BMC Geriatrics

RESEARCH Open Access

Characterizing *sar*copenia and sarcopenic obesity in patients *a*ged 65 years and over, at risk of mobility disability: a multicenter *obs*ervational trial (SARA-OBS)

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Abstract

Background Aging is associated with a progressive change of body composition characterized by muscle mass decline and accumulation of adipose tissue that can lead to sarcopenia and obesity, respectively. The prevalence of sarcopenia is poorly known given the different parameters and thresholds in proposed definitions. The combination of obesity (defined as a percentage of body fat mass of > 25% in men and > 35% in women) and sarcopenia (SO) adds complexity to the characterization of this pathology. SARA-OBS aimed to better characterize sarcopenia (including SO) and its consequences on physical function over time, in community-dwelling older adults at risk of mobility disability, and to support the design of further interventional clinical trials.

Methods This was an international, multicenter, 6-month observational study of men and women aged ≥ 65 years suffering from sarcopenia according to the Foundation for the National Institute of Health (FNIH) cut-offs for Sarcopenia *and* with a Short Physical Performance Battery (SPPB) ≤ 8. The primary endpoint was the change in Gait Speed (GS) in the 400-meter walking test (400MWT), reported at baseline and at Month 6/ end of the study (EOS). Secondary endpoints included changes in handgrip strength (HGS), physical performance (6-Minute Walking Distance [6MWD], SPPB), the Physical Function Domain (PF-10) sub-score and total score of the SF-36 survey and the Sarcopenia and Quality of Life (SarQoL) questionnaire.

Results Overall, the mean (± SD) change from baseline to Month 6/EOS in 400MWT GS was − 0.027 ± 0.171 m/sec ($p = 0.064$). Both GS and 6MWD decreased significantly in subgroup with GS ≥ 0.8 m/sec at baseline (-0.047 ± 0.185 m/sec; $p = 0.017$ and − 24.01 ± 68.24 m; $p = 0.001$, respectively). In subgroup with SPPB = 8 at baseline, 6MWD also decreased (-36.80 ± 67.60 m; $p < 0.001$). We observed a significant change from baseline for 6MWD in the SO subgroup (-18.30 ± 81.95 m; $p = 0.013$). Neither HGS nor SarQoL changed significantly from baseline to Month 6/EOS.

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Conclusions SARA-OBS results contribute to defining subgroups of older adults at risk of functional decline over 6 months, specifically subjects with SPPB = 8, affecting GS and the 6MWD. Additionally, the SO subpopulation exhibited a relevant deterioration in physical function as evaluated by the 6MWD.

Trial registration NCT03021798 (ClinicalTrials.gov). Date of registration 16/01/2017.

Keywords Sarcopenia, Sarcopenic obesity, Mobility disability, Physical performance, Older adults

Background

Sarcopenia is a geriatric condition characterized by a progressive loss of muscle mass and muscle function, beginning to develop by the fifth decade and contributing to an increased risk of falls, fractures and mortality [1]. Sarcopenia prevalence increases with age and may lead to mobility disability and physical dependence of the older person.

Sarcopenia is currently estimated to affect > 50 million people in the world, increasing to > 200 million in the next 40 years [2]. Depending on the definition used, sarcopenia prevalence in 60 to 70-year-old ranges between 5 and 13%, increasing to 11 to 50% at > 80 years. According to the World Health Organization (WHO), the estimated direct healthcare cost attributable to sarcopenia in the United States (US) in 2000 was 18.5 billion US dollars [3] The economic burden of sarcopenia-associated disability is considerable in the US and the total estimated cost of hospitalizations in individuals with sarcopenia was USD $40.4 billion with an average per person cost of USD $260. The total cost of hospitalizations in individuals with sarcopenia (≥ 65 years) was USD $19.12 billion [4].

Despite the recognition of sarcopenia as a clinical syndrome with its own ICD code [5], multiple definitions from several consortia were set sequentially: in 2010, the European Working Group on Sarcopenia in Older People (EWGSOP1) consensus defined sarcopenia based on three diagnostic criteria: (i) muscle mass, as defined by an appendicular lean mass (ALM) normalized to the height squared in participants < 5.5 kg/m² in women and < 7.26 kg/m² in men; (ii) low muscle strength (LMS) as defined by hand-grip strength < 20 kg for women and < 30 kg for men; (iii) low physical performance (LPP) characterized by gait speed (GS) of < 0.8 m/s [1]. The EWGSOP revised their criteria in 2018 [6] in which LMS, considered as the most reliable measure and more effective in predicting adverse outcomes, became the primary parameter for sarcopenia diagnosis [7, 8]. In the meantime, the Foundation for the National Institute of Health (FNIH) derived LMS cut-offs from nine large-scale data sets (< 16 kg for women and < 26 kg for men) and developed a definition of Lean Muscle Mass (LMM) as ALM adjusted for body mass index (BMI), < 0.789 for men and < 0.512 for women [9]. Of note, this last definition of sarcopenia integrating BMI allowed for better evaluation of obese (sarcopenic) individuals. Sarcopenic Obesity (SO) represents a subgroup of sarcopenia characterized by the loss of muscle mass and function and a concomitant increase of fat mass. The progressively increasing population of older people with SO is at particular risk of a negative health impact such as loss of independence, disability, and increased morbidity and mortality [10]. Appropriate clinical studies associating body composition and physical function measurements are needed to better define the prevalence of SO in the aging population. Despite all efforts by different consortia/Working Groups for a consensus definition of sarcopenia [6, 11, 12], questions remain especially on thresholds to be applied for muscle mass, muscle strength and physical performance. This observational study will allow a longitudinal evaluation of the progression of these criteria overtime, thus precising their implementation in subsequent clinical trials. A duration of 6-month follow-up was chosen following recommendations on sarcopenia trials [13]. This recommendation was later confirmed [12].

This **obs**ervational study was planned to better characterize **sar**copenia, including SO, and their short-term (6 months) progression in community dwelling men and women **a**ged ≥ 65 years at risk of mobility disability (SARA-OBS). This study will allow a better definition of population and sub-population(s) in need of therapeutic intervention and refine the possible endpoints of upcoming therapeutic randomized controlled clinical trials. Characterization of the target population, evolution of parameters as well as exploratory subgroup analyses are presented.

