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Authors

Park, Julien
Bremova-Ertl, Tatiana
Brands, Marion
et al.

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ORIGINAL COMMUNICATION

Assessment of the reliability, responsiveness, and meaningfulness of the scale for the assessment and rating of ataxia (SARA) for lysosomal storage disorders

Julien Park[1] · Tatiana Bremova-Ertl[2] · Marion Brands[3] · Tomas Foltan[4] · Matthias Gautschi[5] · Paul Gissen[6] · Andreas Hahn[7] · Simon Jones[8] · Laila Arash-Kaps[9] · Miriam Kolnikova[4] · Marc Patterson[10] · Susan Perlman[11] · Uma Ramaswami[12] · Stella Reichmannová[13] · Marianne Rohrbach[14] · Susanne A. Schneider[15] · Aasef Shaikh[16] · Siyamini Sivananthan[6] · Matthis Synofzik[17] · Mark Walterfarng[18] · Pierre Wibawa[18] · Kyriakos Martakis[7,19] · Mario Manto[20]

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Abstract

Objective To evaluate the reliability, responsiveness, and validity of the Scale for the Assessment and Rating of Ataxia (SARA) in patients with lysosomal storage disorders (LSDs) who present with neurological symptoms, and quantify the threshold for a clinically meaningful change.

Methods We analyzed data from three clinical trial cohorts (IB1001-201, IB1001-202, and IB1001-301) of patients with Niemann–Pick disease type C (NPC) and GM2 Gangliosidoses (Tay–Sachs and Sandhoff disease) comprising 122 patients and 703 visits. Reproducibility was described as re-test reliability between repeat baseline visits or baseline and post-treatment washout visits. Responsiveness was determined in relation to the Investigator's, Caregiver's, and Patient's Clinical Global Impression of Improvement (CGI-I). The CGI-I data was also used to quantify a threshold for a clinically meaningful improvement on the SARA scale. Using a qualitative methods approach, patient/caregiver interviews from the IB1001-301 trial were further used to assess a threshold of meaningful change as well as the breadth of neurological signs and symptoms captured and evaluated by the SARA scale.

Results The Inter-Class Correlation (ICC) was 0.95 or greater for all three trials, indicating a high internal consistency/reliability. The mean change in SARA between repeat baseline and post-treatment washout visit assessments in all trials was −0.05, SD 1.98, i.e., minimal, indicating no significant differences, learning effects or other systematic biases. For the CGI-I responses and change in SARA scores, Area Under the Curve (AUC) values were 0.82, 0.71, and 0.77 for the Investigator's, Caregiver's, and Patient's CGI-I respectively, indicating strong agreement. Further qualitative analyses of the patient/caregiver interviews demonstrated a 1-point or greater change on SARA to be a clinically meaningful improvement which is directly relevant to the patient's everyday functioning and quality of life. Changes captured by the SARA were also paralleled by improvement in a broad range of neurological signs and symptoms and beyond cerebellar ataxia.

Conclusion Qualitative and quantitative data demonstrate the reliability and responsiveness of the SARA score as a valid measure of neurological signs and symptoms in LSDs with CNS involvement, such as NPC and GM2 Gangliosidoses. A 1-point change represents a clinically meaningful transition reflecting the gain or loss of complex function.

Keywords Scale for the assessment and rating of ataxia · Lysosomal storage disorders · Clinical outcome assessments

Introduction

Scale for the assessment and rating of ataxia (SARA)

The Scale for the Assessment and Rating of Ataxia (SARA) was initially developed to be a reliable and valid scale measuring the severity of cerebellar ataxia [1–3]. The SARA scale

Extended author information available on the last page of the article

is composed of eight functional domain ("item") assessments (gait (0–8 points), stance (0–6 points), sitting (0–4 points), speech disturbance (0–6 points), finger chase (0–4 points), nose-finger test (0–4 points), fast alternating hand movement (0–4 points), heel–shin slide (0–4 points)) with total scores ranging from 0 (normal) to 40 (most severe).

The SARA underwent a rigorous validation procedure involving three large multi-center trials in spinocerebellar ataxias (SCAs) and non-spinocerebellar ataxia patients, as well as controls, which found excellent inter-rater reliability, test-re-test reliability, and high internal consistency [2] and has undergone thorough item-response testing for multiple ataxias [4]. The SARA has also been shown to have excellent concurrent validity with other COAs, including the International Cooperative Ataxia Rating Scale (ICARS) [5], barthel index, or with Unified Huntington's Disease Rating Scale. Multiple studies have demonstrated that the scale reflects patient-reported symptoms and the impact of illness in cerebellar motor ataxia disorders and accurately represents patient experience [6–8]. The correlations between total SARA score and measures of daily activities and functional assessment are well-established in patients with inherited cerebellar ataxias, allowing further practical translation into the patient's everyday life. Table 1 provides an overview of each of the eight SARA test items and the patient-reported activities impacted to which each test item relates to [4, 9]. Multiple clinical studies validating the psychometric properties of the SARA scale in patients with inherited cerebellar ataxias showed an individual decrease (improvement) in the total SARA of at least 1–1.5 points as a clinically relevant improvement, and a decrease of 1.1 points at the group level to be clinically relevant [2].

