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 (SARA-INT).

Protocol Number: BIO101-CL03

National Clinical Trial (NCT) Identified Number: NCT03452488

Phase: 2

Principal Investigator: [redacted]

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Funded by: BIOPHYTIS S.A.

Version Number: 1.2.11, FINAL VERSION

Date: 20 APRIL 2020

Summary of Changes from Previous Versions:

Affected Section(s)	Summary of Revisions Made	Rationale
3. Objectives and Endpoints	400MW gait speed became the primary endpoint (replacing 6MWD) (starting on version 1.1.1)	**European Medicines Agency Scientific Advice (June 22, 2017)**
5. Study Population	Low ALM (ALM <19.75kg in men and <15.02kg in women by DEXA scan) criterion added as an alternative sarcopenia cut-off point (starting on version 1.1.1)	**European Medicines Agency Scientific Advice (June 22, 2017)**
Protocol Template	NIH-FDA Clinical Trial Protocol Template – v1.0 7 Apr 2017 (starting on version 1.1.1)	**Updated standard**
Statement of Compliance	EU adaptation (starting on version 1.1.2)	**EU coordinator signature added**
1.1 Synopsis **2.2 Background** **5.2 Exclusion Criteria**	Adding one exclusion criterion, non-clinical safety data update (starting on version 1.2.0)	**US FDA Regulatory considerations based on non-clinical safety data (STUDY MAY PROCEED OCT 31 2017)**
1.1 Synopsis **1.3 Schedule of Activities** **4.1 Overall Design**	Adding one investigation at baseline and Month6 visit, exposure capped at 26 weeks	**Idem**
1.1 Synopsis **1.3 Schedule of Activities** **2.3.1 Known potential risks 4.1 Overall Design,** **7.1 Discontinuation of Study Intervention** **8.2 Safety and Other Assessments**	Safety: 1) Adding blood sampling for (haematology) and biochemistry at M1 and M3 visits; 2) Adding biochemistry parameters (D0, M1, M3 and M6); 3) Defining stopping rules based on ULN; 4) Adding PK sampling at M1, M3 and M6 (starting on version 1.2.2)	**Idem and FAMHP CTA NOV 28 2017**
8.1 Efficacy Assessment	Option to add grip fatigue resistance sub-test (starting on version 1.2.2)	**Clarification**
6.2.2 Formulation, Appearance, Packaging and Labeling	Modified description of the Therapeutic Unit	**Manufacturer's requirements**
1.1 Synopsis	Number of investigation centers	**Updated recruitment estimation per center**

1.3 Schedule of Activities	Adding PK sampling at baseline (D1) (starting on version 1.2.3)	**Editorial changes following FAMHP email 05 DEC 2017**
6.3 Measures to Minimize Bias: Randomization and Blinding	[redacted] will generate the randomization list and details are given on blinding of ICT staff and Sponsor staff. (starting on version 1.2.5)	**Decreasing (unintended) un-blinding risks**
8.1 Efficacy Assessment	Modified instructions and added reference to the use of the script for conducting the 400MW (starting on version 1.2.6)	**Correction and clarification of the test description**
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up	Possibility to order a blood sampling for PK analyses after a SAE (starting on version 1.2.5)	**Clarification of an implicit procedure**
8.3.6 Serious Adverse Events Reporting	Cancelled: direct reporting to the Sponsor; SAE to be reported to the CRO [redacted] (starting on version 1.2.5)	**Streamlining and simplifying of SAE reporting to a single recipient**
10.1.5 Key Roles and Study Governance	Key role added: Bioanalytics for BIO101 plasma quantification center (starting on version 1.2.6)	**Identifying the responsible party for product quantification**
10.1.5 Key Roles and Study Governance	Precision given on one of the tasks of the Adjudication Committee (starting on version 1.2.6)	**Detailing a procedure**
10.1.5 Key Roles and Study Governance	Investigators/Sites list updated (starting on version 1.2.9)	**Based on administrative status**
1.1 Synopsis 5.3. Exclusion Criteria	Exclusion criteria "Febrile Illness within 7 days" removed (starting on version 1.2.9)	**Redundancy with temporary exclusion criteria**
1.1 Synopsis 5.2 Non-inclusion criteria	Non-inclusion criteria for French subjects added (starting on version 1.2.9)	**French CPP requirement**
10.1.5 Key Roles and Study Governance	Key role added: Biostatistics for DSMB reviews (starting on version 1.2.9)	**Identifying the responsible for statistical analyses for DSMB reviews**
1.3 Schedule of Activities	Maximum delay between screening tests and randomization date added (starting on version 1.2.9)	**Clarification**
4.1. Overall design	PK Sub-Study timepoints of blood collection added	**Clarification**