Methods

Study design and participants

The SARA-OBS was a single-arm, 6-month observational clinical trial in non-disabled community-dwelling older patients (≥ 65 years) suffering from sarcopenia (including sarcopenic obesity) at risk of mobility disability. It was conducted in 11 centers in four countries (Belgium, France, Italy and the USA). Participants were recruited from February 2017 to October 2018. For each participant, the trial consisted of: (a) a recruitment phase to validate the eligibility criteria (up to 2 weeks); and (b) an prospective observational phase comprising two in-person visits, the inclusion and the 6-month visits, plus a phone call at month 3.

Participants needed to meet the following eligibility criteria including meeting the FNIH sarcopenia definition: (1) Men and women aged ≥ 65 years and living in the community, (2) Short Physical Performance Battery (SPPB) score ≤ 8, and (3) ALM/BMI < 0.789 in men and < 0.512 in women, or ALM < 19.75 kg in men and < 15.02 kg in women by dual energy X-ray absorptiometry (DXA) scan, based on the FNIH definition.

All concomitant medications, treatments and procedures that were deemed necessary for patient well-being were allowed, except anabolic drugs (i.e., testosterone) and corticosteroids. Menopause hormonal replacement treatment (estrogens plus progesterone) was allowed if started at least 6 months prior to trial inclusion. In addition, current dialysis, physical therapy, and rehabilitation therapy excluded participants from the trial. Further details on inclusion/exclusion criteria are available in supplementary data (Supp Table 1).

Study endpoints

The primary outcome was the change in gait speed (GS) assessed by the 400 m Walking Test (400MWT). The standard indoor course is 20 m with participants walking up to and around a cone and back 10 times at usual pace. Participants were assessed in-person in their respective research center at baseline and at 6 months/end-of-study, interspersed with a telephone interview at month 3 [14]. The need for each participant to stop and rest (yes/no) and the ability to complete the test at all (yes/no) were factored in as variables. Patients able to walk 400 m within 15 min without sitting, leaning against the wall, or assistance of another person or walker were deemed as non-disabled.

The secondary endpoints were:

- Muscle strength assessed by handgrip performance, which is measured by using a Jamar dynamometer handle (Performance Health, Warrenville, IL, USA). HGS is a commonly used measure of upper body skeletal muscle strength and has predictive validity for both mortality and functional limitation [15, 16]. Three measurements were taken for both hands and only the maximum value was kept for further analysis.
- The 6-minute walking distance test (6MWD), a test for functional exercise capacity that involves measuring the distance a participant can cover as fast as possible within 6 min. The indoor walking course was 30 m in length, with the length marked every 3 m, and the distance walked in 6 min was recorded.
- The SPPB [17], a composite measure physical performance test that assesses balance (static standing balance test), GS (4-meter walk test), and strength (5-time chair rise test). Each test is scored from 0 to 4, for a total score of 0 to 12. For the balance test, participants were instructed to maintain their feet in side-by-side, semi-tandem, and tandem positions for 10 s each. For the 4-m walking test, participant's usual speed was measured during a 4-m walk. For the 5-time chair rise test, participants were instructed to stand up and sit down five times as quickly as possible.
- The Sarcopenia and Quality of Life (SarQoL), a sarcopenia-specific, self-administered quality of life questionnaire designed for community-dwelling older patients aged 65 years and older [18]. The questionnaire consists of 22 questions encompassing 55 items, organized around 7 domains: physical and mental health; locomotion; body composition; functionality; activities of daily living; leisure activities; and fears. Each domain is scored from 0 to 100. An Overall score is also derived. The SarQoL questionnaire has been validated to discriminate sarcopenic versus non-sarcopenic participants [19, 20].
- The Short-Form 36 General Health Survey (SF-36) [21], a self-administered generic QoL questionnaire containing 36 questions, which consist of eight subscales covering the following domains: physical functioning (PF-10), bodily pain, general health, physical role functioning, vitality, emotional functioning, social role functioning and general mental health. PF-10 quantifies on a 3-level Likert scale how limited a person's physical functioning is as « a lot », « a little », or « not limited ». The PF-10 mean summary score ranges from 0 to 100 for lowest to highest functioning.

Safety assessments included the report of adverse events, Serious Adverse Events and Adverse Events of Special Interest (falls, injurious falls), using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1; Clinical examination parameters (i.e. systolic and diastolic blood pressure, pulse rate); Electrocardiogram (ECG); Haematology and biochemistry.

Medical history was ICD-10 coded (ICD10CM_FY2017_Full_XML) directly within the eCRF by sites upon data entry. Concomitant medication was coded directly within the eCRF by sites upon data entry using the WhoDrug ATC_2015_ENG dictionary.

Exploratory endpoints

Myostatin, a negative regulator of muscle growth [22], was measured from blood samples as a putative biomarker using Quantikine® ELISA GDF-8/Myostatin Immunoassay (R&D Systems).

Levels of two circulating inflammatory biomarkers, Interleukin-6 (IL-6) and high-sensitivity C-reactive

protein (hsCRP) were also assessed using MILLIPLEX® MAP technology (Millipore) and Multigent CRP Vario immunoassay on the Abbott Architect platform, respectively. These had been shown elevated in older persons and associated with poorer physical performance and disability [23–26].

Statistical analyses

Due to the exploratory nature of the study, no formal sample size calculation was performed. No corrections were made for multiplicity, so *p*-values are nominal. The number of participants enrolled in the trial was deemed appropriate to satisfy the observational goals of this study. After normality of distribution of all variables was assessed, the change from baseline to Month 6 or End of Study (EOS) visit was computed and analyzed with a paired t-test for intra-group comparison.

