



NEW THERAPEUTICS FOR AGING DISEASES

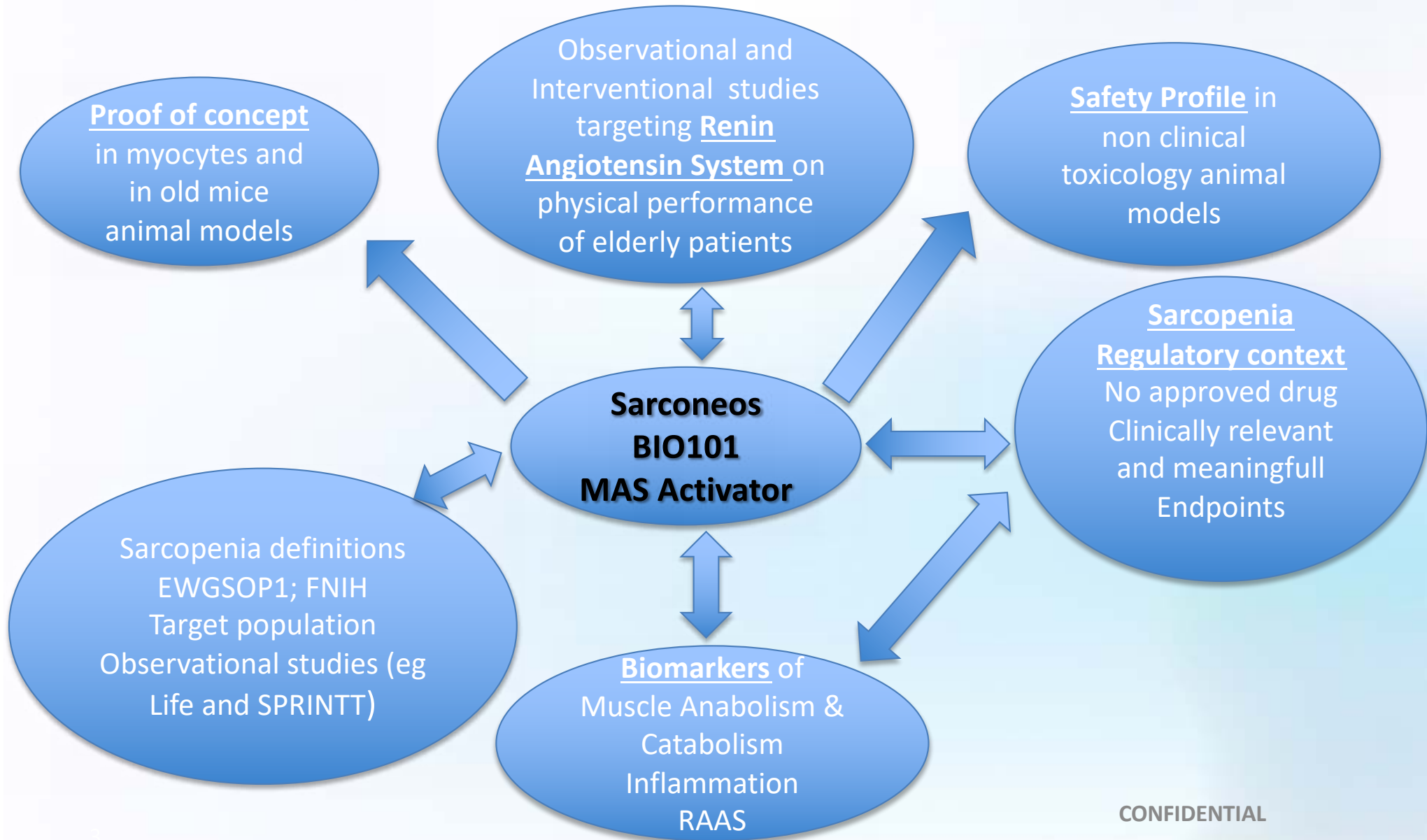
**THE BIOTECH
SPECIALIST
IN AGING DISEASES**

Designing a clinical program for BIO101, a Mas receptor activator to target Age Related Sarcopenia