SARA for non-ataxia *disorders*

The SARA scale was thus initially developed to measure symptoms of cerebellar ataxia in autosomal-dominant Spinocerebellar Ataxias (SCAs). Later, it was validated for use in other various types of ataxias [4, 4, 10]. More recently, the SARA has been increasingly utilized as a clinical outcome assessment for a wide range of disorders, ranging from rare entities such as lysosomal disorders to more common pediatric cancers [11–14]. The generalizability of the SARA may be related to multi-item assessments that can be categorized into 4 disease-agnostic functionally different categories:

A. Ambulation & function of lower extremities: test items (1) gait, (8) heel–shin slide
B. Postural balance: test items (2) stance, (3) sitting
C. Speech: test items (4) speech disturbance
D. Function of upper extremities (fine motor): test items (5) finger chase, (6) nose–finger, (7) fast alternating hand movements

When a patient performs voluntary movements as part of the SARA assessments, such as speaking or walking, this requires a sequence of coordinated actions (e.g., adequate motivation, attention, cognition, hearing, planning of movements, muscle power, strength, control and precision of movements) that involve many regions of the brain from the frontal cortex, somatosensory cortex, basal ganglia, cerebellum, brainstem to the corticospinal tract, and the spinal cord. In LSDs, cellular damage and cell death occur throughout the entirety of the central nervous system, manifesting as a wide range of heterogeneous neurological signs and symptoms (e.g., dysarthrophonia, ocular motor, dysmetria, ataxia, dysdiadochokinesia, dystonia, tremor, hypotonia, dyskinesias, spasticity—see Table 2), each of which could impact the ability of the patient to undertake the necessary sequence and precision of actions required to perform the SARA tasks, ultimately resulting in dysfunction in one or more of the above functional categories.

Therefore, we hypothesized that a change in the functional performance as assessed by the SARA scale could be indicative of broad alterations in many functional neurological networks, allowing its use as a measure of overall neurological disease severity in LSDs, as opposed to an isolated measure of cerebellar ataxia.

Methods

Study objective

Given the increased use of the SARA scale as an endpoint for LSDs, we aimed to evaluate the reliability, reproducibility, and responsiveness of the scale for LSDs that feature central nervous system involvement and investigate the range of neurological signs and symptoms which could be captured and measured. The study also evaluated a minimum threshold of change which would demonstrate clinical and functional significance.

Participants

Data were analyzed from three clinical trials conducted with the agent N-acetyl-L-leucine (IB1001) for LSDs, including 2 Phase IIb, open-label, rater-blinded studies with Niemann–Pick disease type C (NPC) ["IB1001-201", NCT03759639, $n = 32$ patients] and GM2 Gangliosidoses (Tay Sachs and Sandhoff diseases) ["IB1001-202", NCT03759665, n = 30 patients] and a Phase III, double-blind, placebo-controlled trial for NPC ["IB1001-301",

Table 1 Overview of SARA test items

SARA item	Test instructions [1]	Test description	Specific neurological features	Patient-reported activities impacted by specific symptom [8]
Gait	Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support	Assessment of neurological function that measures ambulation, balance, muscle strength, coordination, and postural stability	• Ataxia • Dysmetria • Dystonia • Dyskinesias • Hypotonia • Spasticity • Slowing of rapid alternating movements • Balance problems • Muscle weakness • Loss of muscle coordination	• Walking o Walking alone, walking in crows, walking outside on uneven surfaces, walking dog • Exercise • Leaving the house alone • Cannot carry things as need to hold walking device • Cannot perform house work • Cannot travel (to and from job, to run errands, through airport, etc.) • Falling
Stance	Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touch each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rater	Assessment of neurological function that measures balance, muscle strength, postural stability	• Ataxia • Dysmetria • Dystonia • Dyskinesias • Hypotonia • Spasticity • Slowing of rapid alternating movements • Balance problems • Muscle weakness • Loss of muscle coordination	• Standing up • Standing in the shower • Standing in line • Cannot socialize (cannot hold drink in conversation) • Cannot step on/off curb without aid • Housework • Playing Sports • Cannot squat or reach up • Falling
Sitting	Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front	Assessment of neurological function that measures balance, muscle strength, postural stability	• Dysmetria • Ataxia • Dystonia • Dyskinesias • Hypotonia • Spasticity • Balance Problems • Muscle Weakness • Loss of Muscle Coordination	• Going to the bathroom • Driving
Speech Disturbance	Speech is assessed during normal conversation	Assessment of neurological function that measures communication and speech	• Dysarthria • Dysmetria • Dysphagia • Ataxia • Dystonia • Dyskinesias • Hypotonia • Lower facial weakness/ muscle weakness • Slurred speech • Loss of Muscle Coordination	• Socializing • Working • Having a conversation • Talking on the phone • Communicating with caregiver or family

Table 1 (continued)

SARA item	Test instructions [1]	Test description	Specific neurological features	Patient-reported activities impacted by specific symptom [8]
Finger chase test	Patient sits comfortably. If necessary, support of feet and trunk is allowed Examiner sits in front of patient and performs five consecutive sudden and fast pointing movements in unpredictable directions in a front plane, at about 50% of patient's reach. Movements have an amplitude of 30 cm and a frequency of one movement every 2 s. Patient is asked to follow the movements with index finger, as fast and precisely as possible	Assessment of neurological function that measures smooth, coordinated upper-extremity movement, tremor, and accuracy of fine motor function/ target accuracy	• Dysmetria • Tremor • Dyskinesias • Ataxia • Spasticity • Dystonia • Hypotonia • Muscle weakness • Loss of Muscle Coordination	• Shaving • Using computer mouse /keyboard • Using smartphone/ Dialing phone/ Texting • Going to the bathroom (i.e., buttoning pants) • Dressing • Driving • Food preparation (i.e., cannot lift silverware or a glass to mouth accurately/ feed oneself / serve self-food) • Writing/ writing legibly • Turning lock in key • Self-care (i.e., Cannot brush teeth, cannot put on makeup) • Sewing/needle craft/ handling tools • Car repairs; home repairs • Play instrument
Nose-finger test	Patient sits comfortably. If necessary, support of feet and trunk is allowed Patient is asked to point repeatedly with index finger from their nose to the examiner's finger, which is in front of the patient at about 90% of the patient's reach. Movements are performed at moderate speed	Assessment of neurological function that measures smooth, coordinated upper-extremity movement, tremor, and accuracy of fine motor function/ target accuracy	• Dysmetria • Tremor • Dyskinesias • Hypotonia • Dystonia • Muscle weakness • Loss of Muscle Coordination • Ataxia • Spasticity	
Fast alternating hand movement	Patient sits comfortably. If necessary, support of feet and trunk is allowed Patient is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on their thigh as fast and precise as possible	Assessment of neurological function that measures several aspects of coordination; when a patient has neurological dysfunction, one movement often cannot be quickly followed by its opposite (e.g., movement is not synchronous) and movements are slow, irregular, and clumsy	• Dysdiadochokinesia • Slowing of rapid alternating movements (e.g., due to pyramidal dysfunction) • Ataxia • Dysmetria • Muscle weakness • Loss of Muscle Coordination • Hypotonia • Dyskinesias • Dystonia • Tremor • Spasticity	• Cannot hand things to another person • Unable to turn pages • Cannot open door/ turn doorknob • Inability to lift objects • Brushing Teeth • Turnkey in lock/ a door nob • Knife skills/ preparing food • Sports • Handshakes