Results were shown for the overall included sample with available data at Month 6/EOS and were further reported for the following subgroups: female/male, 400MWT GS < 0.8 m/s and GS ≥ 0.8 m/s at baseline, SPPB score < 8 and SPPB score = 8 at baseline, SO/non SO, deterioration of lean mass as measured with DXA or not, deterioration being defined as a decrease of > 2% in the ALM or BMI value at M6 compared to the baseline value, the aim being to better characterize potential subpopulations having a different pattern of deterioration during the follow-up period. The definition of SO followed the definition of Batsis et al. [27] that integrated the cutoffs for sarcopenia by the FNIH and a percentage of body fat mass assessed by DXA scan corresponding to > 25% in men and > 35% in women. Intergroup comparisons for biomarker subgroups were performed using a t test. Statistical analyses were performed in SAS 9.4. (Cary, NC, USA).

Ethical aspects

Written approval of the protocol, the final informed consent document, relevant supporting material, and patient recruitment information were obtained from the independent ethics committees (IEC)/institutional review boards (IRB) prior to study initiation.

This study was conducted in accordance with applicable regulations, international conference on harmonization (ICH) guidelines, local legal requirements and the Declaration of Helsinki.

The study was registered in ClinicalTrials.gov (NCT03021798).

Results

Participant disposition

A total of 868 participants were screened; 637 (73.4%) were excluded as screening failures, 231 (26.6%) were included, of whom 185 (80%) completed the trial (Fig. 1). The two main reasons for screening failures ($n = 637$ [73.4%]) were body composition criterion (high ALM/BMI or ALM) at DEXA and physical performance criteria (SPPB > 8) ($n = 129$ [20.2%], 245 [38.4%] and 235 [36.9%] for SPPB > 8, high ALM/BMI or ALM, and both, respectively) (Supp Table 1). The reasons for the discontinuation of 46 participants were participant withdrawal ($n = 24$ [10.4%]), protocol deviation ($n = 5$ [2.2%]), loss to follow ($n = 4$ [1.7%]), adverse events ($n = 4$ [1.7%]), physician decision ($n = 1$ [0.4%]) and other reason ($n = 8$ [3.5%]).

Participant demographics and baseline characteristics

The mean (± SD) study duration was 6.8 ± 1.7 months. Overall, the mean age of the study population with available data ($n = 185$) was 79.2 ± 7.5 year and majority of participants were women ($n = 111$ [60.0%]). The participants had a mean BMI of 29.58 ± 6.98 kg/m², among them about 39% had a BMI ≥ 30 (threshold for obesity according to WHO guidelines) (Table 1). 78.4% (145/185 participants) of the population had SO at baseline. At baseline, 185 completing participants presented a mean (± SD) score for SPPB of 6.3 ± 1.6 and 162/185 participants presented a mean (± SD) SF-36 score of 54.9 ± 25.2. Their quality of life was assessed with SarQoL with a score of 61.9 ± 14.6 for 167 participants. Plasma myostatin was measured on 180 patients at baseline with a median (Min, Max) of 2634.55 (786.9, 7115.3) pg/ml. The inflammatory biomarkers IL-6 and hsCRP were also evaluated at baseline with median (Min, Max) of 4.12 (0.27, 171.49) pg/mL and 1.96 (0.11, 46.05) mg/L, respectively. Although these biomarkers are quite variable, the observed median values were lower than the normal value in healthy adults considered for IL-6 at a mean of 5.186 pg/ml [28] and defined for hsCRP < 3 mg/L [29]. Concomitant medication and medical history of these participants are presented in Supp Table 2 & Supp Table 3.

Primary outcome

GS at the 400MWT is summarized in Table 2. Overall, the mean (± SD) change from baseline to Month 6/EOS was − 0.027 ± 0.171 m/sec, which showed a trend towards deterioration, but was not statistically significant ($p = 0.064$).

In the subgroup with a GS ≥ 0.8 m/sec at baseline ($n = 65$ [39.9%]), a statistically significant mean (± SD) change from baseline to Month 6/EOS of GS of -0.047 ± 0.185 m/sec, ($p = 0.017$) was observed. When we considered SPPB score at baseline to distinguish the population, no significant mean change was observed in GS from baseline to Month 6/EOS in the subgroup with SPPB < 8 at baseline ($n = 115$ [70.6%]; -0.019 ± 0.188 m/sec; $p = 0.301$). Conversely, the subgroup with SPPB = 8 at baseline ($n = 48$ [29.4%]) showed a significant mean change from baseline