**ICFSR 2019
Biophytis Lunch Industry Symposium
February 21st 2019**

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VP Clinical Development**

Building BIO101 Clinical Development Program



The SARA Clinical Program

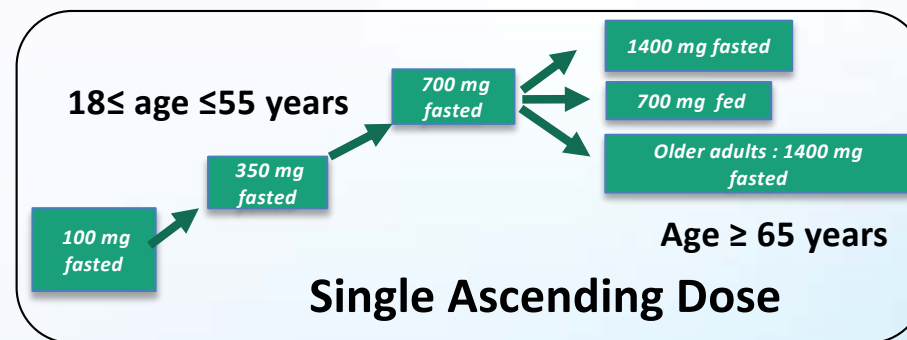
SARA: SARcopenia and sarcopenic obesity in patients Aged ≥ 65 years

SARA clinical program is based on three main studies:

- **SARA-PK**, the completed Phase 1 study that showed safety and pharmacokinetic profiles of BIO101 in older adults and allowed the selection of doses for SARA-INT.
- **SARA-OBS**, the observational study to better characterize the target population and main parameters of SARA-INT.
- **SARA-INT**, the interventional clinical trial to evaluate the safety and efficacy of BIO101 after 6-month administration in sarcopenic patients on mobility function.

SARA-PK: Phase 1 Clinical Trial

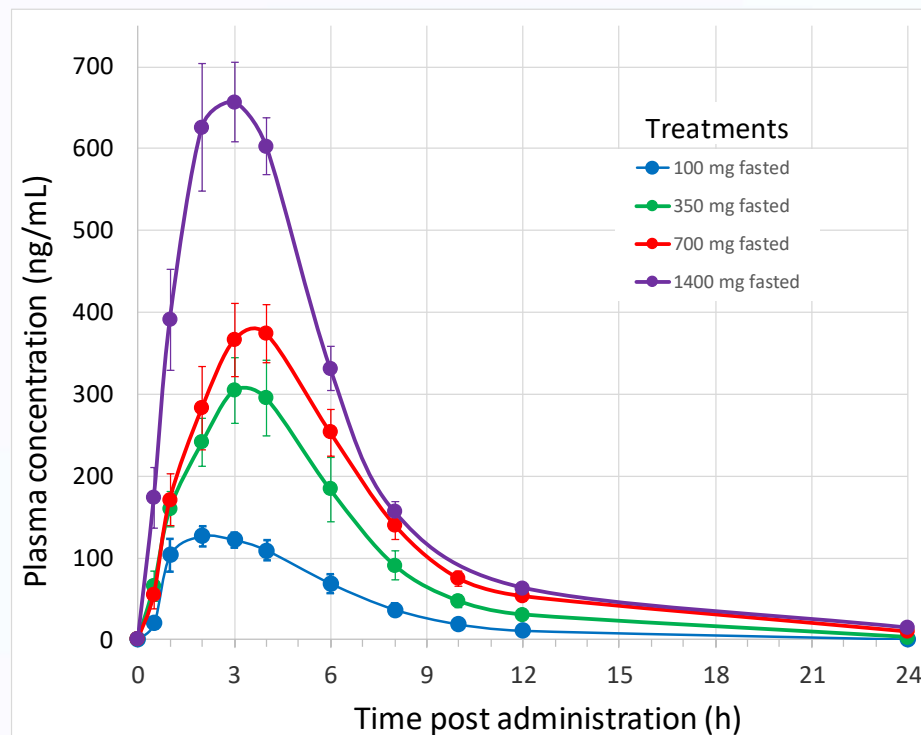
First-In-Human, Randomized, double-blind, placebo-controlled, dose-escalation



- Oral administrations of BIO101 were safe and well tolerated in SAD up to 1400 mg.
- No deaths, Serious Adverse Events or TEAEs leading to treatment discontinuation were reported.
- No abnormal clinical vital signs were reported as TEAE. No clinical laboratory parameters reported as TEAE.

