A NATURAL HISTORY STUDY IN GANGLIOSIDOSES (PRONTO). BASELINE CLINICAL DATA

R Giugliani[1], P Harmatz[2], B Héron[3], M Patterson[4], S A Schneider[5], A Bourchany[6], A Hahn[7], D Almeida do Valle[8], R Barone[9], B Chabrol[10], A Ardissone[11], S Batzios[12], M Scarpa[13], L Crapard[14], L López de Frutos[14], R Medinaceli Quintela[14], E Meyer[14], A Thiers[14], C Paquet-Luzy[14]

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Introduction

PRONTO is a prospective natural history study assessing neurological disease progression in late-infantile and juvenile GM1 and GM2 gangliosidoses. The main study objective is to understand neurological disease progression using three different approaches: clinical scales, caregiver questionnaires, and actigraphy.

Study design

INCLUSION

- GM1 or GM2 (genetically confirmed)
- 2-20 years
- Normal development until the 1st birthday
- SARA score gait or speech > 1

EXCLUSION

- All treatments that can interfere with the natural progression of the disease

CLINICIANS

SARA, INAS, MFM-32, TUG, Swallowing

CAREGIVERS

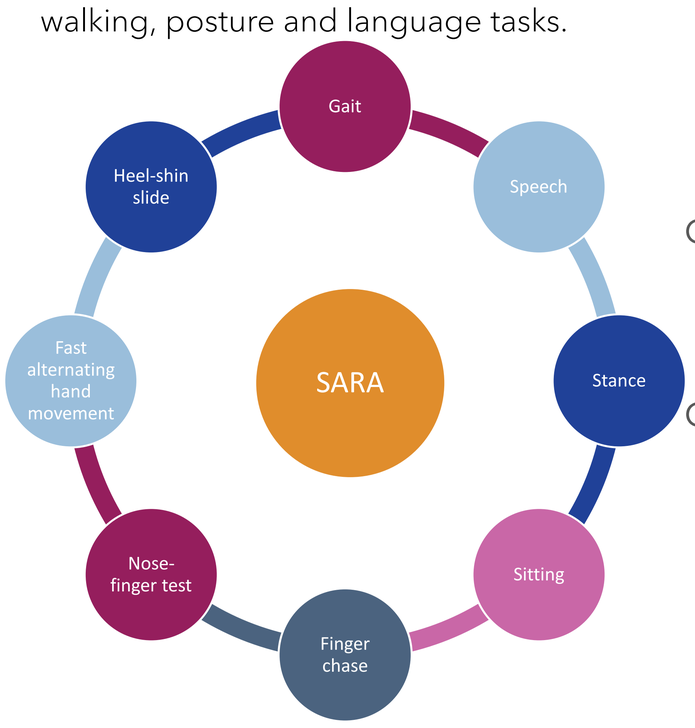
VABS, BSFC,Patient's diary

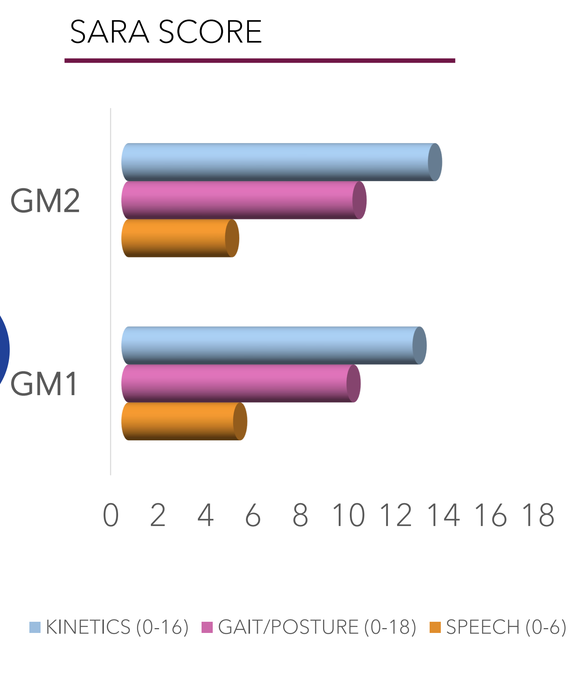
PASSIVE MONITORING

Actigraphy: PhysIQ

SARA scale

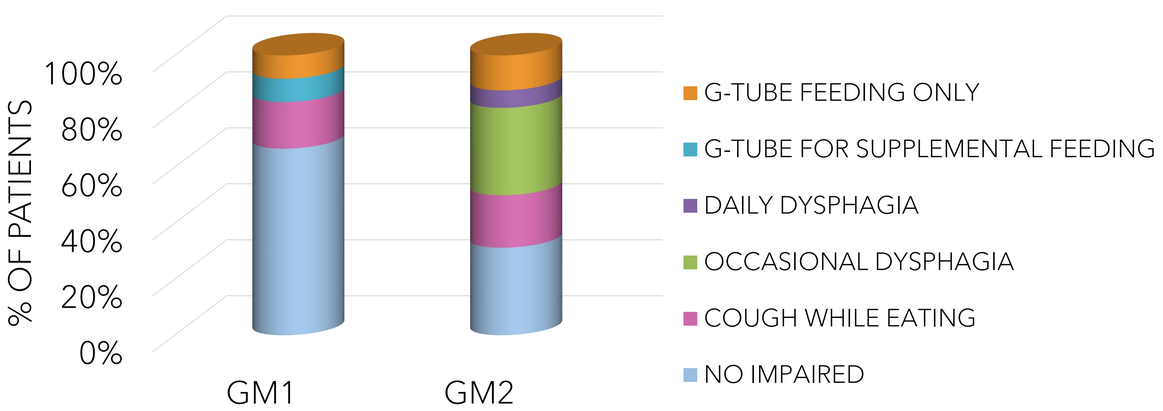
At study entry, similar impairments in ataxic manifestations were observed in the two GM1 and GM2 groups, measured by the mean SARA score of the kinetic, walking, posture and language tasks.





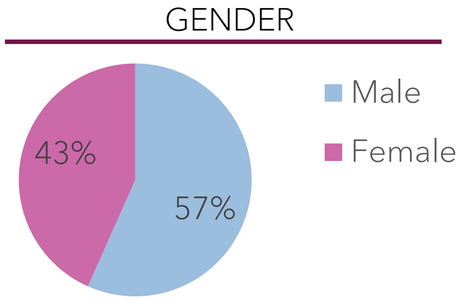
Swallowing

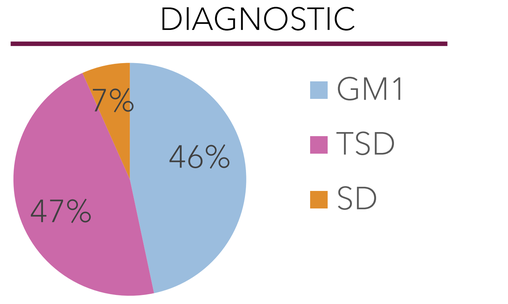
Swallowing disorders were reported more frequently in GM2 than GM1 patients, and only GM2 patients reported episodes of dysphagia. Gastric tube use was, however, reported in similar proportions between GM1 and GM2.

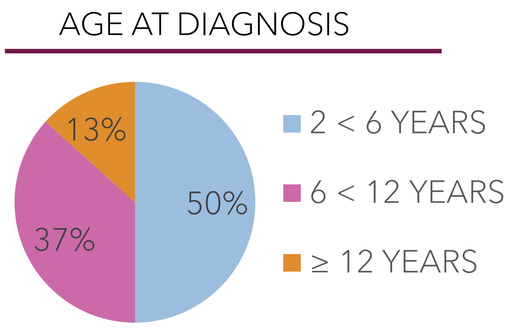


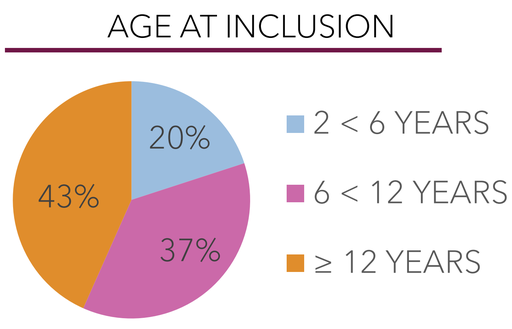
Demographic Data

PRONTO is ongoing in **6** countries, with **30** patients included: **14** GM1 and **16** GM2.