Table 1 (continued)

SARA item	Test instructions [1]	Test description	Specific neurological features	Patient-reported activities impacted by specific symptom [8]
Heel-shin slide	Patient lies on examination bed, without sight of their legs. Patient is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the angle, and lay the leg back on the examination bed. The task is performed three times. Slide-down movements should be performed within 1 s	Assessment of lower limb coordination that measures, smooth, coordinated, precise lower-extremity movement	• Dysmetria • Dyskinesias • Ataxia • Dystonia • Muscle weakness • Loss of Muscle Coordination • Hypotonia • Tremor • Spasticity	• Cannot drive safely • Cannot take shoes on and off • Cannot stand alone in shower • Impairs ability to walk safely/ affects balance

NCT05163288, $n = 60$]. In the IB1001-201 and IB1001-202 studies, the SARA was a secondary endpoint; in the IB1001-301 study, the SARA was the primary endpoint.

Patients were recruited in the three clinical trials between 07-Jun-2019 and 22-Dec-2022 from 17 centers. This study was conducted in accordance with the International Conference for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)—Good Clinical Practice Guideline, the General Data Protection Regulator, and the Declaration of Helsinki. Approval was obtained by the applicable responsible central research ethics committees / institutional review boards for each center. Written informed consent was obtained from all study participants (or their parent/ legal representative) at enrollment. Methodology and results of each trial have been previously published [11–13, 15, 16].

Procedures

The study design/schema for the Phase IIb (IB1001-201, IB1001-202) and Phase III (IB1001-301) trials are presented in Fig. 1A, B [11–13, 15, 16].

In each study, the SARA was assessed by a qualified investigator at every study visit. The investigators underwent standardized training on the assessment and the same investigator was required to perform the SARA assessment at each visit for each patient to exclude confounding by inter-rater variability. For the IB1001-201 and IB1001-202 studies, this included two baseline visits at approximately day 1 (visit 1) and after 2 weeks of screening (visit 2), two treatment visits conducted after approximately 4 weeks (visit 3) and 6 weeks (visit 4) of treatment with IB1001, and 2 washout visits conducted after approximately 4 weeks (visit 5) and 6 weeks (visit 6) of post-treatment from IB1001. In the IB1001-301 study, this included two baseline visits at approximately day 1 (visit 1) and after 2 weeks of screening (visit 2), two treatment visits conducted after approximately 6 weeks (visit 3) and 12 weeks (visit 4) of treatment with IB1001 or Placebo, and two treatment visits conducted after approximately 6 weeks (visit 5) and 12 weeks (visit 6) of the opposite treatment (IB1001 or Placebo).

In addition, the Clinical Global Impression of Improvement was assessed by the investigator, caregiver, and patient (if able) at the end of every treatment period, e.g., at VISIT 4 (versus visit 2) and visit 6 (versus visit 4) [17]. Finally, in the Phase III trial, exit interviews (in the form of semi-structured interviews) were conducted with the patient (if able) and/or caregiver (if applicable) at visit 6 (end of the parent study) or the ET visit to better inform and evaluate the meaningfulness of the within-patient changes on the outcome assessments and document the relevance and meaningfulness of functional improvements in patients' everyday lives (see the

Table 2 Neurological symptoms of lysosomal storage disorders/impact on SARA test item

Region of brain	Specific neurological symptom	Description (if applicable)	SARA item directly affected by the specific symptom
Cerebellum [22]	Ataxia	Lack of precision in voluntary muscle movements and coordination and sequence of movements	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide)
	Dysarthria	Motor speech disorder due to impairments in the muscular control of speech which can affect the strength, speed, range, tone, and accuracy of the speech	Speech
	Dysmetria	Inability to control the distance, speed, and range of motion necessary to perform smoothly-coordinated movements	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide) Note: diagnostic tests for Dysmetria specifically include the nose-finger test and heel-shin slide
	Dysphagia	Difficulty swallowing (which also makes it difficult to eat, drink, and speak)	Speech
	Dysdiadochokinesia	Inability to perform rapid alternating muscle movements (opening and closing fists, tap shoe, alter hands)	Fast alternating hand movement Note: the diagnostic test for Dysdiadochokinesia is the fast alternating hand movement test
Basal Ganglia [23]	Dystonia	Involuntary muscle co-contractions	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide)
	Tremor	Involuntary quivery movement	Finger chase, nose-finger test, fast alternating hand movement (all items may be impacted if essential tremor)
	Dyskinesias	Involuntary, erratic, writhing movements (tics, tremors, shakes, full body movements)	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide)
	Hypotonia	Low (decreased) muscle tone	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide)
Pyramidal tract [24]	Spasticity	Muscle control disorder that causes abnormal muscle tightness, stiffness, or pull	Gait, sitting, stance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide
	Slowing of rapid alternating movements	N/A	Fast alternating hand movement and heel-shin slide
	Lower facial weakness and changes to speech	N/A	Speech
Brain stem [25]	Balance problems	Muscle control disorder that causes abnormal muscle tightness, stiffness, or pull	Gait, sitting, and stance
	Muscle weakness	N/A	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide)
	Slurred speech	N/A	Speech
	Loss of muscle coordination	N/A	All items (gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, and heel-shin slide)

