, Verge Genomics' proprietary artificial intelligence-driven drug target discovery platform, identified the phosphoinositide kinase, FYVE-type zinc finger (PIKfyve) protein complex as a potential target for ALS.
- The PIKfyve protein complex is crucial for regulation of endolysosomal function, exocytosis, and autophagy, processes disrupted in ALS.
- VRG50635 is an orally bioavailable small molecule prodrug that rapidly hydrolyzes to form the active PIKfyve inhibitor small molecule metabolite VRG50468, which efficiently crosses the blood-brain barrier and may correct the endolysosomal dysfunction underlying ALS pathogenesis.

Proof-of-Concept ALS Study VGCS-50635-002 implemented various novel and established digital clinical biomarkers to assess initial efficacy by measuring changes in mobility, sleep and breathing including at home 24/7 with the Emerald touchless sensors, at home or ambulatory with accelerometers, and every 2 weeks by speech biomarkers and slow vital capacity measurements.

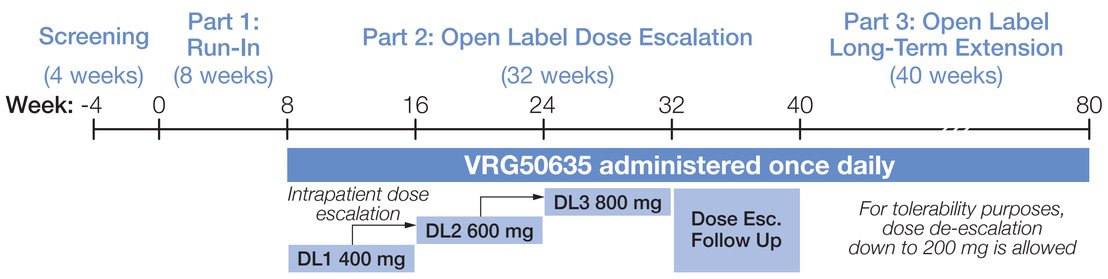
Objective: Evaluate the sensitivity of digital clinical endpoints for measuring short-term functional decline during the 8-week pre-treatment period.

METHODS

Study VGCS-50635-002 Is Testing VRG50635 as a Potential Disease Modifying Treatment for Sporadic and Familial ALS

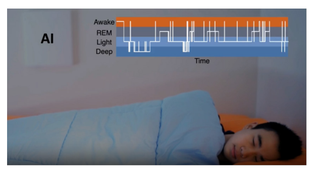
- The study design is an international single arm, open label, within-patient dose escalation with 3 parts: Part 1 is an 8 wk pre-treatment run in period, Part 2 is a 32 week, within patient up to 3-dose level dose escalation design, and Part 3 is an up to 40 wk treatment extension at the highest tolerated dose level.
- The study began in December 2023, fully enrolled by August 2024, completed dose escalation in March 2025, and is on track for Go/No decision in Q3 2025 after the last enrolled participant completes Part 2 in May 2025.
- 54 ALS participants were enrolled, 52 participated in an 8-week pre-treatment run in period (Part 1), and 50 continued into a within participant, 32-week dose escalation period (Part 2).
- Last participant was up-titrated on 10 March 2025.

Study Design



Assessments

Emerald Touchless Sensor[1]



- At-home, passive 24/7 monitoring of (no wearables needed):
  - » Gait measured across walking intervals (m/sec) in ambulatory participants
  - » Turns in bed during the sleep opportunity period and normalized by the duration of the period
  - » Sleep efficiency computed as the ratio of time spent sleeping to duration of the sleep opportunity period
  - » Wake after sleep onset calculated as time (min) awake between falling asleep and waking for the last time during the sleep opportunity period
  - » Breathing variability reported as mean change per night in breathing rate between successive 5-second intervals
- Minimal participant burden

ActiGraph Accelerometer[2]

ActiGraph LEAP® multisensory wearable device

- Measurement of gait and activity of upper and lower extremities through accelerometry
- ALS datasets are available
- Mild participant burden

Modality.AI System[3]

Modality.AI conversational artificial intelligence system

- Measures single breath capacity as sustained phonation duration between the start and end of sustained vowel /i/ on a single breath
- Estimates speaking motor and respiratory function as the length of time it takes to read a passage
- Recognized as sensitive to functional changes in bulbar onset ALS
- Low participant burden

RESULTS

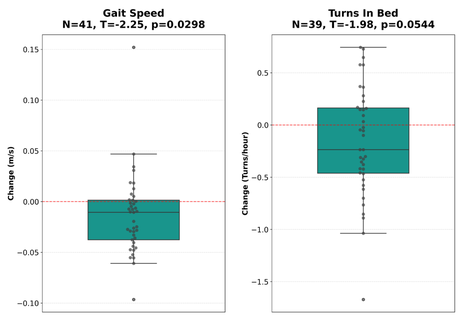
Change in Traditional Endpoints Over 8 Weeks