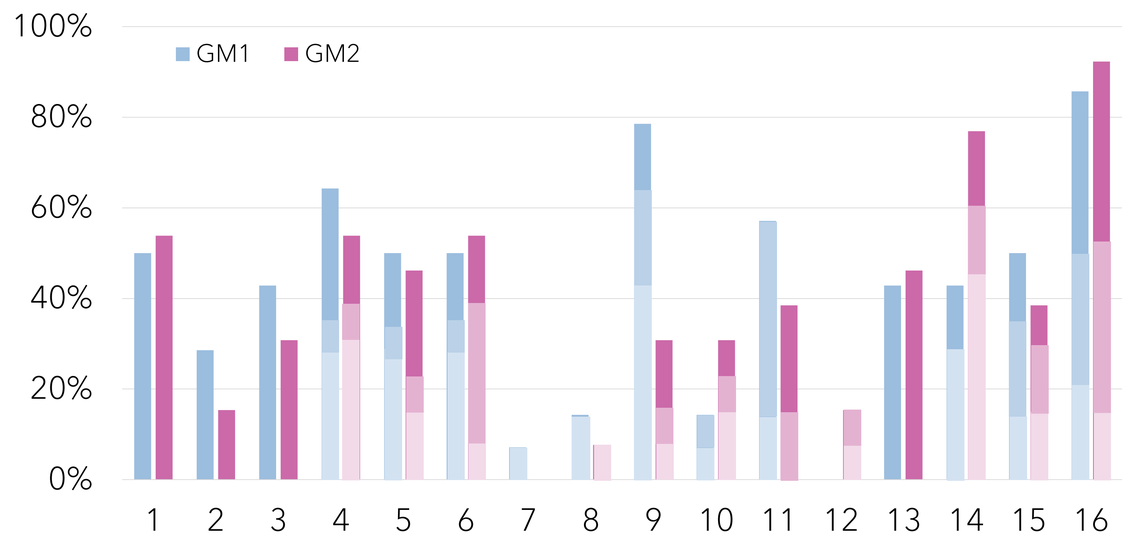






INAS

Among the symptoms reported, cognitive impairment was the most frequent in both pathologies (86% vs. 92% GM1 vs. GM2). Rigidity was more frequent in GM1 patients (79% vs. 31%) and dysphagia in GM2 patients (77% vs. 43%). Fasciculations were reported only in GM1 patients, and tremors at rest only in GM2 patients.



1: HYPERREFLEXIA; **2**: AREFLEXIA; **3**: PLANTAR REFLEX; **4**: SPASTICITY; **5**: PARESIS; **6**: MUSCULAR ATROPHY; **7**: FASCICULATIONS; **8**: MYOCLONUS; **9**: RIGIDITY; **10**: CHOREA/DYSKINESIA; **11**: DYSTONIA; **12**: RESTING TREMOR; **13**: BRAINSTEM OCULOMOTOR SIGNS; **14**: DYSPHAGIA; **15**: URINARY DYSFUCTION; **16**: CONGITIVE DYSFUNCTION;

THE DARKER →MORE SEVERE; **1,2,3 & 13** ONLY REPORTED PRESENCE/ABSENCE

Conclusion

The population recruited in this study shows the heterogeneity of the neurological dysfunctions usually observed in patients with gangliosidosis.

GM1 and GM2 patients showed similar SARA scores and similar INAS cognitive deficit scores at baseline. Dysphagia was more frequently observed in GM2 patients, while GM1 patients are also requiring the gastric tube. As dysphagia is one of the main causes of mortality in neurodegenerative diseases, monitoring its evolution in parallel with other neurological signs in the PRONTO study will enable the identification of better disease assessment criteria for improved follow-up of these patients.

SARA: Scale for the Assessment and Rating of Ataxia; INAS: Inventory of Non-Ataxic Signs; MFM-32: Motor Function Measure; TUG: Time Up and Go; VABS: Vineland Adaptative Behavioral Scales; BSFC: Burden Scale for Caregivers; G-tube: Gastric tube

