**SUPPLEMENTARY MATERIAL**

# Video-based kinematic analysis of movement quality in a phase 3 clinical trial of troriluzole in adults with spinocerebellar ataxia: a post-hoc analysis

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## Methods

Video-based kinematic assessment

Study center personnel designated as video operators were provided with written instructions on camcorder and tripod setup, camcorder operations, positioning the camcorder in the examination room, video recording of the f-SARA exam, and transferring the videos to a central database. Camcorders (Hero 5 Black, GoPro Inc., San Mateo, CA, USA) were pre-programmed with the proper settings; in the event settings needed to be changed, relevant instructions were provided. To verify patient confidentiality and property security, designated video operators were responsible for storing camcorders in a locked location when not in use. To ensure consistency in the gait orientation relative to video cameras, video operators stationed cameras directly in front of participants, and the video-based metrics were evaluated up until the point where participants performed the half-turn.

For the post-hoc analysis, investigators were given access to anonymized structured datasets and the recorded videos of participants, which were processed on a secure server that was compliant with Health Insurance Portability and Accountability Act guidelines and accessible only by authorized users.

*Video pre-processing*

Videos included files of variable duration, including recordings of the standardized assessment of gait for natural and tandem walk, as required for the f-SARA rating. These files were reviewed by 2 independent reviewers and pre-processed to create 2 shorter video clips of gait corresponding to the natural and tandem walk tasks. The videos were manually cropped along

the horizontal (x) axis (width) to ensure anonymity of the participants. The participant was centralized in the frame by adding an equal number of black pixels to the left and right margins of each frame to ensure that the height dimensions of each frame matched its width. Following this step, the spatial resolution of each frame was set to 800 x 800 pixels, and the temporal resolution was set to 5 frames per second.

*Automated pose extraction*

Pose estimation and extraction were performed in all processed videos using a deep neural network architecture and multi-stage classifier specifically trained for human pose estimation (OpenPose) [35]. The first layers of this very deep convolutional neural network architecture (VGGNet) [40] created feature maps. They were followed by a 2-branch multi-stage convolutional neural network, wherein the first branch predicted confidence maps of the possible locations of each body part in the image (i.e., left foot, right foot), and the second branch predicted 2-dimensional vector fields of part affinities, encoding the association between parts. Detected body parts and affinities were parsed by greedy inference to produce the final key points on the image. The process was repeated for each frame with the coordinates of body parts and related associations written into new frames, which were compiled to generate clips of identical length and dimensions. The model output included 15 discrete body part points: head, neck, right shoulder, right elbow, right wrist, left shoulder, left elbow, left wrist, right hip, right knee, right ankle, left hip, left knee, left ankle, chest, background. It was trained against the MPII Human Pose dataset [36, 37].

*Kinematic feature definition*

For each sequential frame in the video of interest, the (height, width) coordinates of key body parts (e.g., right foot, left foot, chest) were extracted to enable the temporospatial tracking of the movement of key body parts and assessment of the relationship between them. To account for the variable distance of each participant from the camera during gait tasks, the distance was indexed to a surrogate of the patient's height, defined as the pixel distance along the y/vertical axis (height) between the average of the right and left foot coordinates and a reference point (i.e., the center of chest). The base support index was tracked for each frame, with higher values and greater variation/dispersion (spreading out of values) during a tandem walk attempt corresponding to a less balanced gait.

$$Base\ Support\ index\ (BSi) = \frac{|x_{right\ foot} - x_{left\ foot}|}{|y_{chest} - \frac{|y_{right\ foot} + y_{left\ foot}|}{2}|}$$

Similarly, the pose asymmetry index was calculated for each sequential frame as the difference between the distance from the patient's right to the left foot, as measured from the patient's chest. The calculated difference was indexed to the patient's base of support, defined as the pixel distance between the left and the right feet along the x-axis (width). If there was overlap between the feet during a gait task, the metric defaulted to zero. Otherwise, assuming ($x_{body\text{-}part}$, $y_{body\text{-}part}$) represents the (x, y) coordinates of a given body part in a still frame, the pose asymmetry index was defined as:

$$Pose\ Asymmetry\ index\ (Ai) = \frac{||x_{right\ foot} - x_{chest}| - |x_{left\ foot} - x_{chest}||}{|x_{right\ foot} - x_{left\ foot}|}$$

Building on this concept, the Pose Dispersion Index was calculated that reflects a global assessment of a given patient's pose symmetry, balance, and stability during a given task based on the continuous data contained in the video. The metric was calculated for each walk task and video.