	(starting on version 1.2.9)	
1.1 Synopsis **2.1 Study rationale** **5.1 Inclusion criteria**	Definition of community dwelling subjects added (updated on version 1.2.10)	**Clarification**
10.1.5 Key roles and study governance	Investigators/Sites list updated (updated on version 1.2.10)	**Based on administrative status**
10.1.6 Safety Oversight	DSMB will meet quarterly (instead of at least – semi-annually at a minimum), for safety data review (efficacy review suppressed), every 3 calendar months once the 25th patient is randomized (and not the first one) (starting on version 1.2.9)	**Clarification**
8.1 Efficacy Assessments **Stair Climb Power Test (SCPT)**	Number of steps changed from 9 to 10 with a 20 cm step height (harmonization of stair climb power test assessment with literature/study scripts) (starting on version 1.2.10)	**Clarification**
1.1 Synopsis **5.3 Exclusion Criteria**	Correction of a discrepancy of an exclusion criterion (occurrence of a safety concern during 6 MWT while the assessment is done after randomization). (starting on version 1.2.10)	**Clarification**
1.1 Synopsis **1.2 Schema** **4.1 Overall Design** **5 Study Population** **9.2 Sample Size Determination**	Change in sample size from 334 to 231 (starting on version 1.2.10)	**New statistical analysis based on SARA-OBS study population preliminary analysis**
1.1 Synopsis **3 Objectives and Endpoints** **9.4.1 General Approach** **9.4.3 Analysis of Secondary Endpoint (s)**	Removal of the chair stand sub-score of the SPPB as a key secondary endpoint (starting on version 1.2.10)	**Decreasing potential data inaccuracies since the SPPB is not assessed at baseline**
1.1 Synopsis **3 Objectives and Endpoints** **9.4.1 General Approach** **9.4.3 Analysis of Secondary Endpoint (s)**	Handgrip strength test added as a key secondary endpoint (starting on version 1.2.10)	**Based on the importance of a strength assessment**
1.1 Synopsis **3 Objectives and Endpoints** **8.1 Efficacy Assessments** **9.2 Sample Size Determination**	Change of the minimum clinically significant benefit set for the primary endpoint from gait speed of 0.05 m/s to 0.1 m/s (starting on version 1.2.10)	**Preliminary analysis of SARA-OBS study population determined a decline of 0.05 m/s at baseline vs. at month 6. This change allows an increase of up to 0.1 m/s for the expected difference between treatment groups**

1.1 Synopsis **9.2 Sample Size Determination**	Rate of non-evaluable withdrawals or lost to follow-up increased from 5 to 10% (starting on version 1.2.10)	**A larger percentage of withdrawals and lost-to-follow ups was observed in the trial so far**
1.1 Synopsis **4.1 Overall Design** **9.4.6 Planned Interim Analysis**	Interim analysis modified to a formal unblinded interim analysis design (starting on version 1.2.10)	**Based on the increase of the expected difference between treatment arms for the primary endpoint**
1.1 Synopsis **3 Objectives and Endpoints**	Safety follow-up phone call added six weeks after the end of the treatment intake (starting on version 1.2.10)	**DSMB recommendation**
8.3.8 Events of Special Interests	Orthostatic hypotension added as an AE of special interest (starting on version 1.2.10)	**New AE reported in the study that requires more vigilance**
1.1 Synopsis **5 Study Population** **9.4.7 Subgroup Analyses**	Definitions of sub-populations (starting on version 1.2.10)	**Clarification**
1.3 Synopsis	Addition of questions for diabetes (starting on version 1.2.10)	**DSMB recommendation**
2.2 Background	Rationale for the study population (starting on version 1.2.10)	**Clarification**
2.3.1 Known Potential Risks	Addition of potential risks for 20E (starting on version 1.2.10)	**Information update**
2.3.2 Known Potential Benefits	Addition of potential benefit of 20E (starting on version 1.2.10)	**Information update**
5.3 Exclusion Criteria and Temporary Exclusion Criteria **5.5 Screen Failures**	Relocation of temporary exclusion criteria (starting on version 1.2.10)	**Clarification**
8.3.5 Adverse Events Reporting	Specified the condition for AE reporting (starting on version 1.2.10)	**Clarification**
9.3 Populations for Analyses	Population analysis criteria specification (starting on version 1.2.10)	**Clarification**
5.6 Strategies for Recruitment and Retention	Addition of strategies (starting on version 1.2.10)	**Information update**
6.2.1 Acquisition and Accountability	Change of distribution company (starting on version 1.2.10)	**Information update**
1.3 Schedule of Activities **8.1 Efficacy Assessments**	Change of the timing to perform the 400MW test during screening from Day 0 to 48 hrs prior to randomization (starting on version 1.2.10)	**To provide more time for the 400 MW test to be performed**
6.5 Concomitant Therapy	Removal of the protocol deviation due to the need to use an excluded medication during the study period	**The investigator has to treat any new symptoms or AEs based on the patient's best interest and it is up to the investigator's discretion if the participant should stay in the study**
1.1 Synopsis	[redacted]	**Information update**