A NATURAL HISTORY STUDY IN GANGLIOSIDOSES (PRONTO). EVALUATION OF DIFFERENT ASSESSMENT' SCALES

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Study design

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CAREGIVERS

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PASSIVE MONITORING

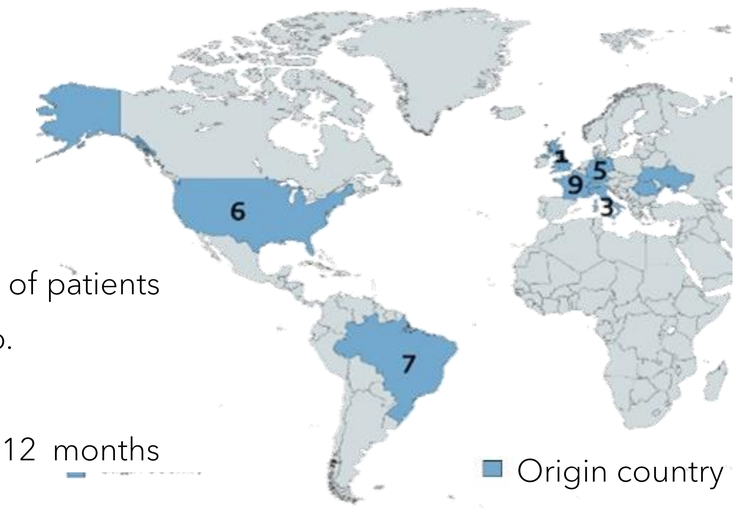
Actigraphy: PhysIQ

Recruitment

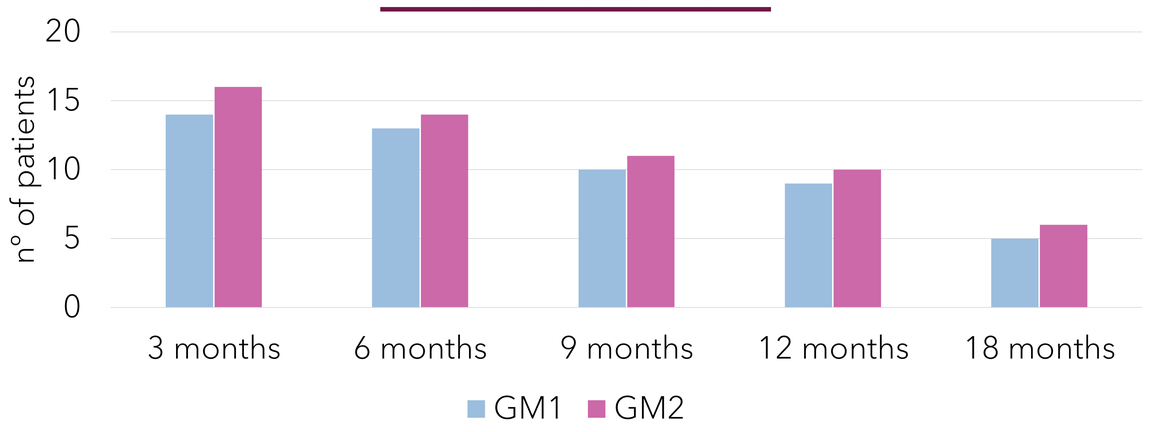
PRONTO is ongoing in **6** countries, with **30** patients included: **14** GM1 and **16** GM2.

In February'24 more than 60% of patients will achieve a year of follow-up.

One patient withdraws after 12 months of study.

