# SARA-INT, A double-blind, placebo controlled, randomized clinical trial to evaluate safety and efficacy of Sarconeos (BIO101)

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## Abstract

**Backgrounds**
The SARA clinical program is built around Sarconeos (BIO101), an oral investigational new drug purified at 97% from the edible plant *Stemmacantha carthamoides*. It includes:
-SARA-PK, the phase1 study that showed safety and tolerability of BIO101 in older healthy volunteers.
-SARA-OBS, the 6-month observational study currently characterizing sarcopenia, including sarcopenic obesity.
- SARA-INT, the 6-month interventional study recently cleared by the FDA.
The SARA program is supported and hosted by SARA-Data, an innovative platform for clinical trial management.
**Objectives**
The objective of SARA-INT is to evaluate safety and efficacy of BIO101 in a randomized placebo controlled study in patients ≥ 65 years suffering from sarcopenia and considered at risk of mobility disability. SARA-INT study will estimate BIO-101 effect on improvement of physical function versus placebo in the target population. SARA-INT will also estimate BIO101 effect on decreasing the risk of mobility disability after a 6-month treatment.
**Methods**
SARA-INT will take place in 21 sites in EU and US and will consist of four main visits (baseline, Month1, Month3, and Month6).The main end-point is the gait speed at the 400-meter walking test). Key secondary end-points are the questionnaire PF-10 within SF-36 and raising from a chair at SPPB. Other endpoints include the 6-minute distance, body composition, grip strength and physical activity by actimetry. Patient Reported Outcomes (SF-36, SarQoL and TSD-OC) and biomarkers of sarcopenia will be also studied. Patients are selected based on the FNIH criteria (Studenski at al., 2014; SPPB ≤ 8 and ALM/BMI < 0.512 in women and < 0.789 in men or ALM <19.75 kg in men and <15.02 kg in women). Patients retained from SARA-OBS and newly recruited will be dosed at BIO101-175 mg b.i.d and 350 mg b.i.d during 26 weeks versus placebo.
**Results**
The rationale behind SARA-INT regulatory strategy will be discussed and the clinical design including main and secondary criteria will be presented.
**Conclusion**
SARA-INT clinical design is based on the European Medicines Agency scientific advice and FDA IND considerations.

## Introduction

Characterized by loss of muscle mass and function, sarcopenia is a key underlying cause of physical frailty, a reversible condition in older subjects, which may lead to mobility disability and dependency. Biophytis has developed the drug candidate Sarconeos (BIO101) whose active principle is 20 hydroxyecdysone (20E), purified at 97% from the edible *plant Stemmacantha carthamoides.* BIO101 has a potential to improve muscle quality and function in *in vitro* and *in vivo* models (see Poster P112).
The SARA clinical trials program, developed for Sarconeos (BIO101) on sarcopenic patients, is hosted in the SARA database and is composed of three main studies (see also Poster P110):

- SARA-INT, the interventional study that evaluates safety and efficacy of Sarconeos in older sarcopenic patients.
- SARA-PK, the Phase 1 study that showed safety and pharmacokinetic profiles of Sarconeos in elderly subjects and that allowed the selection of doses for SARA-INT. Moreover, BIO101 induced increased plasma levels of ProCollagen N Terminal type III peptide (PIIINP) and reduced plasma levels of Creatine Kinase MB (CK MB) and Myoglobin.
- SARA-OBS, the observational study that allows the characterization of population and main parameters of SARA-INT.

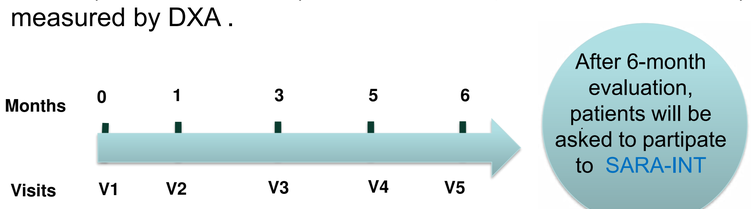
Each of SARA-OBS and SARA-INT study is a 6-month multicenter, clinical trial enrolling community-dwelling persons in Europe and USA and aged 65 years and older at risk of mobility disability across. The main objective is to evaluate 2 selected doses of BIO101 in the targeted sarcopenic population.