2.2 The Investigational Product **5.3 Exclusion Criteria and Temporary Exclusion Criteria** **6.1.1 Study Intervention Description** **6.5 Concomitant Therapy**	[redacted]	
1.1 Synopsis	Measures taken to mitigate the COVID-19 outbreak (starting on version 1.2.11)	**Base on guidance of international and national agencies and the DSMB recommendation, measures taken to ensure the safety of the participants and mitigate the risk on the scientific integrity of the study**
1.1 synopsis	Interim Analysis postponed; Increased population analyzed (starting on version 1.2.11)	**SDV not available on site due to COVID-19 restrictions. Increased population analyzed for the Interim analysis to take into account the data collected during and after the COVID-19 outbreak**
1.1 synopsis **5. Study population**	Correction to 20% for the non-evaluable withdrawals or lost to follow-up (starting on version 1.2.11)	**clarification**
1.2. Schedule of Acivity	SoA updated (starting on version 1.2.11)	**Update of schedule of activity based on the measures, measures taken to ensure the safety of the participants and mitigate the risk on the scientific integrity of the study**
2.2 Background	Addition of a 39-week toxicology study in dog (starting on version 1.2.11)	**update**
2.2 Background	Scientific rationale updated for the measures taken to mitigate (starting on version 1.2.11)	**Based on new evidences and mitigation of measures taken during the COVID-19 outbreak**
2.3.4 Assessment of potential risks during the COVID-19 pandemic	Assessment of potential risks due to COVID-19 outbreak and actions taken (starting on version 1.2.11)	**Addition du to COVID-19 outbreak**
4.1 Overall design **4.2 scientific rationale for Study Design**	Extension of the period of study intervention (starting on version 1.2.11)	**Mitigation for the scientific integrity of the study**
4.1 Overall design **9.2 sample size determination** **9.4.7 Planned interim analysis**	Postponement of the Interim Analysis (starting on version 1.2.11)	**Due to COVID-19 outbreak restrictions**

4.2 scientific rationale for Study Design	Modification of assessments (starting on version 1.2.11)	**Due to COVID-19 outbreak restrictions**
4.4 End of study definition	End of intervention updated (starting on version 1.2.11)	**clarification**
6.2.5 Shipment	Addition of IP home delivery (starting on version 1.2.11)	**Mitigation of the COVID-19 outbreak restrictions**
6.4 study intervention compliance	Addition of IP return from participants home (starting on version 1.2.11)	**Mitigation of the COVID-19 outbreak restrictions**
7.4 Participant discontinuation during the COVID-19	Addition of collection of a reason for participant discontinuation (starting on version 1.2.11)	**Record of the impact of the situation on analyses and conduct of the trial**
8.2 safety and other assessments	Modification of the safety monitoring of participants (starting on version 1.2.11)	**Mitigation of the COVID-19 outbreak restrictions**
9.4.4 impact of the COVID-19 outbreak	Updated strategy for the final statistical analysis (starting on version 1.2.11)	**Addition due to the situation restrictions**
10.1.1.1 consent and other information documents provided to participants	Letter of information and addendum to the ICF provided to participants (starting on version 1.2.11)	**Addition due to th modification of the protocol design during the outbreak**
10.1.5 Key roles & study governance	Additional role and schedule of meeting for the DSMB (starting on version 1.2.11)	**Safety surveillance during the COVID-19 outbreak**
10.1.7 Clinical monitoring	Adaptation of the monitoring (starting on version 1.2.11)	**Mitigation of the COVID-19 outbreak restrictions**
10.1.10 Protocol deviation	Addition Identification of protocol deviations (starting on version 1.2.11)	**Mitigation of the COVID-19 outbreak**

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SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: 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 **(SARA-INT)**

PROTOCOL NUMBER: BIO101-CL03

SPONSOR: Biophytis S.A.