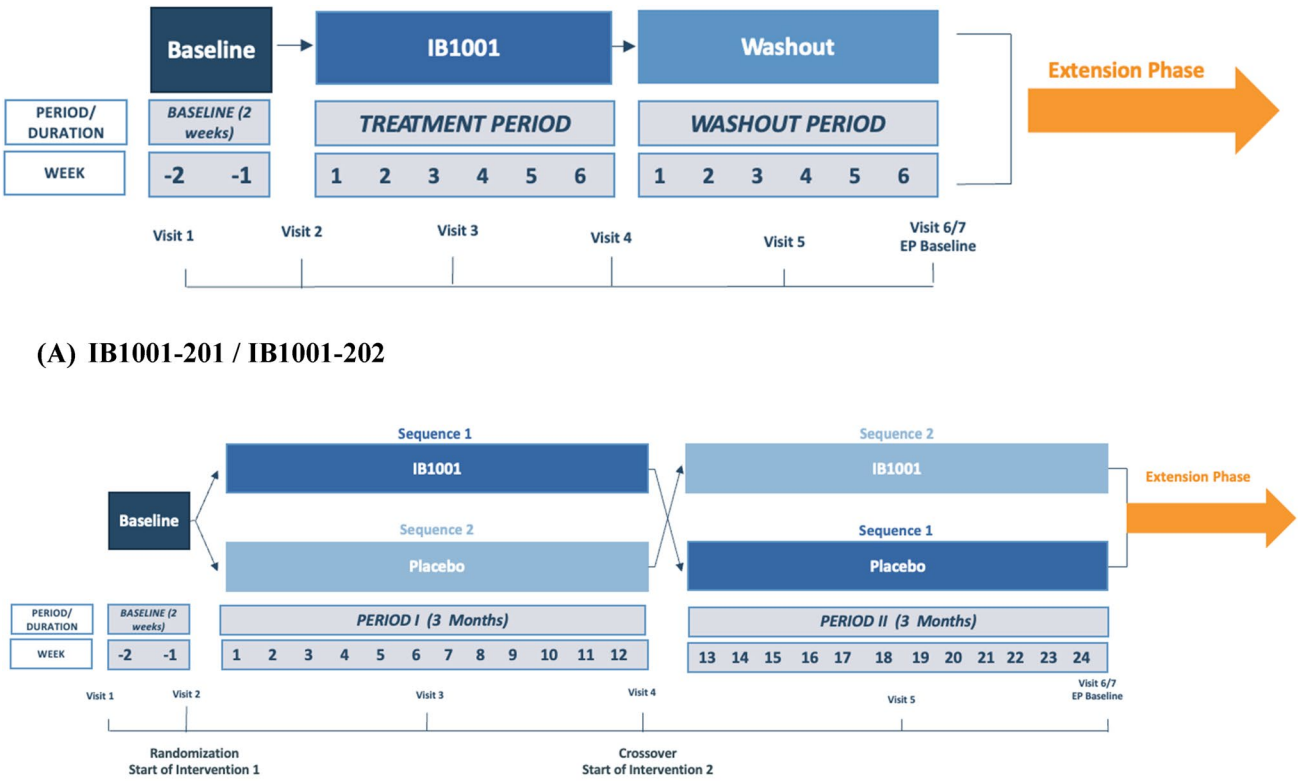

Fig. 1 Study schemes from IB1001 clinical trials

questionnaire in Supplemental Material 1) [18]. These exit interviews were conducted prior to any unblinding.

Statistical analyses

Reliability & reproducibility

In each clinical trial, participants were assessed twice during the baseline period (before any intervention) at visits approximately 14–21 days apart (visit 1 and visit 2). Mean and (SD) were computed for each of the baseline visits as well as the difference between visit 1 and visit 2 for each trial. The results for the three trials were compared for consistency and two-sided t tests were used to test for group differences between the 301 trial and the 201 and 202 trials. In addition, the mean (SD) and the difference between the baseline visit 1 and visit 2 for patients < 10 years old were computed to assess the reliability of the SARA assessment in these younger patients. Given the small sample sizes in the three trials, the data were combined to enable statistical interpretation. These results were compared to the results of patients aged 10 years and older for consistency, and a two-sided t test was used to test for group differences.

To determine the test–re-test reliability of SARA, inter-class correlations (ICCs) were calculated from all three trials for the total SARA score between baseline visit 1 and visit 2, and also by each of the 8 items (e.g., SARA gait visit 1 versus visit 2). For the IB1001-201 and IB1001-202 trials, mean and standard deviation (SD) were also computed for the end of post-treatment washout visit (6), and the mean (SD) difference between visit 1 and visit 6 was calculated. The results were compared for consistency and an independent sample t test was used to test for group differences between the two studies. A calculation of the mean (SD) difference was also calculated for the subgroup of patients aged < 10 years from the IB1001-201 and IB1001-202 trials. These results were compared to the results of patients aged 10 years and older for consistency and a two-sided t test was used to test for group differences. The ICCs between the visit 1 (baseline) and visit 6 (post-treatment washout) scores were also computed for the total SARA scale as well as for the eight individual test items (gait, stance, sitting, speech disturbances, finger-chase, nose-finger, fast alternating hand movement, heel-shin slide).

Coefficients exceeding 0.80 were considered acceptable for the total SARA scale; coefficients above 0.70 were

considered acceptable for each of the 8 single SARA items [19].

Responsiveness

The responsiveness of the SARA scale was defined as the ability to detect clinically important changes. To assess this, for the IB1001-301 trial data, SARA scores were compared with Clinical Global Impression of Improvement (CGI-I) scores in order to determine whether changes in SARA reflect the clinical changes recorded by investigators, caregivers, and patients.

This analysis was carried out for the second treatment period of the IB1001-301 trial (the IB1001-201 and IB1001-202 trials were open-label and therefore not considered appropriate for comparison; in the IB1001-301 trial treatment period 1, 50% of patients were on placebo treatment and therefore this period was not appropriate for comparison). Responsiveness was defined as the ability to categorize patients as Improved (patients rated as minimally, much, or very much improved) or Unchanged (no change) or Worsened (minimally, much, or very much worse) as a function of Δ SARA with re-scored CGI-I as external criteria. Visit 4 (end of treatment with IB1001 or Placebo) to visit 6 (end of opposite treatment) changes in SARA (Δ SARA) scores were compared with CGI-I at visit 6. Approximately half the patients—those randomized in the sequence IB1001-Placebo—were expected to show stable or worsening SARA scores, and the other sequence—Placebo-IB1001—to register improvements.