- Slow Vital Capacity, mean (standard deviation [SD]), N=39, p = 0.001
  - » 3.7 L (1 L) at Week 0
  - » 3.5 L (1 L) at Week 8
- ALSFRS-R, mean (SD), N=31, p < 0.001
  - » 37.5 (3.3) at Week 0
  - » 35.9 (5) at Week 8
- Plasma Neurofilament Light (NfL), mean (SD), N=29, p < 0.001
  - » 76.2 pg/mL (37.17 pg/mL) at Week 0
  - » 92.4 pg/mL (51.93 pg/mL) at Week 8

Emerald Touchless Sensors Measurements Over 8 Weeks of Continuous Monitoring at Home

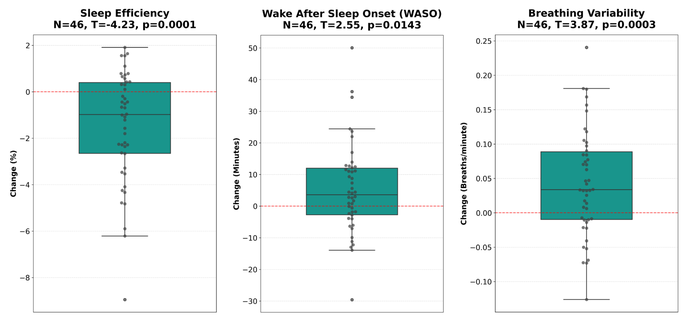
- Gait speed significantly decreased
- Turns in bed were reduced

Quantification of gait speed (left) and turns in bed (right). Green box shows the interquartile range. Solid black line shows the mean across all included participants. Dotted red line shows 0.



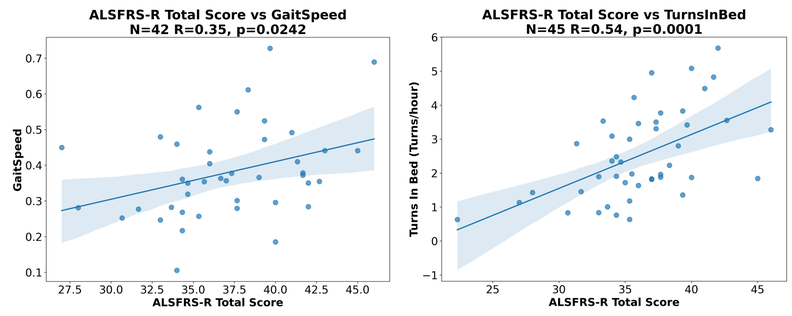
- Sleep efficiency significantly declined
- Wake after sleep onset significantly increased
- Breathing variability significantly increased

Quantification of sleep (left panels) and breathing parameters (right panel). Green box shows the interquartile range. Solid black line shows the mean across all included participants. Dotted red line shows 0.



- Gait speed and turns in bed correlated with ALSFRS-R total scores

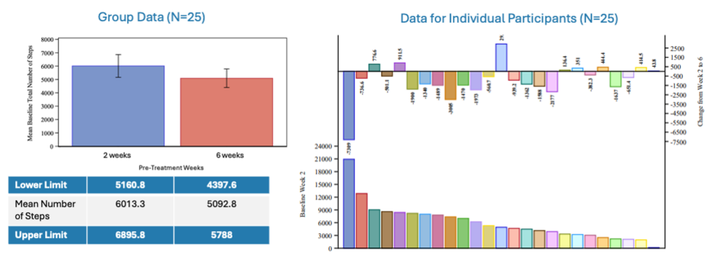
Quantification of gait speed (left) and turns in bed (right) relative to ALSFRS-R total score. There were N=45 participants evaluated for turns in bed, as shown in the figure. Shaded blue region show the 95% confidence interval for the regression line.



ActiGraph Wearable Devices Measurements Over 4 Weeks

- Total steps decreased significantly from Week 2 to Week 6

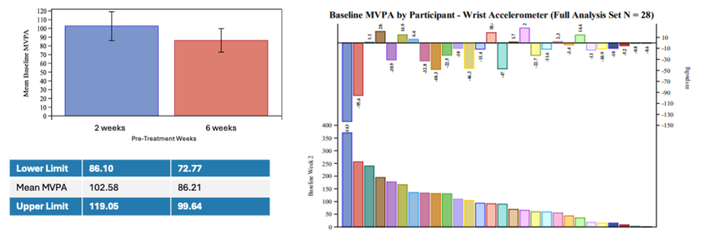
Total steps between pre-treatment Weeks 2 and 6. Average steps for healthy individuals = 5000.[4] Left: mean total number of steps at baseline. Bars represent SEM. N=25, paired t-test for changes in total number of steps at Week 6 compared to Week 2 (baseline), p=0.0186. Right: Change in total number of steps on Week 6 compared to Week 2 (top) and baseline MVPA (bottom) by participant (N=28).