[redacted]

20 April 2020

[redacted]

Date (day/month/year)

[redacted]

April 20, 2020

[redacted]

Date (day/month/year)

STATEMENT OF COMPLIANCE

PROTOCOL TITLE: 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 (SARA-INT).

PROTOCOL NUMBER: BIO101-CL03

SPONSOR: Biophytis S.A.

The trial will be carried out in accordance with Good Clinical Practice (GCP), latest version of the Declaration of Helsinki, the International Conference on Harmonization (ICH) E6 (R2), and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) as applicable. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs), except where necessary, to eliminate an immediate hazard to the trial participants.

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of the clinical trial will have completed ICH GCP Training.

Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator

[redacted]

[redacted]

Date (day/month/year)

European Union Coordinator & Principal Investigator

[redacted]

[redacted]

Date (day/month/year)

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: 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 (SARA-INT).

Study Description:

SARA-INT is a three-arm, interventional, phase 2, randomized, double-blind, placebo-controlled clinical trial. It will be conducted in the European Union (EU) and in the United States (US).

231 community dwelling older adults (men or women ≥ 65 years), living independently at home (homes are any living communities that may or may not offer optional services for the convenience of the residents. Older adults living in nursing homes or in medicalized residences where caretaker services are mandatory are not eligible), able to walk outside from time to time, reporting a loss of physical functions and considered at risk of mobility disability, were selected to perform the Short Physical Performance Battery[1] (SPPB) test.

Those with SPPB scores ≤ 8 were selected to perform a body composition analysis with a dual-energy X-ray absorptiometry (DEXA) scan. (DEXA scans performed no more than 8 weeks before the date of randomization will be acceptable, and in that case, should not be repeated up to the end of the study visit). Participants with appendicular lean mass (ALM) adjusted for body mass index (BMI), or ALM/BMI < 0.789 in men and < 0.512 in women, or ALM <19.75kg in men and <15.02kg in women, corresponding to the operational definition of sarcopenia based on the criteria of the Foundation of National Health Institute (FNIH)[2], were definitively included and randomized if other inclusion/exclusion criteria are also satisfied.

The study plan is divided into: a) screening and randomization phase and b) treatment and evaluation phase. The recruitment lasts approximately 24 months. The investigational phase initially comprises three main visits for measurement of drug efficacy, pharmacokinetics (when appropriate) and safety parameters: 1) the inclusion visit, 2) the 3-month evaluation and 3) the 6-month final evaluation visit. Additionally, three communications (visit and phone calls) were planned for safety measures only: 1) an on-site visit at 1-month after randomization, 2) a telephone call at 5-month after randomization, and 3) a telephone call 6 weeks post drug intervention (i.e. after M6 visit) or after the end-of-intervention visit.

The primary outcome is the change from baseline in gait speed, in meters per second (m/s), between the treatment groups versus placebo based on the 400 meters walking (400MW) test.

The Short Form Health Survey (SF-36) and two other patients reported outcomes (PROs) will be completed by the participants on inclusion day (Day 0), at the month 3 (M3) visit and the month 6 (M6) or end-of-intervention visit. The Physical Function Domain (PF-10) sub-score of the SF36 at M6 will be tested as a key secondary outcome at M6.

Additionally, the change from baseline of muscle strength measured by the handgrip strength test will be used as another key secondary outcome. Additionally, the SPPB will be evaluated at each visit and the 6 Minute Walk Test (6MWT) will also be administered during the two main visits (Day 0 and M6) and considered as part of the secondary criteria at M6.

At any time, participants complaining of meaningfully worsening of physical functions may be invited to an unscheduled visit for further assessment for consideration of their continued participation in the study.

The statistical analyses will describe the demographic and functional characteristics of the three treatment groups at baseline, and compare the evolution (change in each treatment group versus placebo group) of the primary, key secondary, secondary and exploratory endpoints. The evolutions of efficacy parameters will also be analyzed according to specific variables or class of variables, e.g. gender, age, initial SPPB score, ALM, ALM/BMI and etc, in view of identifying a subpopulation at high risk of worsening and/or to show the homogeneity of the treatment effect across subgroups.