## Methods

### SARA-OBS Clinical study design

Sarcopenia is defined according to the criteria of the Foundation of NIH (Studenski et al., 2014); The risk of mobility disability is operationalised using the Short Physical Performance Battery (SPPB; Guralnik et al., 1994)

- SPPB ≤ 8/12; 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 .




**Main objective**

- Characterize the target population in Europe and USA.
- Estimate the prevalence of sarcopenia including sarcopenic obesity in a sample of older persons with poor physical function.

**Primary endpoint:**

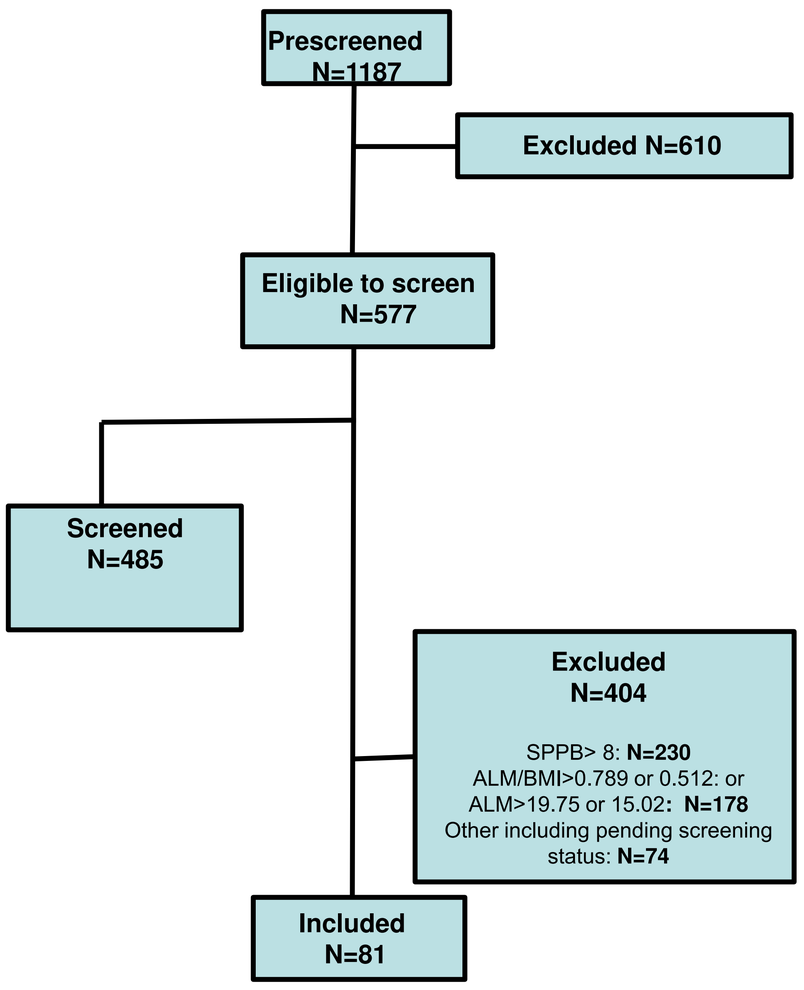
- 400 m walking test gait speed
- Patient reported outcomes (PROs): Short Form Health Survey (SF-36) and Sarcopenia Quality of Life (SARQOL) and TSD-OC for BMI ≥ 30

**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.…)

## Results

### SARA-OBS Workflow




- 59% of the prescreened patients were not retained. Main reasons were the absence of mobility issue and conditions included in SARA-OBS exclusion criteria.
- Prescreening failure (Prescreened vs included) was rather high: only 41% of prescreened were selected.
- Screening failure was high: only 17 % of screened patients were included. This rate was also observed in other sarcopenia clinical trials (Fielding et al., 2015; Fielding et al., 2017).
- Main reasons of screening failure are SPPB>8 (57%), ALM/BMI > 0.789 or > 0.512 and ALM > 19.75 kg or > 15.02 kg (40%) and other including pending screening issues