Lower Limit	5160.8	4397.6
Mean Number of Steps	6013.3	5092.8
Upper Limit	6895.8	5788

- Moderate to Vigorous Physical Activity (MVPA) declined over 4 weeks

Moderate to vigorous physical activity between pretreatment Weeks 2 and 6. Left: mean baseline MVPA. Bars represent SEM. Paired t-test for change in mean MPVA at Week 6 compared to Week 2, p=0.0225. Right: Change in MVPA at Week 6 (top) and baseline MVPA (bottom) by participant (N=28).

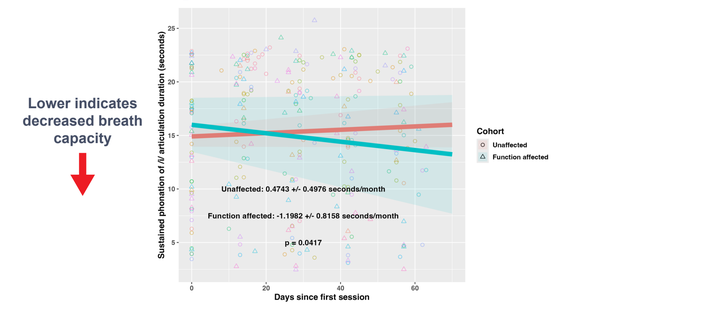


Lower Limit	86.10	72.77
Mean MVPA	102.58	86.21
Upper Limit	119.05	99.64

Modality.AI Voice Analysis

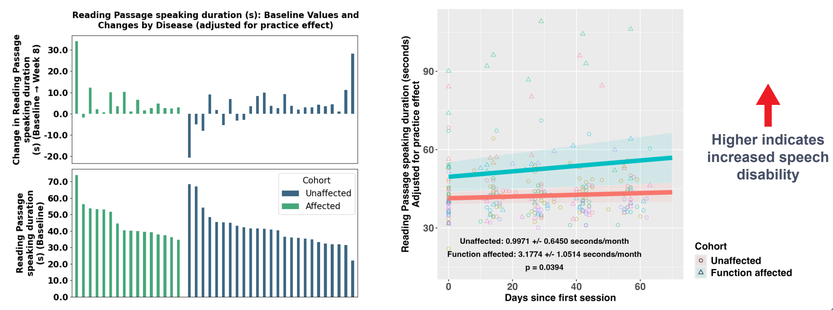
- Single Breath Capacity: Decreased (sustained phonation duration lower in bulbar-affected participants)

Single breath capacity. Red line, unaffected participants (N=31); green line, bulbar function affected (N=19). p = 0.0417.



- Speaking Duration in Bulbar-Affected Participants: Increased (longer time to read passages)

Speaking duration. Left: baseline reading passage speaking duration and change at 8 weeks compared to baseline by participant. Blue, unaffected (N=25); green, bulbar function affected (N=16). Right: Reading passage speaking duration over 8 weeks. Red line, unaffected participants; green line, bulbar function affected. p = 0.0394.



CONCLUSIONS

- All biomarkers detected change in either the total study population or targeted subgroups.
- Touchless, home-based continuous monitoring improves sensitivity while potentially decreasing participant burden.
- Digital clinical endpoints demonstrated sensitivity to detect short-term functional decline in ALS.
- These endpoints could serve as effective alternatives to traditional measures for early-phase ALS trials.
- The within patient study design potentially improves the power to detect changes, even with the traditional endpoints.
- Efficacy results for VRG50635 are anticipated in Q3 this year.

References: 1) Liu, et al., *Sci Transl Med*. 2022;14(663). DOI: 10.1126/scitranslmed.adc9669 2) Van Unnik, et al. *eBioMedicine*. 2024;103:105104. DOI: 1016/j.ebiom.2024.105104. 3) Neumann, et al. *Comput Biol Med*. 2024; 180:108949. DOI: 10.1016/j.combiomed.2024.108949. 4) Althoff, et al. *Nature*. 2017 Jul 10;547(7663):336-339. DOI: 10.1038/nature23018.

Acknowledgements: We thank all the people with ALS who participated in this study, and acknowledge the support of our clinical CRO, Julius Clinical. Medical writing, editorial assistance, and poster production support were provided by Acumen Medical Communications, funded by Verge Genomics.

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