A predefined subgroup efficacy analysis will also be performed on a number of pre-identified, at-high risk of worsening, subpopulations:

- Low gait speed
- Sarcopenic obesity
- Study participants with a chair stand sub-score of ≤2 of the SPPB
- Study participants who experience a deterioration in their ALM/BMI, as measured by the DEXA scan in the M6 visit and compared to the baseline measurement

Subgroup analyses will be provided through a forest-plot approach.

Objectives:

General Objectives:

1. To evaluate the safety and efficacy of two doses of BIO101 (175 mg b.i.d. and 350 mg b.i.d.) orally administered for 26 weeks versus placebo in a population of community dwelling older men and women (aged ≥ 65 years) living at home and at risk of mobility disability.
2. To estimate treatment effect on improvement of physical function after a six-month treatment versus placebo in the target population.
3. To estimate treatment effect on reduced risk of mobility disability after a six-month treatment versus placebo in the target population.

Primary Objective:

- To evaluate the effect of two daily doses of BIO101 versus placebo on mobility function as measured by gait speed using the 400MW test. The absolute change from baseline in m/s observed in each treatment group at M6 will be compared to the placebo group. A minimum clinically significant benefit is set at 0.05 m/s in the mean difference between groups from M6

compared to baseline. The preliminary data from the SARA observational study (SARA-OBS) suggests that the untreated population naturally experienced a deterioration of 0.05 meter per second, when compared at M6 to baseline. Taken together, this increases the expected difference between treatment and placebo groups to 0.1 meter per second at M6 – corresponding to what is considered a clinically significant difference.

Key Secondary Objectives:

a. To compare the change from baseline of a standardized patient reported outcome (PRO): the PF-10 sub-score of the SF-36. A minimum clinically significant benefit is set at 2-point difference of the change at M6 from baseline versus placebo in the mean difference between groups.
b. To compare the change from baseline to month 6 of the muscle strength using the handgrip strength test. A minimum clinically significant benefit is set at 2 kg difference of the change at M6 from baseline versus placebo in the mean difference between groups.

Other Secondary Objectives:

a. To compare appendicular lean body mass and body composition versus placebo, and specifically ALM.
b. To compare muscle strength using the knee extension test and the stair climb power test (SCPT) versus placebo.
c. To compare the rate of successful patients who completed the 400MW test after the 6-month treatment versus placebo.
d. To assess the overall score change on the SPPB as a cumulative expression of a physically frail status.
e. To compare the repeated chair stand test as a sub-score of the SPPB assessment versus placebo.
f. To compare the distance walked during the 6MWT versus placebo.
g. To compare the change from the baseline using the SarQol auto-evaluation questionnaire versus placebo.

[redacted]

Endpoints:

Primary Endpoint:

Gait speed measured during the 400MW test: the change from baseline to month 6 will be compared between groups of treatment (each dose versus placebo).

Key Secondary Endpoints:

PF-10 sub-score of the SF-36: the change from baseline to month 6 will be compared between groups of treatment (each dose versus placebo). Muscle strength as measured by the handgrip test: the change from baseline to month 6 will be compared between groups of treatment (each dose versus placebo). Additionally, a responder analysis will be performed with a responder definition of "study participant with an improvement of gait speed at 400MW test greater or equal to 0.1 m/s versus baseline", at an individual level.

A further responder analysis will be performed with a responder definition of "study participant with an improvement of PF10 greater or equal to 2 points versus baseline", at an individual level.

Other secondary Endpoints:

Change from baseline of ALM and other parameters of body composition by DEXA; the rate of success to complete 400MW test after a 6-month treatment versus placebo; change from baseline of muscle strength as measured by knee extension and SCPT; change from baseline of the total SPPB score and of the sub-score of the repeated chair stands test; change from baseline of the SarQol auto-evaluation questionnaire.

Study Population:

231 community dwelling older adults (men or women ≥ 65 years) and reporting a loss of physical function over the last six-twelve months and considered at risk of mobility disability will be included in the randomized interventional clinical trial SARA-INT (with 64 patients per treatment group) with a treatment period of 26 weeks. 39 additional participants will be randomized to allow 20% of non-evaluable withdrawals or lost to follow-up for a total of 231 older adults included in the US and the EU.

An unblinded 'promising zone' interim analysis will take place, based on the complete efficacy data from half of the randomized participants who completed the trial, to determine if there will be a need to increase the sample size.