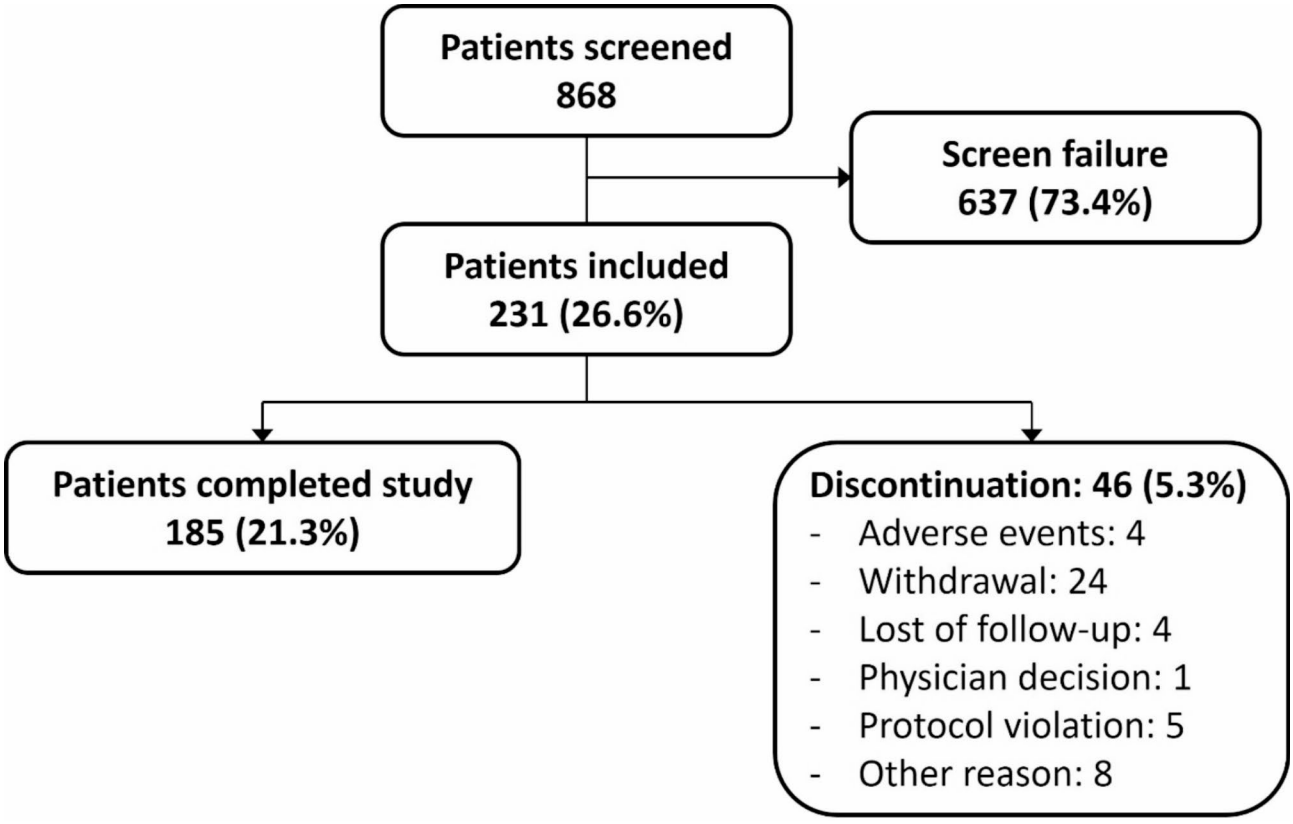

Fig. 1 Participant disposition

Table 1 Demographics and baseline characteristics

		Overall (*N* = 185)
Female	N (%)	111 (60%)
Male	N (%)	74 (40%)
Age, mean (± SD)	Years	79.2 (7.5)
Age ≥ 80 years	N (%)	88 (47.6%)
Weight, mean (± SD)	Kg	75.2 (20.8)
BMI, mean (± SD)	Kg/m^2	29.,58 (6.98)
BMI ≥ 30 kg/m^2	N (%)	73 (29.5%)
SPPB score	Mean ± SD (N)	6.6 ± 1.4 (162)
SPPB < 8	N (%)	134 (82.2%)
ALM and ALM/BMI in Female	**mean (± SD)**	14.33 (2.71) / 0.513 (0.079)
ALM and ALM/BMI in Male	**mean (± SD)**	21.51 (4.50) / 0.699 (0.094)
GS	Mean ± SD (N)	0.856 ± 0.239 m/sec (163)
GS < 0.8	N (%)	65 (39.9%)
6MWD	Mean ± SD (N, missing)	297.56 ± 93.04 m (178, 7)
HGS female	Mean ± SD (N, missing)	19.20 ± 8.17 Kg (79, 32)
HGS male	Mean ± SD (N, missing)	29.44 ± 10.92 Kg (63, 11)
IL6	Median (min – max; N)	4.12 pg/mL (0.27–171.49; 152)
hsCRP	Median (min – max; N)	1.96 mg/L (0.11–46.05; 179)
Myostatin	Median (min – max; N)	2634.55 pg/mL (786.9–7115.3; 180)

Table 2 Gait speed analysis

Gait Speed Analysis m/sec						
			Gait speed at baseline		SPPB at baseline	
		All	< 0.8 m/s	≥ 0.8 m/s	< 8	= 8
Baseline	N (missing)	163 (22)	65 (0)	98 (0)	115 (19)	48 (3)
	Mean (SD)	0.856 (0.239)	0.634 (0.119)	1.003 (0.176)	0.812 (0.247)	0.961 (0.181)
Month 6	N (missing)	154 (31)	53 (12)	91 (7)	109 (25)	45 (6)
	Mean (SD)	0.835 (0.243)	0.649 (0.147)	0.949 (0.190)	0.805 (0.252)	0.908 (0.203)
Change	N (missing)	144 (41)	53 (12)	91 (7)	102 (32)	42 (9)
	Mean (SD)	-0.027 (0.171)	0.009 (0.139)	-0.047 (0.185)	-0.019 (0.188)	-0.044 (0.121)
Paired t-test	*p*-value	0.064	0.657	**0.017**	0.301	**0.022**

Table 3 Handgrip strength analysis

Handgrip strength Test - kg							
		Gait speed at baseline < 0.8 m/s			Gait speed at baseline = > 0.8 m/s		
		Total	Female	Male	Total	Female	Male
		(N = 65)	(N = 39)	(N = 26)	(N = 98)	(N = 64)	(N = 34)
Baseline	N (missing)	64 (1)	39 (0)	25 (1)	95 (3)	63 (1)	32 (2)
	Mean (SD)	21.62 (8.01)	17.86 (6.51)	27.48 (6.51)	26.01 (10.81)	22.04 (7.55)	33.83 (12.05)
Month 6	N (missing)	63 (2)	38 (1)	25 (1)	94 (4)	62 (2)	32 (2)
	Mean (SD)	22.35 (9.32)	17.75 (4.96)	29.34 (10.09)	26.36 (9.81)	23.18 (6.96)	32.53 (11.57)
Change	N (missing)	62 (3)	38 (1)	24 (2)	91 (7)	61 (3)	30 (4)
	Mean (SD)	0.82 (6.96)	-0.21 (5.57)	2.44 (8.62)	0.002 (5.95)	0.94 (4.26)	-1.91 (8.18)
Paired t-test	*p*-value	0.361	0.817	0.179	0.997	0.090	0.212
Handgrip strength Test - kg							
		SPPB at baseline < 8			SPPB at baseline = 8		
		Total	Female	Male	Total	Female	Male
		(N = 134)	(N = 79)	(N = 55)	(N = 51)	(N = 32)	(N = 19)
Baseline	N (missing)	130 (4)	77 (2)	53 (2)	50 (1)	32 (0)	18 (1)
	Mean (SD)	23.48 (10.72)	19.62 (8.01)	29.09 (11.71)	24.42 (7.72)	20.72 (6.24)	30.99 (5.41)
Month 6	N (missing)	131 (3)	77 (2)	54 (1)	48 (3)	31 (1)	17 (2)
	Mean (SD)	24.22 (10.23)	20.25 (6.99)	29.89 (11.43)	24.84 (8.04)	21.74 (6.52)	30.49 (7.58)
Change	N (missing)	127 (7)	75 (4)	52 (3)	47 (4)	31 (1)	16 (3)
	Mean (SD)	0.63 (6.16)	0.39 (4.71)	0.97 (7.84)	0.13 (6.29)	0.87 (5.18)	-1.30 (8.02)
Paired t-test	*p*-value	0.253	0.473	0.378	0.888	0.358	0.526