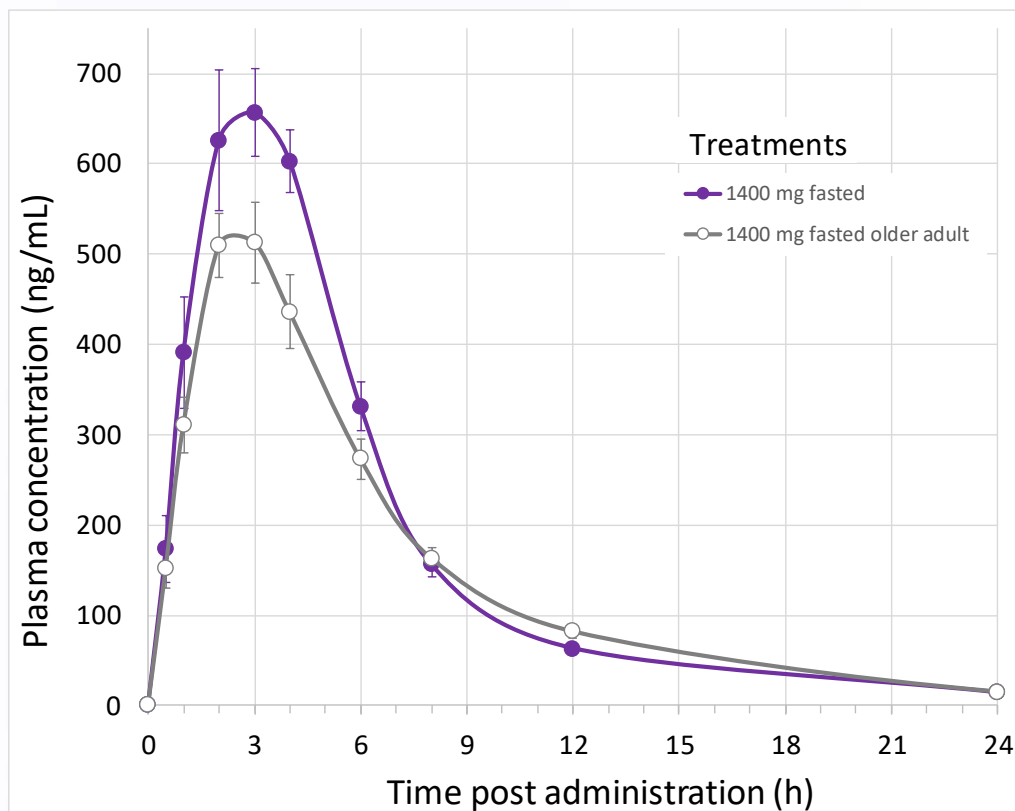
SARA-PK: Phase 1 Clinical Trial

BIO101 plasma concentration increased with the dose



- C_{\max} and AUCs increased, but less than dose-proportionally.

Single Ascending Dose Pharmacokinetics: no meaningful age effect



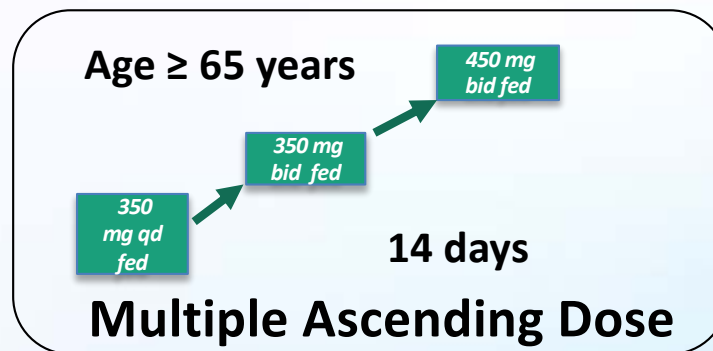
- BIO101 has similar pharmacokinetic profile in older adults vs younger adults: 22% C_{max} decrease.



- Older adults were selected in MAD.

SARA-PK: Phase 1 Clinical Trial

First-In-Human, Randomized, double-blind, placebo-controlled, dose-escalation



- Oral administrations of BIO101 in MAD from 350 mg qd up to 450 mg b.i.d.
- Slight plasma accumulation after b.i.d administrations (350 mg and 450 mg) mean R_{ac} : 1.31 in both cohorts.
- Short half-life (3-4 h) and steady-state reached on day 2 post administration.