A predefined subgroup efficacy analysis will also be performed in a number of pre-identified, at-high risk of worsening subpopulations:

- Low gait speed
- Sarcopenic obesity
- Study participants with a chair stand sub-score of ≤2 of the SPPB
- Study participants who experience a deterioration in their ALM/BMI, as measured by the DEXA scan, in the M6 visit compared to the baseline measurement

Subgroup analyses on these populations will be performed in order to better characterize treatment benefit in patients at increasing risk of mobility disability. Results will be presented in forest-plot graphs, for the primary and the two key secondary endpoints.

Inclusion criteria:

1. Provision of signed and dated **informed consent form (ICF)**
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. **Male or female aged ≥ 65 years, living in the community** (living at home, able to walk outside from time to time. Homes can include any living community that may or may not offer optional services for the convenience of the residents. Older adults living in nursing homes or in medicalized residences where caretaker services are mandatory are not eligible) **and reporting a loss of physical function over the last 6-12 months**
4. **SPPB score ≤ 8**
5. **ALM/BMI < 0.789 in men and <0.512 in women, or ALM < 19.75kg in men and < 15.02kg in women, as measured by DEXA scan**
6. Ability to take oral medication and be willing to adhere to the study intervention regimen (see section 6)
7. Agreement to adhere to the outlined Lifestyle Considerations (see section 5.4) throughout the study duration
8. In the US, women and members of minority groups should not be excluded, in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects.

Non-inclusion criteria

1. In France, non-affiliation to compulsory French social security scheme (beneficiary or right-holder)

2. In France, being under tutelage or legal guardianship

Exclusion criteria

1. Current use of anabolic drugs (e.g. testosterone); current use of Erythropoietin; current use of corticosteroid agents (except local administration route, like eye drops or dermatologic formulations)
2. Non-menopaused women (however, ongoing hormonal replacement hormonal treatment is not an exclusion criterion)
3. Known allergic reactions to sourcing components of the investigational drug (i.e. [redacted])
4. Treatment with another investigational drug or other interventions within three months
5. Unable to understand and perform the functional tests, as judged by the Investigator
6. Inability to perform the 400MW test within 15 minutes
7. Clinical conditions:
    a. Current diagnosis of major psychiatric disorders.
    b. Alcohol abuse or dependence
    c. Severe arthritis
    d. Cancer requiring active treatment (cancer previously treated with chemotherapy and/or radiotherapy and participants currently on remission is not an exclusion criterion)
    e. Lung disease requiring regular use of supplemental oxygen
    f. Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents
    g. 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)
    h. Parkinson's disease or other progressive neurological disorder
    i. Renal disease requiring dialysis, or known renal insufficiency (moderate or severe reduction of eGFR≤30 ml/min/1.73 m2, based on Cockroft & Gault formula)
    j. Chest pain, severe shortness of breath, or occurrence of other safety concerns during the baseline functional tests such as the 400MW test

k. History or active signs or symptoms of gallbladder/biliary disease (e.g. previous episodes of cholestasis/biliary tract obstruction, cholelithiasis, cholecystitis, etc.). Of note, history of cholecystectomy and no active biliary signs or symptoms, is not an exclusion criterion.

8. Current physical/rehabilitation therapy (except for passive physical therapy. However, this should not be initiated the week before an evaluation visit and once started, it should be maintained over the study duration).

Phase:

Phase 2 – with therapeutic intervention

Description of Sites/Facilities Enrolling Participants:

23 clinical investigation sites in the US and in Europe

Description of Study Intervention:

Oral treatment with BIO101 dosing of 350 mg b.i.d. or 175 mg b.i.d. or placebo (identical capsules).

The BIO101 active principle ingredient is 20 hydroxyecdysone (20E), [redacted] he study drug is packaged in individual blisters containing capsules and contained in an elderly- friendly weekly paper box for a monthly kit.

COVID-19 pandemic

Due to the coronavirus disease 2019 (COVID-19) outbreak, the implementation of clinical protocol is affected, including but not limited to the scheduled site visit for safety and/or efficacy, site visit for monitoring, investigational product delivery, collection of adverse events and concomitant medication. Following GCP guidance to the situation of the public health emergencies, the core consensus guidelines for clinical trial management and the study DSMB recommendation, below measures have been taken:

- No additional activity of prescreening, screening and randomization will be performed during the COVID-19 outbreak. Because of the potential impact of the COVID-19 outbreak leading to the withdrawals and lost-to-follow ups from the study, these activities may resume after the COVID-19 outbreak.