to Month 6/EOS of -0.044 ± 0.121 m/sec, ($p = 0.022$). No significant change was observed when evaluating the GS according to the presence of SO at baseline ($n = 129$ [79.1%]; change in GS of -0.034 ± 0.19 m/sec; $p = 0.064$). A meaningful decline in ALM, defined as a decrease of > 2%, at M6, occurred in 50.3% of participants. In the subgroup showing a deterioration, no significant change was observed in GS from baseline to Month 6/EOS (change in GS of -0.023 ± 0.15 m/sec; $p = 0.182$) (Supp Table 4).

Secondary outcomes

Overall, no significant change from baseline to Month 6/EOS was shown in muscle strength based on handgrip performance with a mean (± SD) change of 0.493 ± 6.182 kg ($p = 0.294$) (Table 3). No changes were observed in Females and Males separately or according to GS, SPPB, or SO subgroup analyses. (Supp Table 5).

The overall mean (± SD) change of 6MWD from baseline to Month 6/EOS of -16.66 ± 76.84 m was statistically significant ($p = 0.006$) (Table 4). Similar results were observed in the subgroup with a GS ≥ 0.8 m/s at baseline ($n = 96$ [53.9%]; -24.01 ± 68.24 m; $p < 0.001$) and in the subgroup with SPPB = 8 ($n = 48$ [30.0%]; -36.80 ± 67.60 m; $p < 0.001$) but not in the GS or SPPB subgroup analyses. However, a significant change was observed in the subgroup with SO ($n = 140$ [78.7%]; -18.30 ± 81.95 m; $p = 0.013$) unlike the group without SO (Supp Table 6).

The overall mean (± SD) change from baseline to Month 6/EOS of the SF-36 questionnaire was − 0.07 ± 23.54 points, which was not statistically significant ($p = 0.972$). This was consistent in all the subgroups analyzed (data not shown).

Overall, the mean (± SD) change from baseline to Month 6/EOS in SarQoL was 0.9 ± 10.1 points ($p = 0.261$). The SarQoL mean (± SD) change from baseline to

Table 4 6-Minute walk distance analysis

Six-Minute Walking Distance (6MWD) - meters						
			Gait speed at baseline		**SPPB at baseline**	
		All	**< 0.8 m/s**	**≥ 0.8 m/s**	**< 8**	**= 8**
Baseline	N (missing)	178 (7)	65 (0)	96 (2)	130 (4)	48 (3)
	Mean (SD)	297.56 (93.04)	237.32 (61.71)	357.90 (64.63)	280.16 (94.55)	344.68 (70.41)
Month 6	N (missing)	169 (16)	60 (5)	95 (3)	122 (12)	47 (4)
	Mean (SD)	284.84 (98.72)	228.74 (78.99)	331.84 (84.44)	274.54 (99.75)	311.59 (91.71)
Change	N (missing)	165 (20)	60 (5)	93 (5)	121 (13)	44 (7)
	Mean (SD)	-16.66 (76.84)	-8.01 (86.48)	-24.00 (68.24)	-9.33 (78.93)	-36.80 (67.60)
Paired t-test	*p*-value	**0.006**	0.476	**0.001**	0.196	**< 0.001**

Table 5 SarQoL analysis

SarQoL - points						
			Gait speed at baseline		**SPPB at baseline**	
		All	**< 0.8 m/s**	**≥ 0.8 m/s**	**< 8**	**= 8**
Baseline	N (missing)	167 (18)	57 (8)	89 (9)	119 (15)	48 (3)
	Mean (SD)	61.90 (14.60)	55.73 (11.99)	68.60 (13.37)	58.86 (13.78)	69.45 (13.92)
Month 6	N (missing)	175 (10)	60 (5)	95 (3)	126 (8)	49 (2)
	Mean (SD)	63.67 (16.08)	59.01 (15.16)	69.54 (15.08)	60.94 (15.47)	70.68 (15.65)
Change	N (missing)	161 (24)	54 (11)	88 (10)	114 (20)	47 (4)
	Mean (SD)	0.90 (10.13)	2.90 (11.04)	0.34 (9.78)	0.85 (9.96)	1.03 (10.64)
Paired t-test	*p*-value	0.261	0.059	0.746	0.366	0.509

Month 6/EOS in the subgroup with a GS < 0.8 m/s at baseline ($n = 57$ [39.0%]) was 2.90 ± 11.04 ($p = 0.059$) and 0.34 ± 9.78 ($p = 0.746$) in the group with a GS ≥ 0.8 m/s ($n = 89$ [61.0%]) (Table 5). Considering SPPB score at baseline (Table 5) or the presence of SO (Supp Table 7) no significant SarQoL mean change from baseline was shown to Month 6/EOS. Note that there was a disproportionate number of participants in groups according to the SO status at baseline for all subgroup analyses.

Exploratory outcomes

The level of hsCRP was negatively correlated with 6MWD at baseline but not at Month 6/EOS. This was not observed with 400MWT (Supp Table 8). No correlation was shown with 400MWT and no correlation was observed for both assessments with IL-6, nor any other correlation with other clinical outcome parameters was observed.