### Baseline characteristics of SARA-OBS included patients

**After an average period of 7 months post SIV, the following characteristics can be outlined**

| Characteristics | Absolute | Standard Deviation |
|---|---|---|
| Age | 78.47 | 7.87 |
| BMI | 30.10 | 7.29 |
| Male:Female | 33:48 | NA |
| SPPB | 6.46 | 1.63 |
| Gait Speed in SPPB (sec) | 0.74 | 0.18 |
| Chair stand | 1.55 | 0.77 |
| Appendicular Lean Mass (ALM) | 16.53 | 4.67 |
| Men | 19.52 | 4.96 |
| Women | 14.44 | 3.37 |
| ALM/BMI | 0.57 | 0.14 |
| Men | 0.66 | 0.16 |
| Women | 0.51 | 0.10 |
| 6MWD | 314.07 | 98.17 |
| 400M (min) | 7.10 | 3.74 |
| Gait speed 400M (m/sec) | 0.87 | 0.27 |

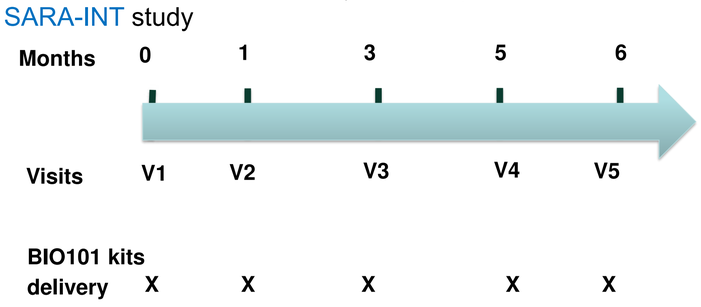
| Characteristics | Absolute | Standard Deviation |
|---|---|---|
| hsCRP (mg/L) | 5.44 | 10.20 |
| IL-6 (pg/ml) | 6.33 | 4.10 |
| Aldosterone (ng/dL) | 13.91 | 11.62 |
| Renin (pg/mL) | 30.98 | 54.73 |
| CK (U/L) | 98.38 | 73.27 |
| Creatinin (umol/L) | 80.40 | 21.95 |
| VitD25OH (nmol/L) | 81.82 | 36.85 |
| Albumine (g/L) | 41.77 | 2.38 |
| Ind Bilirubin (µmol/L) | 6.43 | 3.35 |
| LDL (mmol/L) | 2.84 | 0.92 |
| Trig (mmol/L) | 1.36 | 0.65 |
| eGFR (mL/min) | 70.69 | 28.31 |
| AlkPhos (U/L) | 79.15 | 34.40 |
| Glc Serum (mmol/L) | 5.62 | 1.04 |

- 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 (6.46/12), corresponding to patients at risk of mobility disability and comparable to other sarcopenia studies (the Life study with 7.4±1.6 in the physical activity group, Pahor et al., 2014).
- Gait speed SPPB is <0.8 m/s, and fits the EWGSOP definition of sarcopenia.
- ALM/BMI in men is lower than the FNIH threshold (0.66 vs 0.789) but is similar in women (0.51 vs 0.52)
- The 6MWD at 314.86 meters was expected for patients of the mean age (78.65 years) and BMI (30.78). 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).
- IL-6 and hsCRP plasma levels are consistent with values reported by Wyczalkowska-Tomasik et al., 2016 (hsCRP: 2.65 mg/mL) and (IL-6: 2.18 pg/mL) in elderly people (70-90 years).

## Next Steps

### 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 are currently recruiting 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




**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.
The recruitment criteria are similar to the Foundation of NIH (Studenski et al., 2014)

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

## Conclusions

- Preliminary observations in SARA-OBS confirmed recruitment 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.
- Similarly to SPRINTT study, we selected 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).
- Target population derived from SARA-OBS will be eligible to the SARA-INT phase 2 interventional study.
- SARA-INT clinical trial received all due authorisations from Competent Authorities in USA and Belgium.

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