No Serious Adverse Events

Mild or Moderate Treatment Emergent Adverse events

Phase	Dose	# of treated subjects with TEAE Type of TEAE	# of placebo subjects with TEAE
MAD 8 active and 2 placebo per dose	350 mg qd	<u>2 subjects.</u> 1 (poisoning); 1 (wound); 1 (pain in extremity)	<u>3 subjects:</u> 1 (musculoskeletal and connective tissue); 1 (nervous system disorders); 1 (skin and subcutaneous tissue disorders)
	350 mg b.i.d	<u>7 subjects .</u> 7 (gastrointestinal disorders); 2 (infections and infestation); 1 (General disorder and site administration) 4 (musculoskeletal and connective tissue); 1 (nervous system disorders); 1 (Respiratory, Thoracic and Mediastinal disorders)	
	450 mg b.i.d	<u>8 subjects :</u> 4 (gastrointestinal disorders); 2 (administration site disorders); 3 (infections : 3 (musculoskeletal and connective tissue); 5 (nervous system) : 1 (reproductive sytem and breast disorders); 2 (respiratory and thoracic disorders); 3 (skin and subcutaneous tissue)	

- Oral administration of doses of 350 mg qd, 350 mg b.i.d and 450 mg b.i.d were safe and well tolerated in 14-day MAD.
- No abnormal clinically vital signs were reported as TEAE. No laboratory parameters were reported as TEAE.
- All TEAEs were mild or moderate (3 cases in the 450 mg b.i.d from two volunteers)

Characterising SARcopenia and sarcopenic obesity in patients Aged 65 years and over, at risk of mobility disability.

An OBServational Clinical Trial (SARA-OBS)

- **Main Objectives**
- To characterise **sarcopenia, including sarcopenic obesity**, in older patients (>65 years) **living in the community and at risk of mobility disability**
- Evaluate physical performance and body composition in view of the design of a phase 2 interventional study on the efficacy and safety of BIO101
- Estimate the relative prevalence and recruitment rate in sarcopenia

Diagnosis and criteria for inclusion

Sarcopenia according to FNIH criteria and SPPB

1. Men and women aged ≥ 65 years, living in the community, and reporting loss of physical function
2. Short Physical Performance Battery (SPPB) score ≤ 8
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 DXA

Target Population:

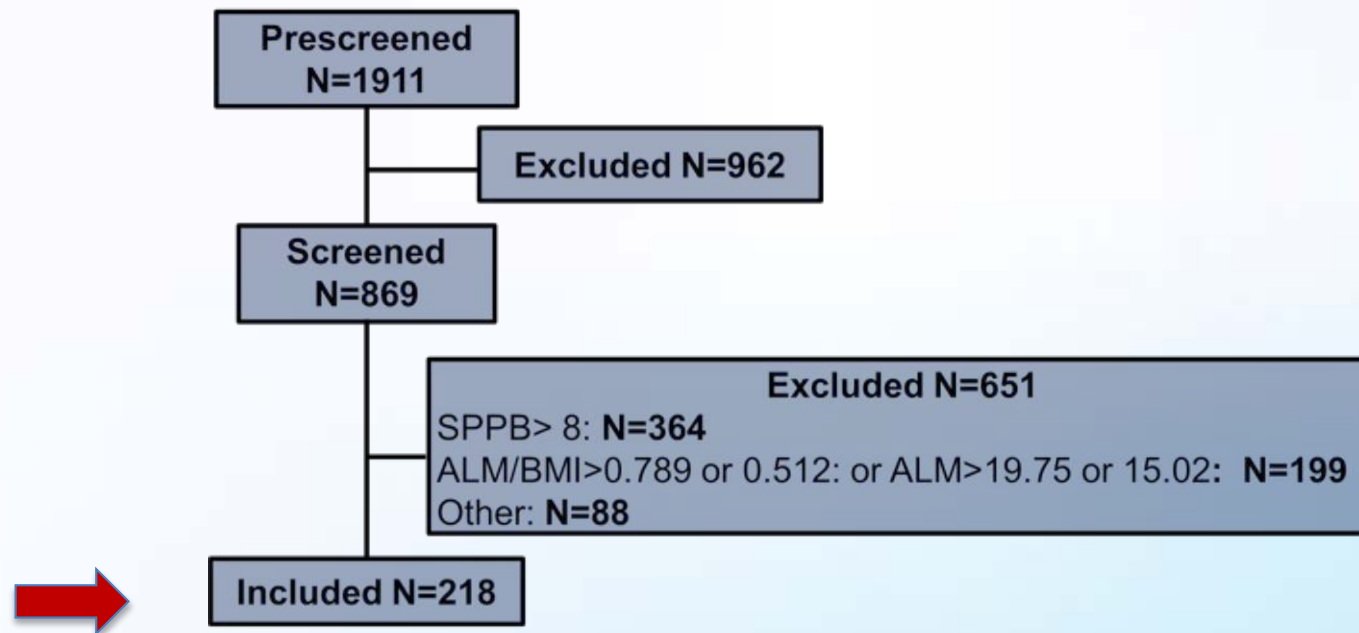
- 300 patients: community dwelling older adults (men or women ≥ 65 years) at risk of mobility disability
- 11 Clinical centers in USA, France, Belgium and Italy