A subgroup analysis was performed in which all patients were divided into two categories (considered as "low" and "high" level) according to the median value of the biomarker for the whole population. In this context, when the median of Myostatin blood level (2651.55 pg/mL) was used to determine the two subgroups, we observed that the group of patients with a "high" level of myostatin (> 2651.55 pg/L) had a significant reduction in the GS/400MWT change from baseline to Month 6/EOS of -0.05 ± 0.208 m/s ($p = 0.044$), but not the group with a "low" level of myostatin (-0.005 ± 0.12 m/s; $p = 0.732$). Similar results were observed for the 6MWD but not for the HGS or SarQoL (Supp Tables 8 and 10).

In the same fashion, we used the median of hsCRP at baseline (1.96 mg/L) to categorize the patients into "low" and "high" level of this biomarker. For both GS/400MWT and 6MWD, only the group with a "low" level of CRP (≤ 1.96 mg/L) showed a significant reduction with a mean ± SD; change of -0.04 ± 0.14 ($p = 0.018$) m/sec and -24.2 ± 81.2 m ($p = 0.008$), for GS/400MWT and 6MWD respectively (Supp Tables 9 and 10).

Safety evaluation

In total, 60 (32.4%) participants experienced at least one adverse event (AEs) during the trial period (Supp Table 11). Fifteen cases of fall occurred in 14 (7.6%) participants and ten (5.4%) patients experienced arthralgia, which were the most frequent AEs. A total of 23 unanticipated events that could be related to study procedures were reported. The possibility that the AE was caused by the assessment procedures was rated as not related in the majority of patients with AEs. The AE was assessed as possibly, probably, or certainly related in 3, 5 and 3 patients, respectively. Unknown relationship was assessed in 6 patients.

Eight (4.3%) participants experienced 10 serious adverse events (SAEs), including 7 of severe intensity. No participants died during the trial. The AEs of severe intensity included gastroenteritis (serious), hepatobiliary infection (serious), transaminases increased (serious), fall, laceration (serious), arthralgia, back pain (serious),

COPD (serious), dyspnea, exertional dyspnea, coronary artery occlusion, and sepsis (serious). In most participants with AEs, AEs were either recovered, recovering or recovered with sequalae, the outcome was unknown in 9 participants.

Discussion

This observational trial was designed to examine changes in physical function and mobility in older adults with sarcopenia by collecting and analyzing data on the natural evolution of their physical functioning and muscle strength over a 6-month period.

The included sample is from a true geriatric population (age = 79.2 ± 7.5) with gender distribution as expected (women = 60.0%) and a relatively high BMI (29.58 ± 6.98 kg/m²).

The most frequent adverse event was falls, a further recognized hallmark of an at-risk sarcopenic geriatric population.

GS at the 400MWT was chosen as primary endpoint. Gait speed slower than 1.0 m/s has been predictive of negative outcomes, like frailty, mortality, mobility limitations, falls and decreased quality of life [30, 31]. This is a continuous variable that expresses in a reliable manner the grade of residual (lower limbs) muscular function in older persons. Both GS and 6MWD decreased after 6 months in participants with GS ≥ 0.8 m/sec and SPPB = 8 at baseline. This may be due to a higher amplitude of deterioration in these better performers' subgroups, easier to detect compared to the most severe subgroups (floor effect). Interestingly, the SO subgroup showed a significant decrease in the 6MWD, close to clinically meaningful change of 20 m as defined in [31]. The association of obesity and sarcopenia could be detrimental to the deterioration rate of the gait speed, and may need a specific focus following the effect of new therapies targeting obesity showing a loss of fat mass and lean mass [32]. Conversely, HGS and SarQoL did not significantly change from baseline to Month 6/EOS in the overall population or any analyzed subgroups. These data suggested that in the study population, a subgroup of sarcopenic patients with a potential for rapid functional loss could be identified and corresponds to those individuals with a "residual" functional reserve. These findings may help to better characterize the sarcopenic population and facilitate the design of RCT targeting the sarcopenic subjects who are most likely to benefit from an intervention.

Nevertheless, the inclusion of low GS (≤ 0.8 m/s) has recently reached a consensus among recommendations of working groups [6, 12] to define sarcopenia. Low GS has been shown to be associated with many relevant clinically important outcomes in older adults including physical disability, hospitalization, fall risk, and death [33, 31, 34], and is part of the definition of severe sarcopenia from the EWGSOP2 [6]. However, it is possible that patients with a very low function may have already reached a floor, thereby being relatively insensitive to further decline, at least in the time window of a comparative clinical trial, and thus unsuitable for testing a therapeutic intervention. The 400MWT and 6MWD were initially developed and used to assess cardiorespiratory fitness [35, 36]. The 6MWD has gained importance in the assessment of functional exercise capacity in participants with chronic respiratory disease and in many studies of older adults. The 6MWD has proved to be reliable, inexpensive, safe and easy to apply [1]. In addition, it correlates well with important outcomes including death [37, 38]. Correlation between 6MWD and 400MWT at M6 End of study was $r = 0.78$, statistically significant (p value < 0.001).

Compared to SPPB which includes a 4-meter walk test, the mean usual GS calculated from completion time is less prone to variability and to ceiling effects in older adults [30, 39]. Results from this observational study suggest that a more severe subgroup of sarcopenic population, at risk of mobility disability, can be selected using the threshold of SPPB ≤ 8. The latter point was the main difference from other previous studies like LIFE [40] and its preparatory trial LIFE-P [41] or SPRINTT [42], which had a SPPB threshold ≤ 9. These studies compared a structured physical intervention arm with health education and showed an increased risk of mobility disability when sarcopenic participants had a baseline SPPB of 8 or lower. The threshold of SPPB ≤ 8 is now part of the definition of sarcopenia [6].