The CGI-I scale has been shown to be able to successfully differentiate between responders and non-responders to investigational study drugs [20]. Accordingly, CGI-I scores were allocated to categories "improved", "unchanged" and "worsened". The mean and 95% CI for the no-change group were calculated. The mean values of ΔSARA for the improved and worsened categories were calculated and compared with the no-change 95% CI to determine whether the mean change of either group overlapped with the 95% CI for the no-change group.

To further quantify the ability of SARA to assess clinically meaningful improvements, a second analysis was carried out on the CGI-I data. Here, CGI-I data were further collapsed into the binary categories "improved" (minimally, much, or very much improved) and "not improved" (no change, minimally, much, or very much worse) For each CGI-I, the confusion matrix was computed at each value of Δ SARA, and a Receiver Operating Characteristic (ROC) curve was calculated for the true positive rate as a function of the false positive rate [FDA Guidance for Industry 2023]. The area under the curve (AUC), equating to the ability to detect a clinical change, was calculated. An AUC value greater than 0.70 was considered the minimum threshold for discriminative ability [19, 21].

Correlation between total SARA score and activities of daily life

To assess whether changes on the SARA scale correlated with patient/caregiver-reported clinically meaningful improvements in everyday function, activities of daily life, and/or quality of life, the exit interviews from the IB1001-301 study were qualitatively assessed. For patients who experienced a 1-point or greater improvement on the SARA scale after treatment with IB1001 or, for those randomized to receive IB1001 followed by Placebo, a 1-point worsening or greater on the SARA, a qualitative system review aggregated their exit interviews into "responders" versus "non-responders". "Responders" were defined as exit interviews where the patient/caregiver described the changes during the IB1001-301 clinical trial to be beneficial, and reported improvement in everyday function and quality of life which were considered to be clinically meaningful. Content Analysis was applied to determine if the reported changes were limited to the symptom of cerebellar ataxia, or if changes in other neurological signs and symptoms could potentially be associated with changes on the SARA scale.

Results

Patients

The analyzed subset of 122 patients (mean age 27.1, range 5–67, years; 66 male, 56 female, 81 NPC, 30 GM2) had a mean SARA score of 15.17 (7.28) at Visit 1. As indicated by the distribution of the SARA baseline scores (SD 7.28, range 4.5 to 35), the cohort was representative of a broad range of disease severity except asymptomatic patients or the most severely impaired patients. In total, 122 Δ SARA scores from Visit 1 and Visit 2 (from the IB1001-201, IB1001-202, and IB1001-301 study) and 57 Δ SARA scores from Visit 1 and Visit 6 (from the IB1001-201 and IB1001-202 study) were evaluated for reliability and reproducibility. 58 Investigator CGI-I scores, 50 Caregiver CGI-I scores, and 49 Patient CGI-I scores comparing Visit 4 to Visit 6 (from the IB1001-301 study) and were evaluated against the corresponding 58 Δ SARA scores for responsiveness. Across the three trials, there were 15 patients aged < 10 years (range 5–9 years); in the IB1001-201 and IB1001-202 trials, there were seven patients aged < 10 years (range 6–9 years).

Table 3 Test–re-test data baseline visit 1 & baseline visit 2

Trial	Baseline visit 1 vs baseline visit 2		
	IB1001-201	IB1001-202	IB1001-301
n	33	29	60
Mean (SD) visit 1	14.65 (7.48)	14.36 (7.11)	15.85 (7.32)
Mean (SD) visit 2	14.35 (7.06)	14.38 (7.30)	15.88 (7.50)
Mean (SD) change	−0.30 (1.75)	0.02 (1.23)	0.03 (1.96)
SEM	1.24	0.99	0.97
p value (vs IB1001-301)	0.4	0.96	N/A

Table 4 Interclass correlations between baseline visit 1 & baseline visit 2 (approximately 2–3 weeks apart)

	Trial		
	IB1001-201	IB1001-202	IB1001-301
Total score			
SARA	0.971	0.986	0.966
Individual test item			
Gait	0.973	0.988	0.965
Stance	0.943	0.945	0.895
Sitting	0.919	1	0.898
Speech	0.923	0.94	0.933
Nose finger	0.756	0.963	0.882
Finger chase	0.857	0.902	0.793
Hand movements	0.94	0.9	0.887
Heel Shin	0.976	0.927	0.921

Table 5 Test–re-test data baseline visit 1 & post-treatment washout visit 6 (approximately 14 weeks apart)

	Trial	
	IB1001-201	IB1001-202
n	31	26
Mean (SD) visit 1	14.94 (7.64)	14.19 (7.48)
Mean (SD) visit 6	14.90 (8.16)	14.15 (8.31)
Mean (SD) change	−0.03 (2.61)	−0.04 (2.07)
SEM	0.97	0.97
p value	0.99	

Table 6 Interclass correlations between baseline visit 1 & post-treatment visit 6

	Trial	
	IB1001-201	IB1001-202
Total score		
SARA	0.947	0.967
Individual test item		
Gait	0.942	0.894
Stance	0.888	0.854
Sitting	0.839	1
Speech	0.731	0.896
Nose finger	0.826	0.889
Finger chase	0.62	0.767
Hand movements	0.781	0.894
Heel shin	0.878	0.972

Reliability & reproducibility

Test–re-test data for all three trials for the baseline period (Visit 1 and Visit 2) are shown in Table 3. The mean (SD) changes between baseline Visit 1 and Visit 2 for the IB1001-201, IB1001-202 and IB1001-301 trials were −0.30 (1.75), + 0.02 (1.23), and + 0.03 (1.96) respectively (Table 2). There was no statistically significant change in the mean value from Visit 1 to Visit 2 for any study or statistically meaningful difference found between the re-test IB1001-301 score and the IB1001-201 or IB1001-202 scores, reflecting the SARA was highly reliable/reproducible. For patients < 10 years, the mean (SD) change from baseline visit 1 and visit 2 was 0.27 (2.05) which was not statistically significantly different from the cohort of patients aged 10 years and older ($p = 0.50$), reflecting the SARA was also reliable/reproducible in this population.