The Pose Dispersion Index consists of two parts that represent the dispersion of the gait asymmetry and base support indices. The first part is the non-parametric skew ([mean-median]/standard deviation) of the gait asymmetry index within the frames of a given video. This represents a non-parametric equivalent of the coefficient of variation for the gait asymmetry, which is not normally distributed. This can have either negative or positive values, with more negative values representing a left-skewed distribution. To ensure positive values, an exponential (quadratic) transformation of the non-parametric skew of the gait asymmetry index was included in the Pose Dispersion Index. The second part represents the dispersion of the base of support. This was calculated by estimating the coefficient of variation of the base support index, defined as the standard deviation of the base support index divided by its mean. Given that higher coefficients of variation values describe greater variation/dispersion in the base of support during a tandem walk attempt, the Pose Dispersion Definition incorporates the inverse of the coefficient of variation (i.e., mean divided by the standard deviation). Higher Pose Dispersion Index values thus reflect a more consistent change in pose and motion across time.

$$\boldsymbol{Pose\ Dispersion\ Index} = e^{\frac{\frac{\sum_{i=1}^{n} Ai}{n} - \widetilde{Ai}}{\sqrt{\frac{\sum_{i=1}^{n}(Ai-\mu)^2}{n}}}} x \frac{\frac{\sum_{i=1}^{n} BSi}{n}}{\sqrt{\frac{\sum_{i=1}^{n}(BSi-\mu)^2}{n}}}$$

Figure S1. Instructions for Administration of The Walking Item of the F-SARA

f-SARA Rating Form

| | |
|---|---|
| Subject ID | |
| Examiner | |
| Date | |
| Visit | |

# f-SARA
# Item 1 – Gait

## Item 1 Instructions

- Encourage patient to only use assistance required for safety in performing gait tasks (i.e., patient is to perform activity with as few aides as safely possible).
- Gait task is not timed. Patient is instructed to walk at a comfortable pace.
- Instruct patients to bring and wear **solid shoes** for each visit. Conduct all exams with similar type of shoe.
- Item may be performed on carpeted or uncarpeted floors. The same flooring should be used for all exams.
- Mark the floor to show the start, turning point, and beginning of tandem walk location. [Avoid positioning the turning point at the end of a hallway]
- Patients are asked to walk **10 meters** followed by a half-turn (**without pausing**) and then return to the starting point for the tandem walk (approximately 5 meters toward the start-point).
- For a patient's first administration of the f-SARA the examiner should demonstrate the gait and tandem items.
- Walk should be performed at a safe distance from a wall so that the patient is able to use the wall for intermittent support, if needed.
- "Walks independently" is defined as not requiring a walker or constant assistance from another individual to perform the 10-meter gait task.
- Tandem walk is only to be performed by patient who performs gait task with no assistance.
    - Scoring is based upon initial 10-step attempt (task is not repeated).
    - The tandem walk should be performed with **both feet on one line** and with no space between the heel and toe.
    - More than 1 misstep is scored as a failure.

## Item 1- Gait Scoring

Proband is asked to walk 10 meters at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait). If able to walk independently proband is asked to walk 10 steps in tandem (heel to toes) without support.