SARA-OBS Endpoints

- **Primary Endpoint:** Gait speed at the 400m Walking Test (400MW).
- **Co-Primary Endpoints:** The Physical Function Domain (PF-10) of the Short Form Health Survey (SF-36).
- **Key secondary endpoint:** Raising from a chair (at the SPPB);
- **Other Secondary Endpoints:**
 - Handgrip or knee extension
 - 6 MWD
 - 400 meter Walking Test
 - Stair climbing Power Test
 - DXA
 - SPPB
 - Patient Reported Outcomes: SF36; SarQoL; TSD-OC for subjects with BMI ≥ 30
- **Exploratory Endpoints:** Myostatin; PIIINP; IL6; hsCRP; aldosteron; renin; VitD 25 (OH)D; isolated white blood cell count (WBC)/peripheral blood mononuclear cells (PBMC).
- Actimetry: Daily physical activity recording with a connected wearable device.

SARA-OBS Enrollment Status



- **50 % of the prescreened patients were not eligible for screening**
 - Absence of reported mobility issue and conditions in SARA-OBS exclusion criteria list
- **High Screening failure:**
 - Only 25 % of screened patients are included
 - Similar or lower rates observed in sarcopenia clinical trials: 23% (Marzetti et al., 2018), 5% (Fielding et al., 2017a) and 11% (Fielding et al., 2017b)
 - 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 Baseline characteristics

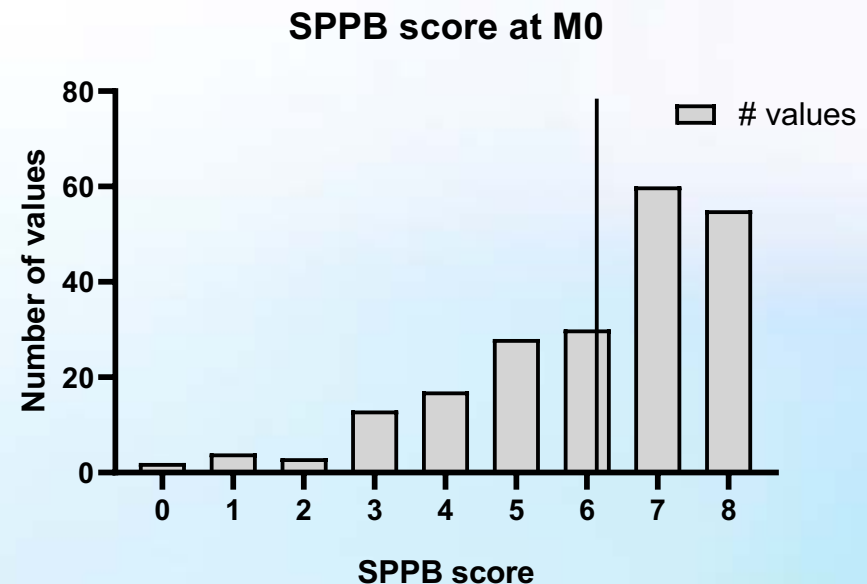
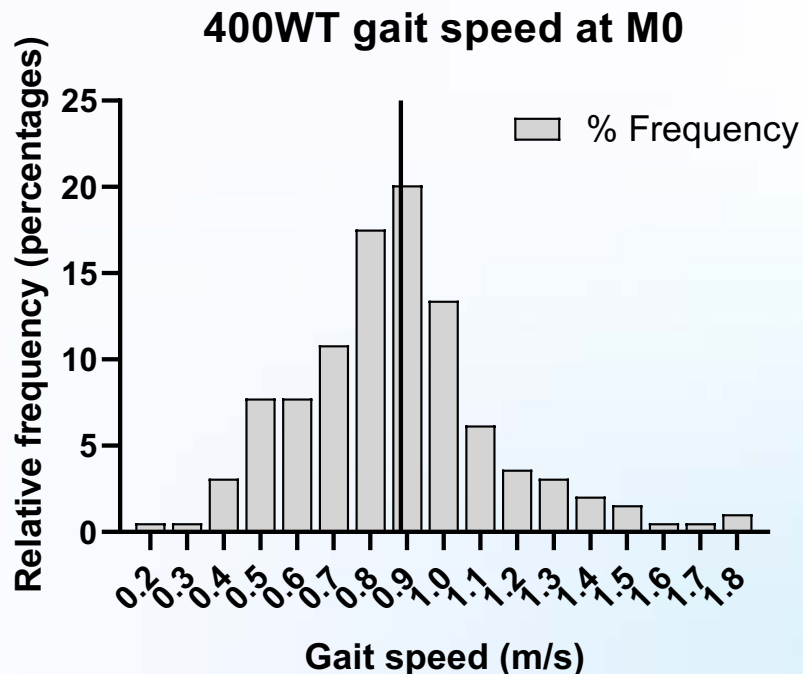
• Demographics & Body composition

