Evaluation of safety and efficacy of BIO101, a new investigational drug for Sarcopenia: a double-blind, placebo controlled,randomized clinical trial.

Waly Dioh[1], Cendrine Tourette[1], Carole Margalef[1], René Lafont[12], Philippe Dupont[1], Pierre Dilda[1], Stanislas Veillet[1] , Susanna Del Signore[3] and Samuel Agus[1]

[1] Biophytis, UMPC – BC9, 4 place Jussieu, 75005 Paris, France. [2] Sorbonne Université, UPMC Univ Paris 06, Paris-Seine Biology Institut (BIOSIPE), CNRS, 75005 Paris, France. 3 Bluecompanion ltd, London, United Kingdom

Introduction

Sarconeos (BIO101), purified at 97% of 20 hydroxyecdysone (20E) from the edible *plant Stemmacantha carthamoides* has shown a true potential to improve muscle quality and function in *in vitro* and *in vivo* models. BIO101 also accelerates differentiation and enhances mitochondrial function in skeletal muscle cells.BIO101 was developed as an investigational drug for Age related Sarcopenia including sarcopenic Obesity. Sarcopenia is characterized by the loss of muscle mass and muscle strength leading to a global muscle functional impairment and physical disability. This poster is focusing on two main studies of the SARA programme. First, SARA-OBS, the ongoing observational study dedicated to characterize a sarcopenic population. Second, SARA-INT, the interventional study with the investigational drug BIO101.

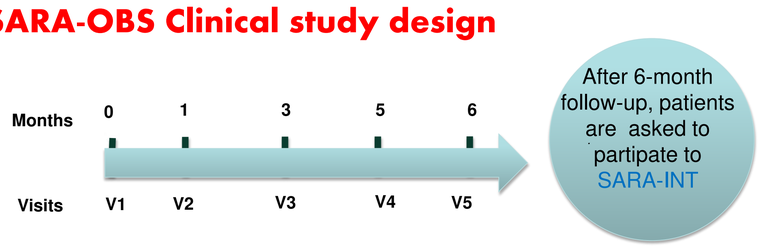
Each of SARA-OBS and SARA-INT study is a 6-month multicenter, clinical trial enrolling community-dwelling persons in Europe and USA aged 65 years and older at risk of mobility disability. The main objective of SARA-INT is to evaluate 2 selected doses of BIO101 in the targeted sarcopenic population.

SARA-OBS, the observational study

Sarcopenia definition used the criteria of the Foundation of NIH (Studenski et al., 2014) with the risk of mobility disability operationalised using the Short Physical Performance Battery (SPPB; Guralnik et al., 1994)

- Absolute ALM (< 19.75 in men and < 15.02 in women) and ALM/BMI (< 0.789 in men, < 0.512 in women) measured by DXA .
- SPPB ≤ 8/12;

SARA-OBS Clinical study design



Main objective

- Characterize the target population in Europe and USA and estimate the prevalence of sarcopenia including sarcopenic obesity in the study sample.

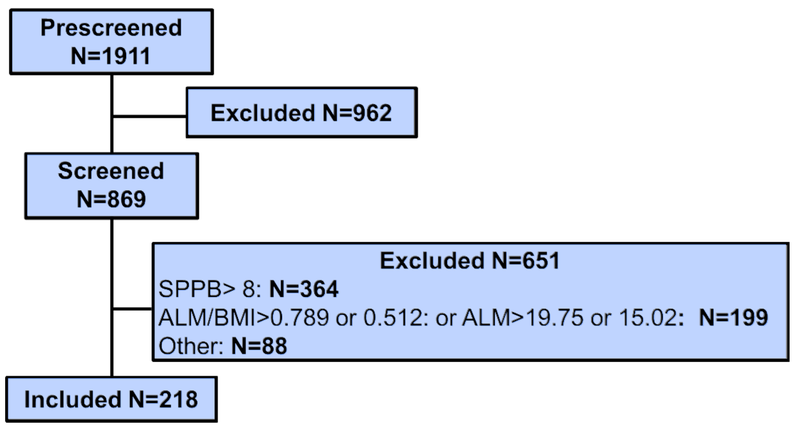
Primary endpoint:

- 400 m walking test gait speed
- Patient reported outcomes (PROs): Short Form Health Survey (SF-36) and Sarcopenia Quality of Life (SARQOL) and TSD-OC for BMI ≥ 30

Secondary and exploratory endpoints

- Body composition, Gait speed; Grip strength, 6 minutes walk.
- Actimetry; Biomarkers (Myostatin; PIIINP; IL-6; HsCRP; Aldosterone; Renin; Isolated PBMC, etc…)

SARA-OBS Workflow



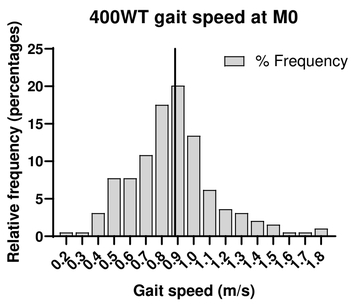
- 50 % of the prescreened patients were not retained. Main reasons were the absence of reported mobility issue and conditions included in SARA-OBS exclusion criteria list.
- Prescreening failure (Prescreened vs included) was rather high: only 11 % of prescreened were selected.
- Screening failure was high, and only 25 % of screened patients were included. Similar or even lower rates were also observed in other sarcopenia clinical trials: 5% (Fielding et al., 2017a), 11% (Fielding et al., 2017b) and 23% (Marzetti et al., 2018)
- Main reasons of screening failure are SPPB > 8 (56%), ALM/BMI > 0.789 or > 0.512 and ALM > 19.75 kg or > 15.02 kg (31%), other screening failures representing 14%.