The ICCs for the SARA scale and each of its 8 items are given in Table 4. The SARA scale correlations were 0.971, 0.986 and 0.966 for the three trials. These item-level correlations all exceeded the 0.70 threshold and showed strong agreement, demonstrating a high degree of internal consistency. The Sitting test ICC was 1.0 for the IB1001-202 which was an indication of the flooring effect for that item (20 of 29 scores were 0).

Test–re-test data for the IB1001-201 and IB1001-202 trials for the baseline versus post-treatment washout period data (visit 1 and visit 6) are shown in Table 5**.** There were no differences observed between the baseline visit and the post-washout visit (visit 1–visit 6); the mean change (SD) in SARA score was −0.03 (2.61) in the IB1001-201 study and −0.04 (2.07) in the IB1001-202 study. This further reinforced the reliability of the administration of the SARA scale, and also demonstrated the absence of a learning effect on the 8 SARA items. For patients < 10 years, the mean (SD) change from baseline Visit 1 and post-treatment washout Visit 6 was 0.00 (1.61) which was not statistically significantly different from the cohort of patients aged 10 years and older ($p = 0.95$), reflecting the SARA was also reliable/reproducible in this population.

The ICCs for this comparison are shown in Table 6. The total SARA scale ICCs were high and above the 0.80 threshold. These item-level correlations all exceeded the 0.70 thresholds and showed strong agreement. There was

also further evidence of the flooring effect in the Sitting test where the IB1001-202 trial ICC was 1.0.

Responsiveness

The CGI-I scores categorized as "unchanged", "improved" and "worsened" and corresponding Δ SARA values for the IB1001-301 trial (Visit 4 to Visit 6) are summarized in Table 7**.** Δ SARA values ranged between −5.5 and + 6.5 (expected variance given approximately 50% of patients in this treatment period were commencing IB1001, and 50% were stopping IB1001 treatment). The mean (SD) was −0.06 (2.72).

The results were studied to determine whether the mean change of either the Improved and Worsened group overlapped with the 95% CI for the unchanged group for each of the three assessor groups: investigator, caregiver, and patient.

The CGI-I values categorized as "improved" or "not improved" used for the AUC calculations are summarized in Table 8. As described above, patients randomized in the sequence Placebo-IB1001 were expected to show improvement during this period. Those randomized in the sequence IB1001-Placebo were expected to show worsening during the second period if the patient was a responder to the study drug. The AUC for Investigator CGI-I was 0.82, for Caregiver CGI-I, it was 0.71, and for Patient CGI-I, AUC was 0.77. All CGI-Is were above the threshold for discriminative ability, supporting changes in SARA aligned with CGI-I assessments of changes in patients' overall function and well-being.

Correlation between total score and activities of daily life

42 exit interviews were qualitatively assessed for patients who experienced a 1-point or greater improvement on the SARA scale after treatment with IB1001 or, for those randomized to receive IB1001 followed by Placebo, a 1-point worsening or greater on the SARA. 70% of patients were identified to be responders to the study drug, meaning that the patient/caregiver described clinically meaningful, relevant changes in exit interviews, reinforcing previous findings that there is a close correlation between total SARA score and measures of daily activities and functional assessment and that a minimum 1-point change is clinically meaningful [2]. The exit interviews further elucidated that clinically meaningful changes included: increase in strength and energy; improved cataplexy, dysphagia, ataxia, dystonia; reduced (less) pain in muscles/general; improved speech, more easily understood/fluent speech, easier to integrate into a conversation, easier to communicate with; improved ambulation, mobility, balance, coordination, and autonomous gait; reduced falls; improved fine motor skills/general motor skills, less tremor; improved cognition, concentration, brain fog, focus, memory, cooperation, behavior, mood; reduced anxiety; less swallowing problems, less coughing while swallowing; improved incontinence (urine and anal); reduced seizures; improved sleep; improved ability to perform everyday tasks (feeding, dressing, playing, work, following orders, participating in leisure activities), and were not limited to the isolated measure of cerebellar ataxia. Examples from the exit interviews are provided in Table 9.

Table 8 Patient count for CGI-I collapsed to a binary classifier "improved" or "not improved" for each of the three assessor groups: investigator, caregiver, and patient

	CGI-I improved	CGI-I not improved
	n	*N*
Investigator	24	34
Caregiver	20	30
Patient	15	34

Discussion

Previous validation data on the SARA scale has demonstrated construct validity, internal consistency, and inter-rater reliability, and high reproducibility and responsiveness in patients with inherited Cerebellar Ataxias [2]. This analysis demonstrated the reproducibility, reliability, and responsiveness of the SARA scale in patients with LSDs, and the results of qualitative and quantitative analysis support the SARA scale as a valid measure of neurological status in LSDs that feature central nervous system involvement.