**Circle one**

**0 Normal: no impairment in walking, turning, and tandem walk**

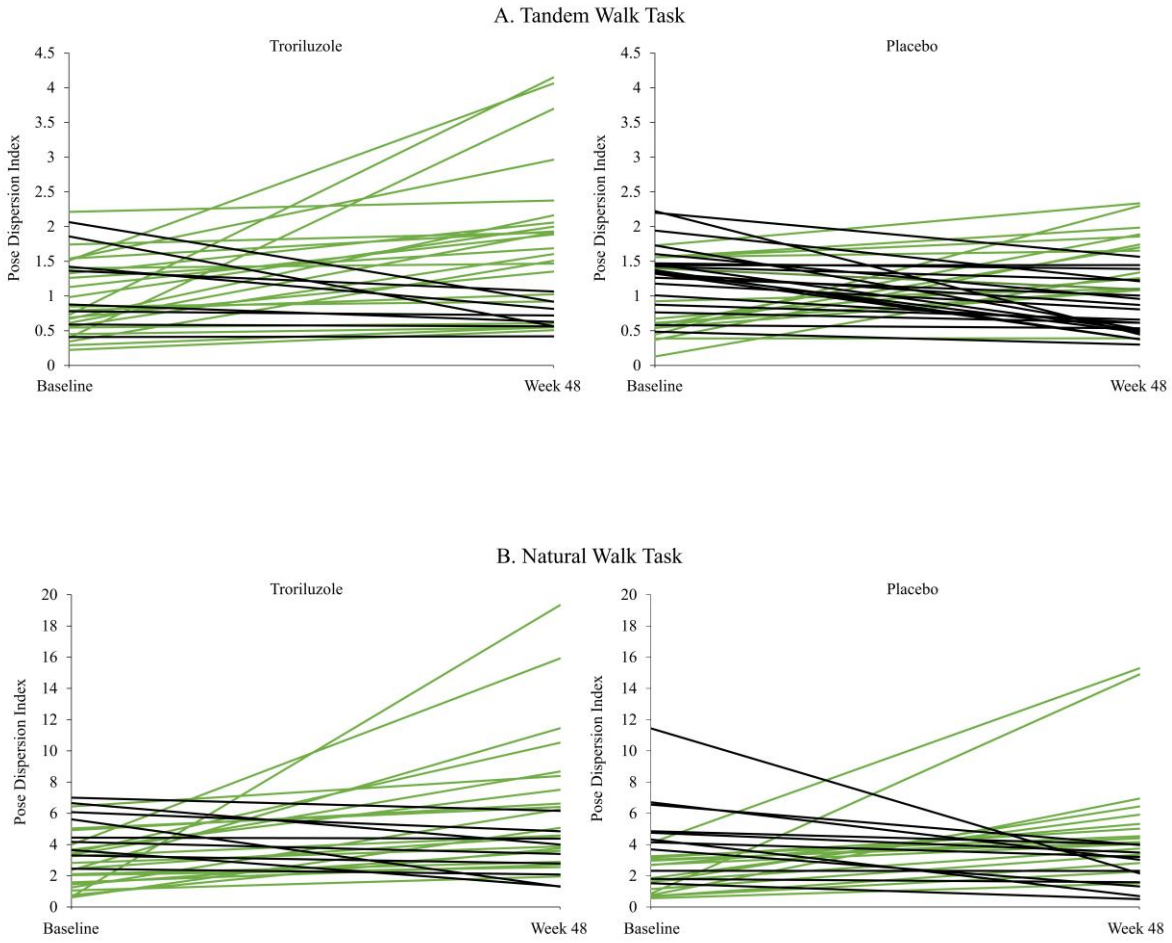
**1 Mildly impaired: abnormal gait, but no assistance needed with walking and/or fails tandem walk**

**2 Moderately impaired: staggers, but walks independently (intermittently touches wall, uses examiner's arm, or uses cane)**

**3 Severely impaired: subject dependent upon assistance (requires constant assistance from an accompanying person or uses walker)**

**4 Unable to walk, even supported**

Figure S2. Change in Pose Dispersion Index Values During Tandem Walk Task (A) and Natural Walk Task (B) from Baseline Through Week 48



**Participating Institutions and Ethics Committees**

| Institution | Ethics Committee / Institutional Review Board |
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| UCLA | Office of the Human Research protection Program<br>Los Angeles, CA, USA |
| Johns Hopkins Medicine | Johns Hopkins University Review Board<br>Baltimore, MD, USA |
| Massachusetts General Hospital | Advarra IRB<br>Columbia, MD, USA |
| University of Colorado Hospital | Advarra IRB<br>Columbia, MD, USA |
| Emory University | Western Institutional Review Board<br>Puyallup, WA, USA |
| University of South Florida | Advarra IRB<br>Columbia, MD, USA |
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|---|---|
| Northwest Neurology, Ltd | Advarra IRB<br>Columbia, MD, USA |
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