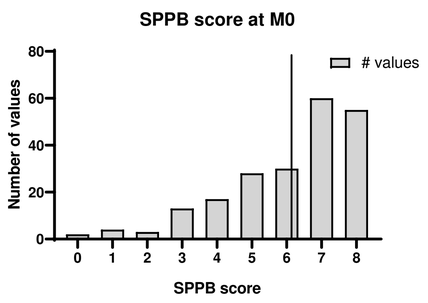
SARA-OBS Main characteristics

Baseline characteristics

Characteristics	Absolute	Standard deviation
Age	79.29	7.39
BMI	29.3	6.8
Male:Female (%)	39:61	NA
SPPB	6.12	1.83
Gait Speed in SPPB (sec)	0.70	0.29
Chair stand	1.73	0.97
Appendicular Lean Mass (ALM)	17.17	5.07
Men	21.30	4.81
Women	14.28	2.69
ALM/BMI	0.59	0.12
Men	0.69	0.10
Women	0.52	0.09
6MWD	295.14	95.99
400M (min)	8.41	3.20
Gait speed 400M (m/sec)	0.88	0.27

Characteristics		Mean	SD
SF36	Physical function (PF)	52.32	26.08
	Role, physical (RP)	42.42	34.47
	Role, emotional (RE)	68.33	29.88
	Bodily pain (BP)	62.29	25.70
	Mental health (MH)	68.88	21.82
	Vitality (VT)	56.47	21.78
	Social function (SF)	73.36	24.96
	General health (GH)	56.87	19.07
Maximum Grip strength (kg)		26.7	13,0
Men		31,6	12,8
Women		23,3	12,0



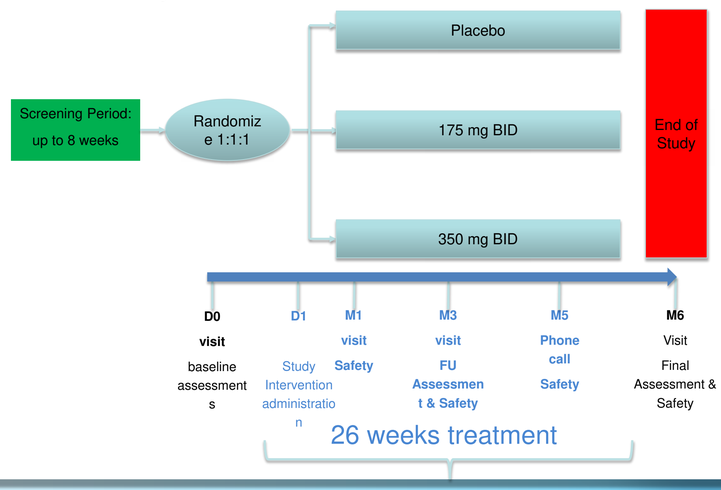


- As seen in other large sarcopenia clinical trials, patients showed high BMI allowing to incorporate sarcopenic obese patients.
- 400 m gait speed is similar to the Life study (0.83 m/s at baseline; Pahor et al., 2014).
- Mean SPPB is rather low (6.12/12), corresponding to patients at risk of mobility disability and comparable to other sarcopenia studies (Life study with 7.4±1.6 in the physical activity group, Pahor et al., 2014 and SPRINTT with 6.7±1.4, Marzetti et al., 2018).
- Gait speed SPPB is <0.8 m/s, and fits the EWGSOP definition of sarcopenia and is comparable to value in SPRINTT.
- ALM/BMI in men is lower than the FNIH threshold (0.69 vs 0.789) but is similar in women (0.52 vs 0.52).
- The 6MWD at 295.14 meters was expected for patients of the mean age (79.29 years) and BMI (29.3). This is low compared to data from sarcopenic patients (575.7±91.8 in men and 523.3±83.4 in women; Pederso-Chamizo et al., 2014) or (461.8 (108.6) in men and 392.8 (118.2) in women; (Gouvea et al., 2013).

SARA-INT

SARA-INT clinical study design

- SARA-INT is an EU and US double-blind, placebo controlled, randomized INTerventional Clinical trial.
- SARA-INT aims to evaluate safety and efficacy of Sarconeos (BIO101), the investigational drug orally administered for 6 month.
- Most of the sites that participated in SARA-OBS, and additional sites are currently being selected.
- All the patients recruited in the SARA-OBS study are ready to be randomized in the SARA-INT study.
- A pharmacokinetic sub study in Europe is also included in the SARA-INT study



SARA-INT, the interventional study

SARA-INT objectives

Primary objectives:

- Evaluate the effect of two daily doses of BIO101 versus placebo on gait speed at the 400MW test.