- the complete assessment and tests per protocol requiring on-site visits have been suspended. every investigational visit within the protocol will now be performed remotely (e.g. by phone) for all participants still active in the study by the investigational site staff. These calls will be used to continue monitoring the health status of the participants by collecting information on Concomitant Medication (CM) and Adverse Events (AE). In addition, study questionnaires will be administered and study drug intake will also continue to be monitored following the same schedule.

- Study drugs will continue to be dispensed and provided to participants through direct shipping from study site to the participants' home after the site investigator/staff(s) have completed reviewing all relevant safety study assessment results from the calls.

- An updated strategy for the final analysis will be implemented, to account for the missing data on safety and efficacy which will have impact on the final analysis. The planned interim analysis is postponed to a time after the restrictions are lifted. Both updated are described in a new version of the Statistical analysis Plan.

- As certain assessments/tests cannot be conducted per protocol, the investigator/site staff(s) should evaluate the overall risk/benefit, and contact the sponsor related staff(s) promptly should there be any safety concerns in order to reach agreement on how to proceed. This may require *ad hoc* safety assessments (e.g. safety blood draw, communication with participant's HCP). Additional checks should be performed as soon as the conditions allow it or at the end of the outbreak restrictions based on the national/federal, state and local governance.

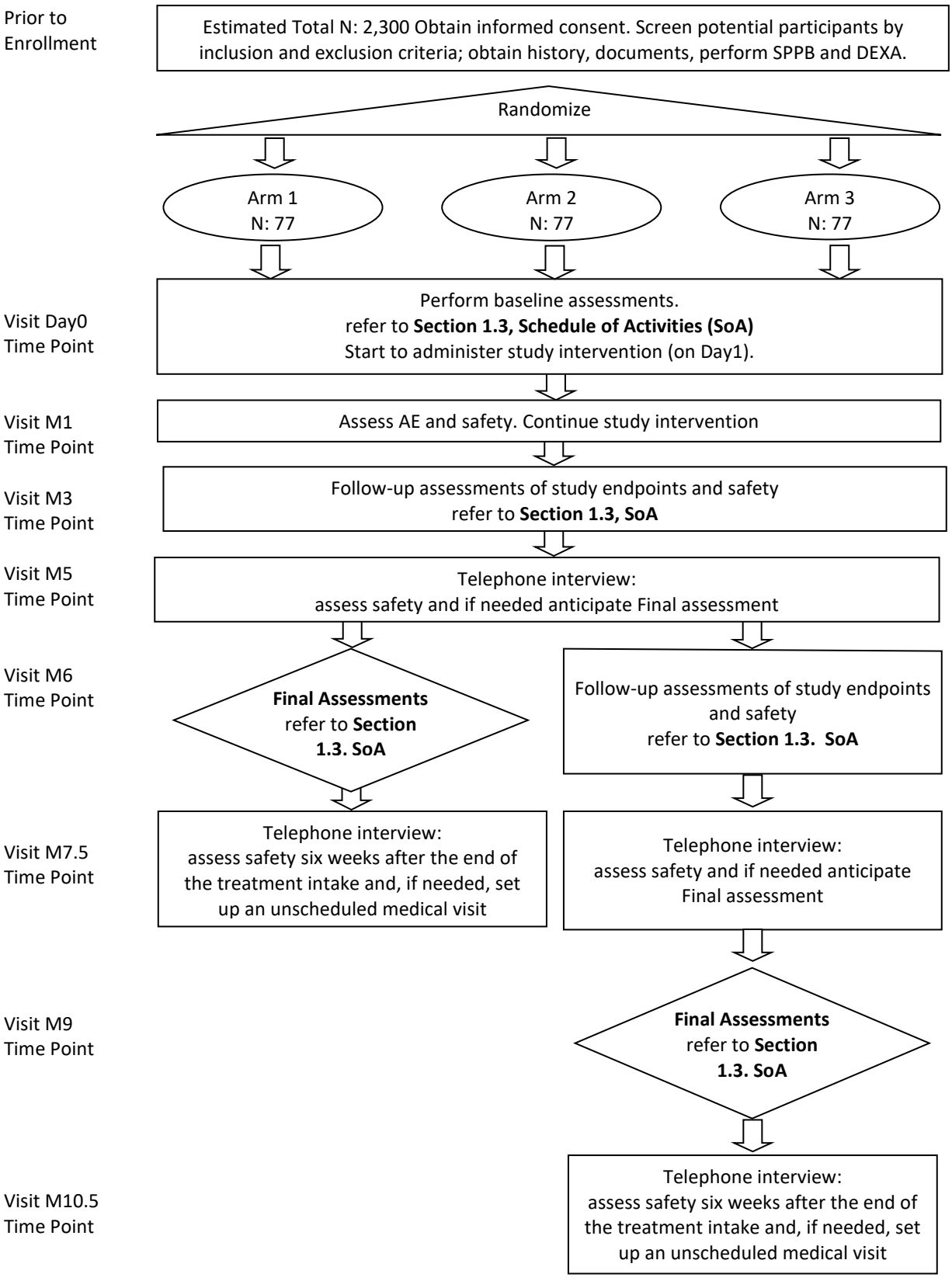
- An extension for treatment of 3 additional months is proposed for those participants missing the efficacy assessments at Month 6 visit/End-of-intervention. This would allow for the addition of data on safety and efficacy for the final analysis. [redacted]