Table 7 Patient count and mean ΔSARA for the collapsed CGI-I assessment categories

CGI-I	CGI-I improved		CGI-I unchanged		CGI-I worsened	
	n	mean ΔSARA (95% CI)	*n*	mean ΔSARA (95% CI)	*n*	mean ΔSARA (95% CI)
Physician	24	−1.79 (−2.71, −0.88)	16	−0.09 (−0.83, 0.64)	18	1.16 (0.05, 2.27)
Caregiver	20	−1.18 (−2.53, 0.18)	14	−0.07 (−1.30, 1.15)	16	0.78 (−0.50, 2.07)
Patient	15	−1.90 (−3.20, −0.60)	22	0.41 (−0.81, 1.62)	12	0.87 (−0.65, 2.38)

Table 9 Exit interview responses

Exit interview completed by	Reported improvements	How these improvements (or any magnitude) were relevant/meaningful
Patient	"My speech patterns improved and I am understood more easily. I am less likely to fall now than before the study. When I drink water I am less likely to have problems swallowing. More energy, less falls, better speech. No influence on my digestions which is good."	"During lunch it is easier to talk to people around me. And I need to concentrate less on eating itself. Per the father: "patient seemed more content/independent, called less home for help."
Parent	"Not as shaky with her hand when feeding and drinking. speech more clear"	"Allows her to be more independent in feeding and drinking. Not having to repeat as much what she says to others. Lovely to see her laughing and joking. Seeing a slight change gives me hope in her life improving a little for the better."
Parent	"He became much more stable + rarely fell over. His speech became much clearer, his vocabulary has massively improved. His swallowing has been better."	"Hugely [meaningful] gave him more independence to move around. Hugely [meaningful] he's, been able to have meaningful conversations with others. [He has] hugely improved + his daily life"
Parent	"It was like hitting the pause button on his symptoms everything improved."	"Getting participant to a level point in his life. Without the trial we would feel as parents that he would be a vegetable in a wheelchair or dead. We finally believe that the intrabio trial has bought us years with him. If the trial had been introduced in infancy the issues the participant faces today would have been immensely reduced in there levels now. We have a lucid son. Not everything is great as can be expected with NPC-type C. But lives better when on. again speech, swallow, balance normal"
Parent	"Cataplexy improved a lot energy level improved"	"Very meaningfull, He can handle himself better, can watch a movie without constant cataplexy. Mother does not have to sit next to him every minute because cataplexy is less."
Patient	"Can stand up better, has better balance. More alert, less problems with digestion"	"Everyday life is a little easier, and that increase the patients [my] mood. More motivation, better mood"
Parent	"Small improvement in swallow and tremor and balance; sleep improved; speech a bit clearer"	"Eating and drinking with less coughing, less of a tremor when using hands so easier to complete tasks"
Parent	"Last 1.5 months he seems to be more stable and increased strength. [He] is able to walk the stairs in alternating steps. Gets on a swing by himself. Seems more connected to his body. Walks alternating steps more, strength in his hands, gets on a swing by himself, feels when [needs] to pee (and goes)."	"More self reliant for instance initiating to go on a swing anf felling urinating, parents find this very important."
Patient	"Less pain in the muscles in my hand and arm. Which made zippers of clothing easier. Less trouble with dystonia in the lower arm."	"Less pain in daily life. Dressing is better due to less cramps. Therefore less pain."
Patient & parent (quotations provided are from Parent)	"More alert and more talkative."	"This is important she can more easily join a conversation and is more sociable"

Table 9 (continued)

Exit interview completed by	Reported improvements	How these improvements (or any magnitude) were relevant/meaningful
Patient	"Patient stumbled less often, better balance, motor sense has improved over all, speech is more clear and understandable after the first phase."	"Over all well-being was improved"
Patient & Parent (quotations provided are from Parent)	"Cataplexy got better. I felt her coordination and steadiness improved notably during the first phase. She would often be able to either turn on the spot without falling or grab a bottle from the table with firmness, and this was seen during the first phase, with noted decline in the second phase."	"It meant she was more independent, and maybe not dependent on me."
Patient & parent (quotations provided are from patient & parent)	"More fluent speech"	"Could talk more with his mother."
Patient & parent (quotations provided are from patient & parent)	"Improvement in swallowing & speech, patient is more "awake", walks faster & fine motor is faster"	"She is more awake & can stay longer awake, she can talk easier. However she swears now more. She is pretty much more continent with urine & stool. [The changes were] very relevant. She expresses feelings now ("mom, I'm cold/I'm hungry"), she talks and reacts faster, she swallows better."
Parent	"He could dress up himself. He could follow orders. he did not give up putting his shoes on. He could focus better. He responded better. Speech was better."	"Very relevant. He was socially more integrated."
Parent	"More attention, understands small prompts. Walks more steadily, maybe faster. [I can] scolds a little less."	"Very meaningful"
Parent	"Cognitive improvement, he remembers everything fast, memory improvement, walking more stable & faster. He raises his legs better"	"Massive improvement. They have started practice his walking indoor. Massive improvement of absences (from > 5 to max 1 × day), slight improvement of swallowing. He can follow better instructions."
Patient	"Less coughing/no cough while eating, better swallowing, less tired/more energetic. No more falls!"	"Very meaningful, no falls, no swallowing problems"
Parent	We noticed an improvement in our son's language**.** The communication with others outside our family improved; our son made himself understood more easily."	"The communication with people outside our family was easier."
Patient	"Improved significantly. Improve mood, speech, walking."	"Yes. Made patient more positive"
Patient	"Slight improvement in overall daily activities. Hand dexterity improve."	"Less burden on carer"
Patient	"My fine motor skills improved and I felt more awake"	"Thanks to the improvements, I can take part in everyday life and enjoy me leisure activities. Thanks to my improved alterness/feeling more awake I took part in more leisure activities and felt generally better."
Parent	"Taking part in leisure activities is easier and his stamina improved."	"Thanks to the improvements, my son can take part in more leisure activities and has more joy in life."
Parents	"There were improvements in her fine motor skills as well as her general motor skills and balance. There were significant improvements in our daily life. Regular activities are possible more often without limitations."	

Test–re-test data indicate a high degree of consistency between three distinct study cohorts and a high degree of consistency/reliability between visits conducted 2–3 weeks apart (ICC > 0.96), as well as for visits conducted 14–15 weeks apart (ICC > 0.95). The mean change in SARA between assessments in all trials was small indicating that learning effects and other systematic biases are not significant. Notably, the SARA was also demonstrated to be reliable/reproducible in patients < 10 years of age. Responsiveness measured as SARA's ability to classify whether patients had improved or not was above the discrimination threshold for all three Investigator, Caregiver, and Patient CGI-I measures (0.82, 0.71, and 0.77 respectively). Notably, the Caregiver CGI-I and Patient CGI-I could be accurately classified with the directional change in SARA (as neither the caregiver or patient are responsible for assessing the SARA scale), and the analysis supports the use of SARA as an endpoint that can detect changes that patients and caregivers consider clinically meaningful.