Key secondary objectives

- Compare the change from baseline of the Patient Reported Outcome (PRO): The Physical Function Domain (**PF-10**) of the Short Form Health Survey (SF-36).
- Rising from a chair

Other Secondary , Tertiary and Exploratory Objectives

- Body composition; Muscle strength; Stair climbing; SPPB;
- PRO (SF-36, SarQoL, TSD-OC);
- Actimetry; Biomarkers (Myostatin; PIIINP; IL-6; HsCRP; Aldosterone; Renin; Isolated PBMC, etc.…)

Target population

334 sarcopenic patients reporting loss of physical function and considered at risk of mobility disability will be recruited for the SARA-INT study.

As for SARA-OBS, the main inclusion criteria follow the Foundation of NIH (Studenski et al., 2014)

SARA-INT preliminary baseline characteristics

Characteristics	Absolute	Standard deviation
Age	79.15	5.74
BMI	28.19	7.42
Male:Female (%)	62/38	NA
SPPB	6.84	1.16
Gait Speed in SPPB (m/s)	0.76	0.18
Chair Stand Score	1.59	0.73
Chair Stand (s)	19.03	6.56
Appendicluar Mean Mass (ALM)	17.75	4.98
Men	20.26	4.47
Women	13.74	2.50

Characteristics	Absolute	Standard deviation
ALM/BMI	0.64	0.13
Men	0.71	0.08
Women	0.52	0.10
6MWD (m)	297.75	103.20
400MWT (min)	8.48	2.21
Gait Speed in 400MWT (m/s)	0.84	0.22

- As of today, 28 patients are randomized.
- About one third of randomized patients are coming form SARA-OBS clinical study
- Overall, SARA-INT population shares the same characteristics as SARA-OBS.
- Mean SPPB score and 400 m gait speed are very similar to the LIFE study (6.84 vs 7.4 and 0.84 vs 0.83 m/s respectively)
- ALM/BMI in men is lower than the FNIH threshold (0.71 vs 0.789) but is strictly similar in women.

Conclusions

- Like for other sarcopenia observational studies, SARA-OBS confirmed recruitment challenges and opportunities in sarcopenia trials when using the FNIH criteria (Studenski et al., 2014, ALM/BMI<0.789 in Men and <0.512 in Women) and Absolute ALM <19.75 kg in men and <15.02 kg in women.
- Similar to SPRINTT study, both SARA-OBS and SARA-INT select low performers at SPPB≤8/12 as an index of mobility disability risk.
- Baseline characteristics are comparable to other sarcopenia studies (Life study, Pahor et al., 2014; SPRINTT Marzetti et al., 2018).
- Preliminary analysis confirmed that target population derived from SARA-OBS is eligible for the SARA-INT phase 2 interventional study.

References

- Fielding RA, Travison TG, Kirn DR et al. Effect of Structured Physical Activity and Nutritional Supplementation on physical Function in Mobility-Limited Older ADULTS: results from the VIVE2 Randomized trial. J Nutr Healthy Aging. 2017. Online First Articles. 1-7
- Fielding RA, Guralnik JM, King AC, Pahor M, McDermott M, Tudor-Locke C, Manini TM, Glynn NW, Marsh PA, Axtell RS, Hsu Fang-Chi, Rejeski WJ, For the LIFE study group. Dose of physical activity, physical functioning and disability risk in mobility-limited older adults: Results from the LIFE study randomized trial PLOS One August 2017
- Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Maren, Fragala, MS, Kenny AM, Kiel, DP, Kritchevsky SB, Shardell MD, Dam T-T L, and Vassileva MT. The FNIH Sarcopenia Project: Rationale, Study Description, Conference Recommendations, and Final Estimates J Gerontol A Biol Sci Med Sci. 2014; 69(5): 547-558
- Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994 Mar;49(2):M85-94. PubMed PMID: 8126356.
- Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, King AC, Kritchevsky SB, Manini TM, McDermott MM, Miller ME, Newman AB, Rejeski WJ, Sink KM, Williamson JD; LIFE study investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA. 2014 Jun 18;311(23):2387-96
- R.Pederso-Chamizo R, Gomez-Cabello A, Melendez A, S. Vila-Maldonado, Espino L, Gusi N, Villa G, Casajus JA, Gonzalez-Gross M, Ara I, THE JOURNAL OF NUTRITION, HEALTH & AGING. April 18; 2014: 1-7.
- Gouveia ÉR, Maia JA, Beunen GP, Blimkie CJ, Fena EM, and Freitas DL Functional Fitness and Physical Activity of Portuguese Community-Residing Older Adults Journal of Aging and Physical Activity, 2013, 21, 1-19
- Cruz-Jentoft A et al., Sarcopenia: revised European consensus on definition and diagnosis Age and Ageing, 2018. 0: 1-16
- Marzetti E et al., The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of Eligible participants. Experimental Gerontology, 2018. 113. 48-57