HGS is a proxy measurement for overall muscle strength and a primary parameter, together with LMM, to diagnose sarcopenia in the latest EWGSOP2 [6]. The different consortia suggest a wide range of cut-offs that is confusing, given the importance of LMS in the characterization of the pathology. In our study, the population could be considered sarcopenic or not according to the definition of low grip strength (Means ± SD at baseline were 19.2 ± 8.2 kg in women and 29.4 ± 10.9 kg in men). EWGSOP2 [6] and ESCEO [12] recommended cut-off values of ≤ 27 kg and 16 kg, for men and women, respectively. This threshold was based on normative data for grip strength across the life course in men and women in the UK from 12 British studies (almost 5,000 participants, aged 4 to 90 years), the cut-off being based on T-Score of ≤-2.5 [43] but no association was shown with physical performance or higher risk of adverse outcomes. Some other groups proposed cut-off values based on association with slow measured walking speed and self- reported difficulty with mobility: Lauretani and colleagues proposed 30 kg and 19 kg in males and females, respectively [44], Sallinen and colleagues proposed 37 kg and 21 kg in males and females, respectively [45]. More recently, the SDOC group analyzed data from

more than 18,000 community-dwelling older adults [11]. Grip strength was identified as a primary discriminator from classification and regression trees (CART) and receiver operator characteristics (ROC) curves including area under the curve (AUC) were used to identify variables (and cut-off points in these variables) that best discriminated older adults with slowness (usual walking speed < 0.8 m/s) from those without. The resulting cut-off for grip strength was 35.5 kg and 20 kg in males and females, respectively. More importantly, this group showed an association between HGS variables with incident clinical outcomes of falls, self-reported mobility limitation, hip fracture, and mortality. The retrospective analysis of international datasets showed the better performance characteristics (i.e. sensitivity and specificity) of this test using the proposed cut-off compared to cut-offs proposed by FNIH (< 26 kg for men and < 16 kg for women) and EWGSOP [46]. Our data did not highlight any deterioration in HGS in the SARA-OBS population, which could be explained partly by the short follow-up period (only 6 months). Of note, we did not apply any eligibility criteria based on this parameter.

The Short Form-36 (SF-36) is one of the most widely used, validated generic measures of health-related quality of life and has been shown to discriminate between patients with different chronic conditions and between patients with different severity levels of the same disease. Low SF-36 score has been shown related to severe sarcopenia [47]. In the current study, no change from baseline to Month 6/EOS was detected, whatever the subgroup analyzed. This might be explained by the short follow-up period in this study.

SarQoL has been reported to be responsive and correlated with the change in GS [48]. During a validation study of the SarQoL, the authors reported in a cohort of 42 sarcopenic patients, a significant median change in the GS of -0.10 (IQR – 0.26; 0.14; $p = 0.032$) and a median change in SarQoL score of 5.23 (IQR – 12.46; 1.61; $p = 0.002$) during a 2-year interval.

In SARA-OBS population, SarQoL score did not significantly change over time. Similar results were observed in the subgroup of participants with a baseline GS ≥ 0.8 m/s, while they did experience a significant decline in their GS and the 6MWD. This suggests that the physical function decline was either still too early to translate into an alteration of the quality of life, the measurement instrument is not sensitive enough and/or may have ceiling effects, psychological adaptation of older persons to the very gradual decline in physical performance that is not reflected significantly in terms of QOL and/or the period of observation was too short. Another explanation could be the large difference between the sample size (up to ten times less in SO group versus no-SO group, for instance).

Recently, a study suggested a correlation between the SarQoL score and the risk level of suffering sarcopenia [49]. The cut-off between high and moderate risk of sarcopenia was set to 60 points. This is consistent with the definition of sarcopenia applied in the SARA-OBS study for the SarQol baseline values of the most vulnerable subgroups (SPPB < 8 and GS ≤ 0.8 m/s at baseline). Based on that we can understand the SARA-OBS population have a moderate risk for sarcopenia.

The identification of specific biomarkers allowing the early identification of Sarcopenia and the monitoring of this pathology overtime is still needed. In this study, no correlation was observed between biomarkers and no difference from baseline at 6-Months for assessed biomarkers. The short duration of the study may explain this result.

Myostatin has been associated with reduction in muscle mass and its mRNA expression was shown to be higher in sarcopenic population and associated with BMI [50]. In SARA-OBS study, patients with a "high" level of myostatin (based on median level at baseline) had a statistically significant reduction in the GS/400MWT change from baseline to Month 6/EOS of -0.05 ± 0.208 m/s ($p = 0.044$) unlike the group with a "low" level of myostatin (-0.005 ± 0.12 m/s; $p = 0.732$).

Association between chronic low-grade inflammation, CRP and sarcopenia remains unclear since correlation with muscle strength was shown but not with muscle mass. A high level of hsCRP was independently associated with an impairment of muscle strength, but this relationship was not observed in low muscle mass [29]. In this study, patients with a low hsCRP level showed a significant reduction with a mean ± SD change of GS (-0.04 ± 0.14 m/sec; $p = 0.018$) and 6MWT (-24.2 ± 81.2 m; $p = 0.008$). However, no significant changes were observed in HGS.

SARA-OBS will be used to define the target population, endpoints, and duration of treatment in the forthcoming pivotal clinical trials for a New Chemical Entity (NCE) in sarcopenia, with SARA-INT, a phase2b study for the evaluation of the safety and efficacy of BIO101 (20-hydroxyecdysone) in sarcopenic patients.

Study limitations

Observational by nature, the control of the daily activity and physical exercise (both prescribed or performed) was limited.

Missing data were observed in this observational study, which is unfortunately inherent to observational studies. Another limitation of this trial is related to the definition of SO, based on an observational study [27]. Since then, the ESPEN group showed the limit of this definition in a meta-analysis [51] and suggested a new consensual

definition of SO [52]. New studies will necessarily consider this new approach to SO.

Considering the importance of nutritional status in the evolution of sarcopenia, the lack of information on patients' nutritional status, as well as in the use of nutritional supplements, such as proteins, is a limitation of the study.

The observation duration of 6 months may be considered as relatively short to detect worsening of functional outcomes in a slowly progressing disease such as age-related sarcopenia. The SarcoPhAge study has brought interesting results on the long-term follow-up on 534 older participants and did not show a difference after 1 year [53] in mean HGS but rather after 5 years, even though the level of physical activity was increased [54]. Likewise, SPPB score did not evolve after 1 year of follow-up, but the GS was significantly lower after 5 years. Note that GS was measured over 4 m, a hundred time shorter than in our study.