According to the US Food and Drug Administration, for a clinical endpoint to be meaningful, it should properly reflect or describe how a patient feels, functions, or survives [18]. The high degree of agreement between the SARA scores and the investigator's, caregiver's, and patient's CGI-I, as well as significant improvements in everyday function and quality of life captured in the IB1001-301 exit interviews, supports the establishment of a meaningful change threshold of 1-point on the SARA (e.g., a clinically meaningful improvement at −1 point or greater, or a clinically meaningful worsening of +1 point or greater). This was further supported by an analysis of the IB1001-301 exit interviews, where patients/caregivers described how a transition of 1 point or greater reflected the gain or loss of complex functions that were highly relevant to everyday activities, function, and quality of life. That a 1-point change on the SARA is clinically meaningful is consistent with previous literature and the nature of the assessment [2]. The gradation of scoring in the 8 SARA test items was defined to cover the full range of disease severity (from asymptomatic to unable to perform the task in any fashion) and the full spectrum of abilities between these two extremes [1]. Thus, each score can be considered to reflect a distinct degree of disease progression and distinct neurological function, so that a 1-point difference is meaningful clinically as observed by the Investigator assessors, and importantly reflects a meaningful difference to a patient's quality of life.

Our analysis demonstrated that the SARA may be utilized as an outcome assessment in LSDs that feature central nervous system involvement as a wider measurement of neurological function, far beyond the assessment of cerebellar ataxia. Although the analysis was based on populations of NPC and GM2 Gangliosidoses, there were no differences in the reliability, reproducibility, or responsiveness of the SARA in these two different disease states, supporting the extrapolation of these findings to other related LSDs, such as GM1 Gangliosidoses and Gaucher's disease, which share the same hallmark patterns of neurodegeneration, and neurological signs and symptoms. Analysis of the exit interviews supports that the SARA scale, when applied and assessed in complex diseases like LSDs that feature a range of heterogeneous neurological symptoms, represents a broad assessment of neurological status, namely to signs and symptoms of cortical (understanding of instructions and other cognitive functions, motivation, and planning of movements), basal ganglia, cerebellar, brainstem, pyramidal and extrapyramidal tracts function and dysfunction. The findings from this analysis are supportive of the SARA assessment as a reliable measure of neurological function in patients with LSDs who present with neurological signs and symptoms.

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Declarations

Conflicts of interest T. Bremova-Ertl received honoraria for lecturing from Sanofi and Acetlion and fees from IntraBio to serve as a blinded rater for the IB1001-201 and IB1001-202 clinical trials. P. Gissen received consulting fees from Mandos Health and is the Co-Founder and shareholder of Bloomsbury Genetic Therapies. M. Patterson is a shareholder in IntraBio and his institution has received research grants from Azafaros, Glycomine, Idorsia, Maggie's Pearl, Takeda, and Zevra, and consulting fees (directed to his institution) from Zevra. U. Ramaswami has received research and/or investigator-initiated research grants from Amicus and Takeda and honoraria for advisory boards and lectures from Amicus, Takeda, and Sanofi. All other authors. The authors have no competing interests to declare that are relevant to the content of this article.

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Authors and Affiliations

Julien Park[1] · Tatiana Bremova-Ertl[2] · Marion Brands[3] · Tomas Foltan[4] · Matthias Gautschi[5] · Paul Gissen[6] · Andreas Hahn[7] · Simon Jones[8] · Laila Arash-Kaps[9] · Miriam Kolnikova[4] · Marc Patterson[10] · Susan Perlman[11] · Uma Ramaswami[12] · Stella Reichmannová[13] · Marianne Rohrbach[14] · Susanne A. Schneider[15] · Aasef Shaikh[16] · Siyamini Sivananthan[6] · Matthis Synofzik[17] · Mark Walterfarng[18] · Pierre Wibawa[18] · Kyriakos Martakis[7,19] · Mario Manto[20]

✉ Julien Park
Julien.Park@ukmuenster.de

[1] Department of General Paediatrics, University of Münster, 48149 Münster, Germany

[2] Department of Neurology, University Hospital Bern (Inselspital), Bern, Switzerland

[3] Department of Paediatric Metabolic Disease, Amsterdam University Medical Center, Amsterdam, Netherlands

[4] Department of Pediatric Neurology, National Institute of Children's Diseases, Comenius University in Bratislava, Bratislava, Slovak Republic

[5] Division of Paediatric Endocrinology, Diabetology and Metabolism, Department of Paediatrics, and Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[6] NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London, London, UK

[7] Department of Child Neurology, Justus Liebig University, Giessen, Germany

[8] Willink Unit, Manchester Centre for Genomic Medicine, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK

[9] SphinCS–Institute of Clinical Science in Lysosomal Storage Disorders, Hochheim, Germany

[10] Departments of Neurology, Pediatrics and Clinical Genomics, Mayo Clinic Children's Center, Rochester, MN, USA

[11] Department of Neurology, University of California, Los Angeles, CA, USA

[12] Lysosomal Storage Disorder Unit, Royal Free London NHS Foundation Trust, London, UK

[13] Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[14] Division of Metabolism, University Children's Hospital and Children's Research Centre, Zurich, Switzerland

[15] Department of Neurology, Ludwig Maximilians University, Munich, Germany

[16] Department of Neurology, Case Western Reserve University School of Medicine, Cleveland, OH, USA

[17] Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany

[18] Department of Neuropsychiatry, The Royal Melbourne Hospital, Melbourne, VIC, Australia

[19] Department of Pediatrics, Medical Faculty and University Hospital, University of Cologne, Cologne, Germany

[20] Unité Des Ataxies Cérébelleuses, Service de Neurologie, Médiathèque Jean Jacquy, CHU-Charleroi, 6000 Charleroi, Belgium