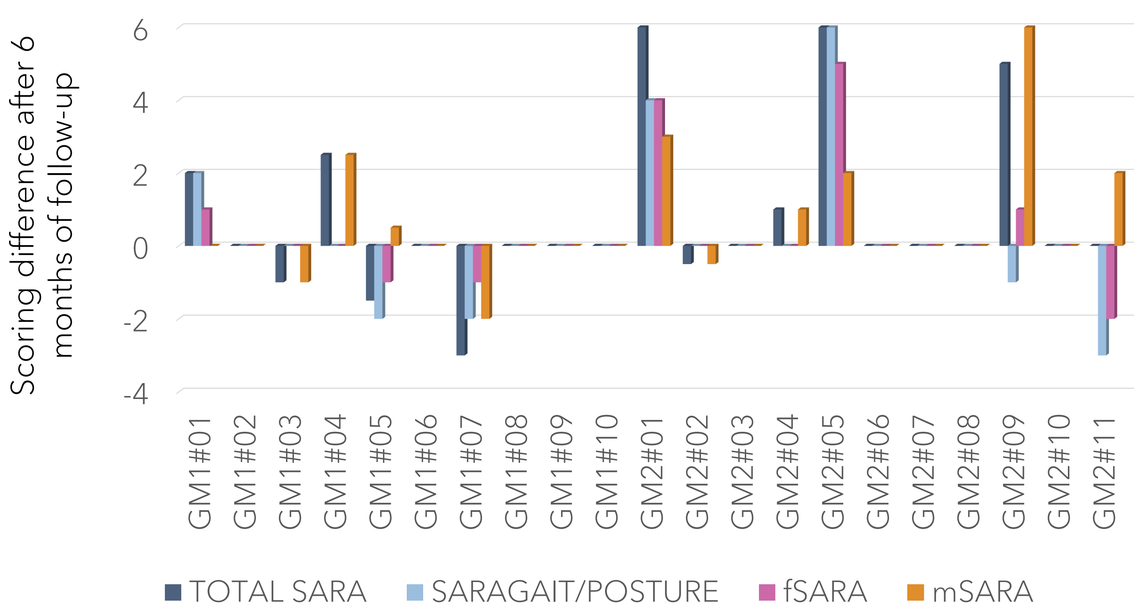


PATIENTS FOLLOW-UP

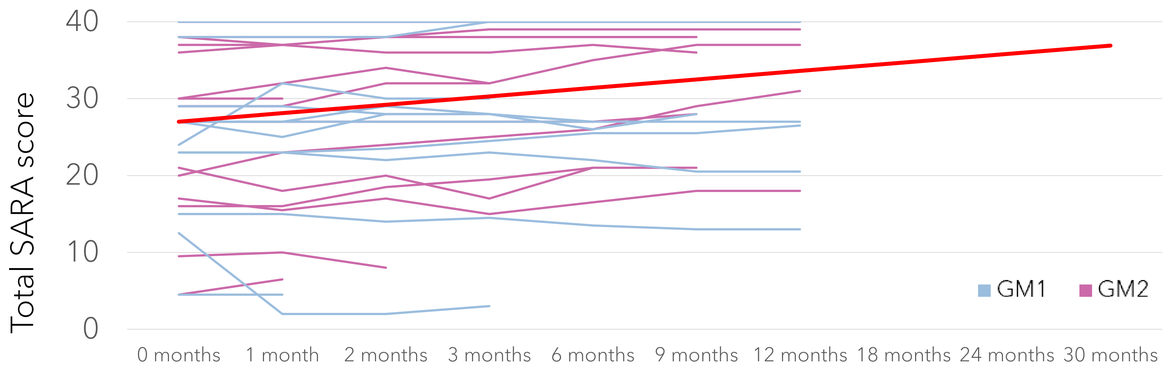


SARA assessment: different approaches

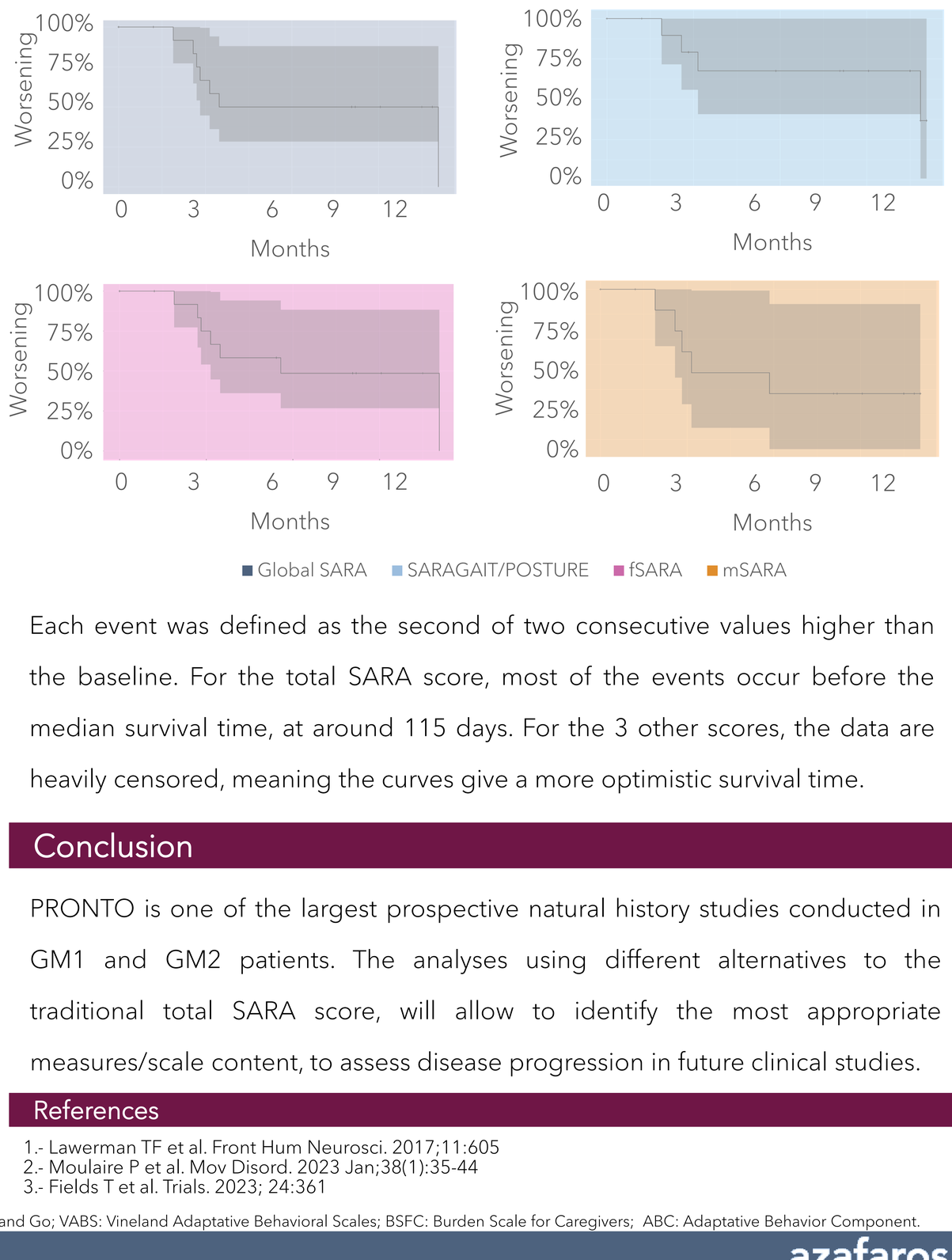
The Total SARA includes 8 domains with accumulative scoring ranging from 0 to 40. The subscore $SARA_{GAIT/POSTURE}$[1] assesses only the gross motor function (excludes speech and kinetics). Functional SARA[2] (fSARA), used by Biohaven on clinical trials after discussion with the FDA, excludes the kinetics evaluation, and all the scores are normalized between 0 and 4, and the modified SARA[3] (mSARA) used by IntraBio assesses all the domains except Sitting and Stance.



A predictive model using Total SARA score, shows a classical linear regression, with a slope of 0.284.



EVENT DRIVEN ANALYSIS (16 patients)



Each event was defined as the second of two consecutive values higher than the baseline. For the total SARA score, most of the events occur before the median survival time, at around 115 days. For the 3 other scores, the data are heavily censored, meaning the curves give a more optimistic survival time.

Conclusion

PRONTO is one of the largest prospective natural history studies conducted in GM1 and GM2 patients. The analyses using different alternatives to the traditional total SARA score, will allow to identify the most appropriate measures/scale content, to assess disease progression in future clinical studies.

References

1.- Lawerman TF et al. Front Hum Neurosci. 2017;11:605
2.- Moulaire P et al. Mov Disord. 2023 Jan;38(1):35-44
3.- Fields T et al. Trials. 2023; 24:361

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A NATURAL HISTORY STUDY IN GANGLIOSIDOSES (PRONTO). PATIENTS AND CAREGIVERS' ASSESSMENTS

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Study design: Inclusion / Exclusion criteria

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- Any treatment that can interfere with the natural progression of the disease