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

- Average BMI is high allowing to incorporate sarcopenic obese patients.
- 61 % of recruited patients are women.
- 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).

SARA-OBS Baseline characteristics

- Walking speed and SPPB**

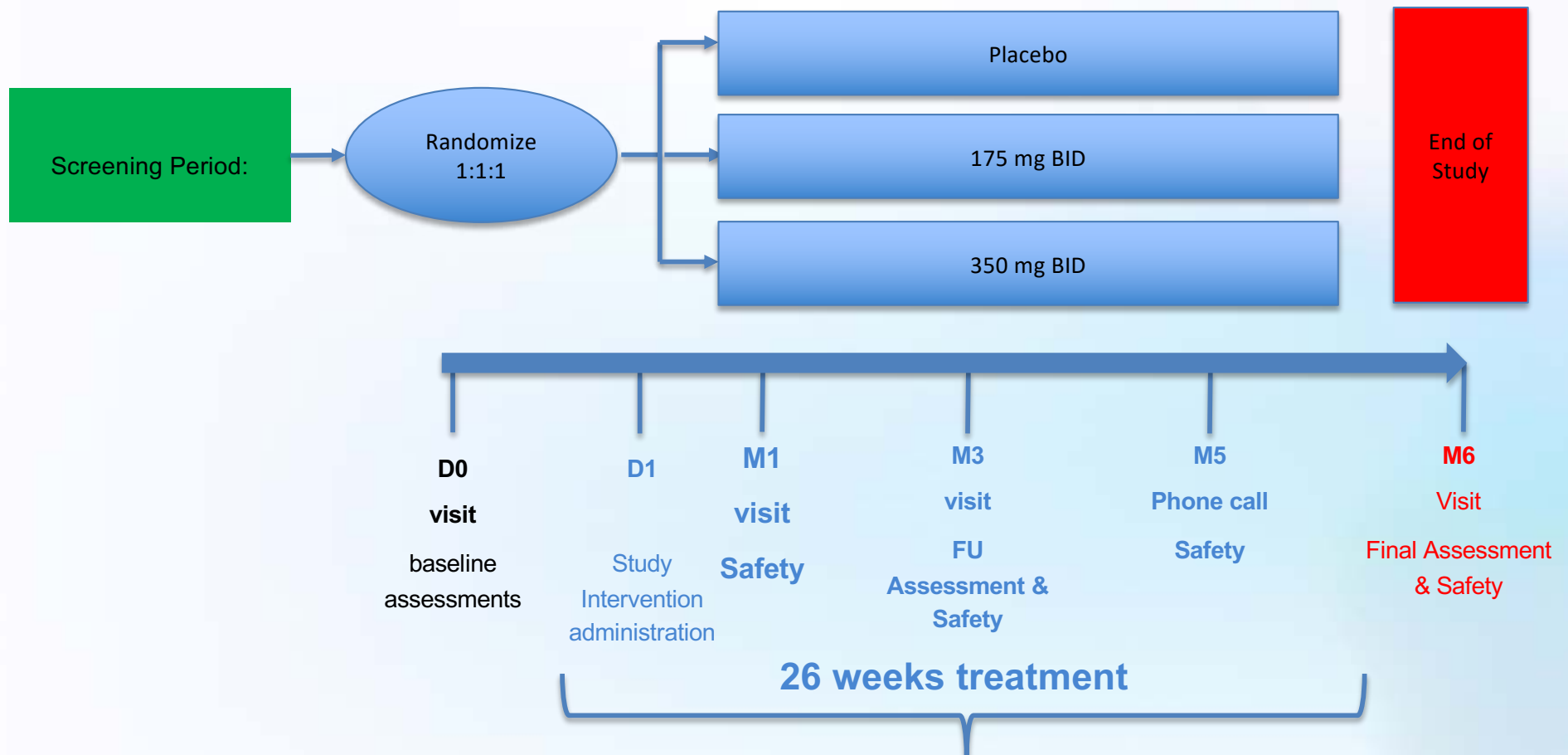


- 400 m gait speed is similar to the Life study (0.83 m/s at baseline; Pahor et al., 2014).
- Mean SPPB is low (6.12/12), corresponding to patients at risk of mobility disability and comparable to other sarcopenia studies (Life study with 7.4 ± 1.6 in the physical activity group, Pahor et al., 2014 and SPRINTT with 6.7 ± 1.4 , Marzetti et al., 2018).
- Gait speed SPPB is <0.8 m/s, fits the EWGSOP definition and is comparable to value in SPRINTT study.
- Chair stand score of 1,73 comparable to 1,4 for SPRINTT (Marzetti et al., 2018).

ONGOING SARA-INT

Safety and Efficacy of BIO-101 175 mg b.i.d. and 350 mg b.i.d. 26-week oral administration to patients suffering from age-related SARcopenia, including sarcopenic obesity, Aged ≥ 65 years and at risk of mobility disability.

A double-blind, placebo controlled, randomized INTerventional Clinical Trial.



ONGOING SARA-INT

Safety and Efficacy of BIO-101 175 mg b.i.d. and 350 mg b.i.d. 26-week oral administration to patients suffering from age-related SARcopenia, including sarcopenic obesity, Aged ≥ 65 years and at risk of mobility disability.

A double-blind, placebo controlled, randomized INTerventional Clinical Trial.

- Multicenter (US and EU), double-blind, placebo-controlled study
- Population: 334 community dwelling adults ≥ 65 years
- Inclusion criteria similar to SARA-OBS study
- Primary Endpoint: 400 meters gait speed
- Secondary Endpoints:
 - Key secondary: Raising from a chair, ePROs (PF-10 subscore of SF-36)
 - 6mn walk test
 - Stair climbing power test
 - Muscle strength & muscle mass
 - Biomarkers

Conclusions