Recently, a meta-analysis showed that prevalence of sarcopenia concerns more men than women using the EWGSOP2 criteria [55]. However, in this work, but also in general, more women are included in the studies.

Since SARA-OBS was an observational study, no prior hypothesis was set and multiple outcomes and subgroups analyses were performed without adjustment to control type I error inflation. Thus, interpretation and conclusions drawn from this study should be considered with precautions. In SARA-OBS, the non-SO participants were a very small number in some groups at Month 6/EOS, further complicating the interpretation of the findings.

Conclusion

SARA-OBS revealed a geriatric population at risk of functional decline over 6 months using relative cut-off values for GS (≥ 0.8 m/sec) in the 400MWT and/or the SPPB = 8 at baseline. Of interest, the presence of SO at baseline was associated with a significant decrease in the 6-minute walking distance. In conclusion, SARA-OBS results are an important step forward to the characterization of a population of sarcopenic subjects at high risk of functional decline within 6 months. This work will contribute to define the inclusion criteria and endpoints for an intervention study with BIO101 by targeting patients with sarcopenia including sarcopenic obesity, likely to benefit from it.

Abbreviations

400MWT	400-meter walking test
6MWD	6-minute walk distance
ALM	Appendicular lean mass
AUC	Area under the curve
BMI	Body mass index
BW	Body weight
CART	Classification and regression trees
DXA	Dual-energy x-ray absorptiometry
EOS	End of study
ESCEO	European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases
EWGSOP	European Working Group on Sarcopenia in Older People
FNIH	Foundation for the national institute of health
GS	Gait Speed
HGS	Handgrip strength
LMM	Low muscle mass
LMS	Low muscle strength
LPP	Low physical performance
PF-10	Physical functioning (10 items)
QoL	Quality of Life
ROC	Receiver operator characteristics
SaRQoL	Sarcopenia and Quality of Life
SDOC	Sarcopenia definition and outcomes consortium
SF-36	Short-Form (36 items)
SO	Sarcopenic obesity
SPPB	Short physical performance battery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05895-9.

Supplementary Material 1

Acknowledgements

The authors thank Marie-Blanche Onselaer (Soladis Clinical Studies by EFOR) for the assistance in drafting the manuscript and Dr Eleonora Poggiogalle for the assistance in data acquisition.

Author contributions

RAF and YR contributed to study concepts, study design, data acquisition and contributed revising and editing the manuscript. OB contributed to study concepts, study design, analysis, and interpretation of the data, as well as revising and editing the manuscript. MD, LMD, RAI, MM, AT, MB and MR contributed to data acquisition and contributed revising and editing the manuscript. CT contributed to acquisition, analysis, and interpretation of the data, as well as revising and editing the manuscript. RvM and JM contributed to analysis, and interpretation of the data, as well as revising and editing the manuscript. CM contributed to study concepts, study design and data acquisition. SDS contributed to study concepts, study design and contributed revising and editing the manuscript. WD contributed to study concepts, study design, acquisition, analysis, and interpretation of the data, as well as revising and editing the manuscript. SV contributed to study concepts, critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors approved the final version of the manuscript and contributed to conducting the trial.

Funding

This study was fully supported by BIOPHYTIS SA, 4 Place de Jussieu, 75252 Paris Cedex 05.
R.A.F. is partially supported by the US Department of Agriculture (USDA), under agreement No. 58-8050-9-004, by NIH Boston Claude D. Pepper Center (OAIC; 1P30AG031679). Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the USDA.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Biophytis SA.

Declarations

Ethics approval and consent to participate

This study was submitted and approved by local and central Ethics Committees in France (Comité de Protection de Personnes Sud-Ouest &

Outre-Mer IV), Belgium (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège), Italy (Comitato Etico dell'Universita SAPIENZA and dell'Universita Campus Bio-Medico Di Roma) and the US (Western Institutional Review Board-Copernicus group and Columbia University Institutional Review Board 2). We certify that this study has received approvals from the appropriate ethical committees as described above. Written informed consent were obtained from the patient or legal authorized representative.

Consent for publication
Not applicable.

Competing interests
RAF reports grant support from Lonza, Biophytis, National Institutes of Health, and USDA, scientific advisory board membership for Biophytis, Amazentis, Inside Tracker, Rejuventate Biomed, Aging in Motion, consultancies for Embion, Biophytis, Amazentis, Pfizer, Nestle, Rejuvenate Biomed.YR reports support from CHU Toulouse, University Paul Sabatier and INSERM CERPOP1295 (employee), to be a shareholder of SARQOL SPRL, a spin-off of the University of Liege, consultancy fees from Longeveron, to be a Scientific Advisory Board member to Biophytis, and have received honoraria for lectures for Pfizer.OB reports to be stakeholder of SARQOL SRL, a spin off of the University of Liege in charge of the interest of the SarQoL and reports consulting or lecture fees (in the last 5 years) from Amgen, Aptissen, Biophytis, IBSA, Mylan, Novartis, Nutricia, Orifarm, Sanofi, UCB and Viatris.CT, RVM, SV and WD are employees of Biophytis SA.JM is the President of the Scientific Advisory Board of Biophytis SA.CM and SDS are former employees of Biophytis.AT, LMD, MB, MD, MR, RAI declare that they have no competing interests.
YR reports support from CHU Toulouse, University Paul Sabatier and INSERM CERPOP1295 (employee), to be a shareholder of SARQOL SPRL, a spin-off of the University of Liege, consultancy fees from Longeveron, to be a Scientific Advisory Board member to Biophytis, and have received honoraria for lectures for Pfizer.
OB reports to be stakeholder of SARQOL SRL, a spin off of the University of Liege in charge of the interest of the SarQoL and reports consulting or lecture fees (in the last 5 years) from Amgen, Aptissen, Biophytis, IBSA, Mylan, Novartis, Nutricia, Orifarm, Sanofi, UCB and Viatris. CT, RVM, SV and WD are employees of Biophytis SA.
JM is the President of the Scientific Advisory Board of Biophytis SA.
CM and SDS are former employees of Biophytis.
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Received: 28 March 2024 / Accepted: 28 March 2025
Published online: 04 August 2025

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