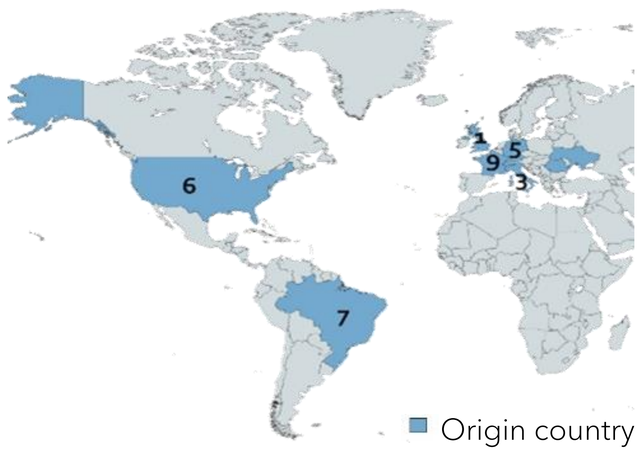
Study design: Assessments

CAREGIVERS
VABS, BSFC,
Patient diary

PASSIVE
Actigraphy: PhysIQ

CLINICIANS
SARA, INAS,
MFM-32, TUG,
Swallowing

Study design: Recruitment



6 countries

14 sites activated

12 sites recruiting

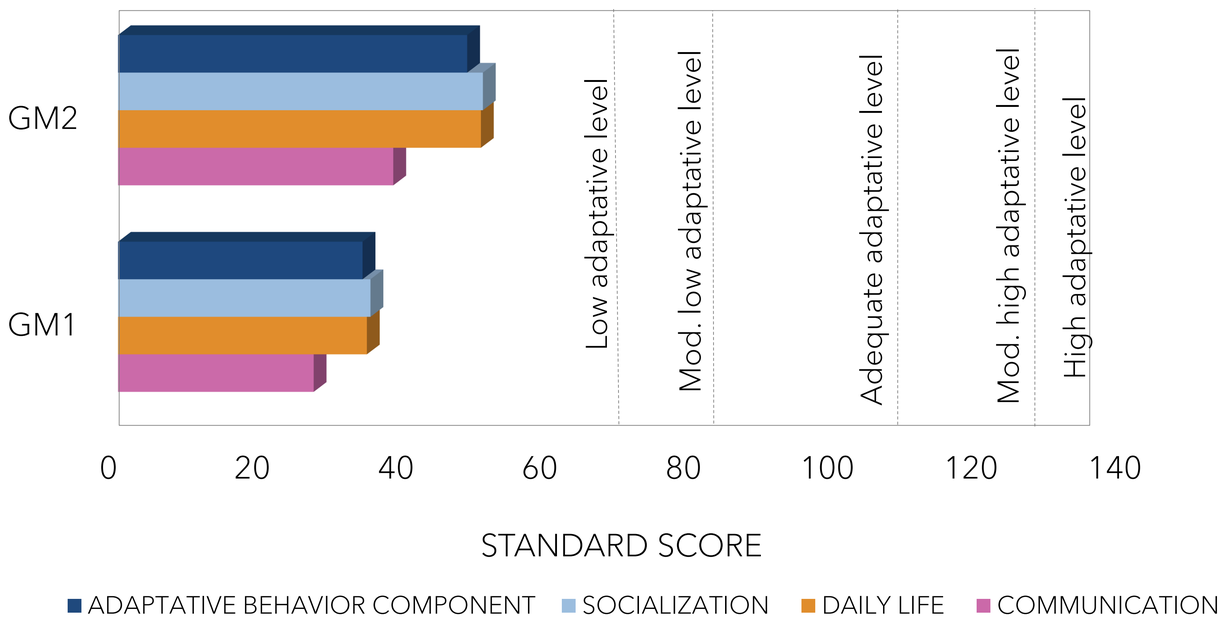
30 recruited patients:

14 GM1

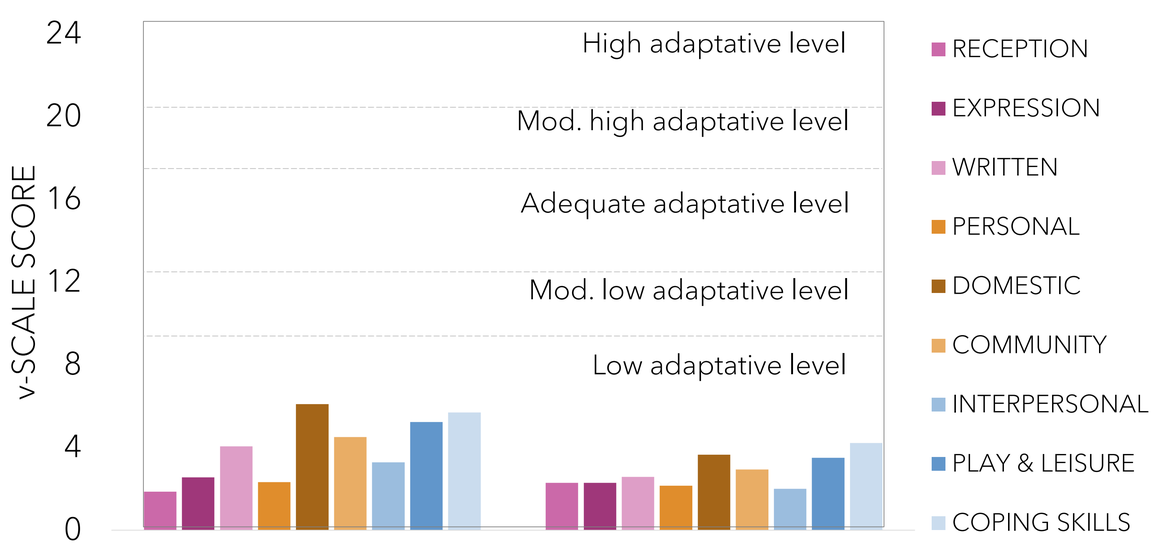
16 GM2

Vineland Adaptative Behavioral Scale (21 patients)

At study entry, all patients scored in the lowest adaptative level for the Adaptative Behavioral Component. GM1 patients being more affected than GM2 patients in their adaptative capability.



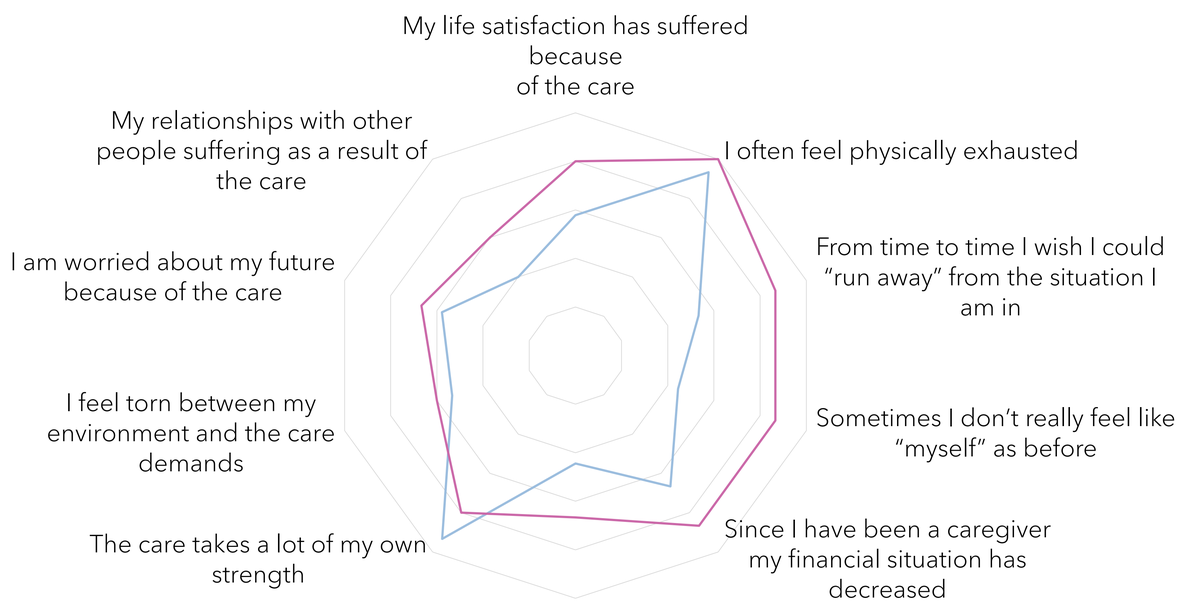
The most impaired component is the communication skill, mainly because of low scoring on the Reception subdomain which assesses the capability to attend, understand, and respond appropriately to information from others.



Burden Scale for Caregivers (15 patients)

At baseline, the higher global burden was reported by GM2 families, presenting the highest impact on the economic, mental, and physical stress.

The question with the lowest impact on the GM1 caregivers is related with the mental burden ("sometimes I don't feel like myself as before"), as well as on the GM2 caregivers ("I feel torn between my environment and the care demands")



Conclusion

Usually, the impact of diseases is measured only with the clinical evolution of the patients, but with severe chronic diseases there are very important impact on the rest of the family (caregivers, siblings,…).

This data set gives caregivers' perception of the disease and its evolution based on activities of daily living. These data are key information to understand if the changes measured with clinical scales correlate with impactful changes in patients'/caregivers' lives.

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