- Baseline characteristics of SARA-OBS confirmed recruitment opportunities in sarcopenia trials when using the FNIH criteria.
- Similar to SPRINTT study, low performers at SPPB \leq 8/12 as an index of mobility disability risk were selected.
- Baseline characteristics are comparable to other sarcopenia studies (SPRINTT study and Life study, Pahor et al., 2014).
- SARA-OBS population is suitable for interventional studies in Age-Related Sarcopenia.
- SARA-INT clinical trial is ongoing with already activated USA and European sites.
- Preliminary baseline confirmed sarcopenic target population.

Biophytis Research and Development Team

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- Blaise Didry-Barca

- **Pharmaceutical Operations and Non Clinical Toxicology Team**

- Philippe Dupont
- Marie-Noelle Ly
- Hélène Nloka

Thank you

Main exclusion criteria

- Current treatment with anabolic drugs, i.e. testosterone
- Clinical conditions:
 - Current diagnosis major psychiatric disorders.
 - Alcohol abuse or dependence
 - Severe arthritis
 - Cancer requiring active treatment
 - Lung disease requiring regular use of supplemental oxygen
 - Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents
 - Severe cardiovascular disease (including New York Heart Association [NYHA] class III or IV congestive heart failure, clinically significant valvular disease, history of cardiac arrest, presence of an implantable defibrillator, or uncontrolled angina)
 - Parkinson's disease or other progressive neurological disorder
 - Renal disease requiring dialysis
 - Chest pain, severe shortness of breath, or occurrence of other safety concerns during the baseline the 6MWT, or the 400-meter walk test
- Current physical/rehabilitation therapy except for passive physical therapy.
- Current enrolment in another clinical trial
- Concomitant condition implying life expectancy ≤ 6 months
- Any other condition precluding the regular participation to the clinical trial, as judged by the Investigator.