Study Duration: 33-35 months

Participant Duration: Up to 39 weeks + screening (1-8 weeks) + follow-up at 6 weeks post study conclusion

1.2 SCHEMA

Flow diagram



1.3 SCHEDULE OF ACTIVITIES (SOA)

During the COVID-19 outbreak, no additional activity of prescreening, screening and randomization will be performed based on GCP guidance on the situation of the public health emergencies, the core consensus guidelines for clinical trial management and the DSMB recommendation, during the COVID-19 outbreak. For all active participants in the study, measures are as follows:

- Screening activities listed below are being put on hold:
    - Activities can be performed only after the participant has signed the ICFs
    - SPPB should be performed prior to DEXA and ultrasound scans
    - DEXA can be conducted only after the medical history, concomitant medications, physical exam, and SPPB inclusion criteria are met
    - DEXA results can be collected for the study if a DEXA scan was conducted for a non-study related purpose within 8 weeks prior to the randomization date
    - Gallbladder ultrasound can be conducted, only if the medical history, concomitant medications, physical exam, SPPB and DEXA exclusion criteria are met
    - The 400MW test must be the last activity performed during the screening period and within 48 hours of randomization. This last screening assessment can be performed on the same day as the baseline visit, but it must be performed **before randomization and baseline assessments** occur
- Randomization is being put on hold:
    - Randomization can occur only after all screening assessments results are available, specifically blood tests results for safety reasons
- Baseline (Day 0) is being put on hold:
    - All baseline assessments are performed only after randomization
    - Extra blood sampling will be performed for participants partaking in the Population PK (Pop-PK) sub-study at Day 1
- M1 Visit is replaced by a telephone call
    - Safety focused phone call after the first month of investigational treatment
- M3 visit is replaced by a telephone call
    - Intermediate phone call for safety and fora reduced number of efficacy measurements (ePRO)
- M5 Phone call
    - Safety focused phone call after 5 months of investigational treatment
- M6 (end-of-intervention visit) visit is replaced by a telephone call
    - phone call for safety and fora reduced number of efficacy measurements (ePRO)
- M7.5 Phone call
    - Safety focused phone call after 7.5 months of investigational treatment
- M9 visit
    - M9 visit must be scheduled 39 weeks after Day 0. This end of intervention visit can be scheduled before M9 in case of patient withdrawal or based on modification of public health emergencies and the core consensus guidelines for clinical trial management.
    - All safety and efficacy measurements previously listed for the M6/end-of-intervention visit are to be performed.

- M10.5 phone call
    - Post study intervention phone call 6 weeks after the end of intervention visit to follow up on safety parameters

	Screening	Randomization & Baseline Visit	M1 Visit	M3, M5, M6, M7.7 and M9 Visits					Post study Intervention Phone Call
Weeks	**-8 – 0**	**Day 0**	**4**	**12**	**21**	**26**	**32**	**39 (or End of intervention)**	**45 (6 weeks after end of intervention)**
Visit Window	**n.a.**	**n.a.**	**+/-3 days**	**+/- 1 week**	**+/- 1 week**	**- 1 week**	**+/- 1 week**	**8 weeks**	**+/- 1 week**
Telephone call			**X**	**X**	**X**	**X**	**X**		**X**
Informed consent, including secondary research	X (before any study activity)								
Informed consent (2) for biobank and DNA tests	X (before any study activity)								
New informed consent, including secondary research			X£	X£	X£	X£			
Demographics	X (4 weeks)								
Medical history	X (4 weeks)								
Concomitant medication review	X		X	X		X		X	
Physical exam & Anthropometry	X	X						X	
Safety measurements including vital signs and weight		X						X	
SPPB	X (4 weeks)							X	
ECG	X (1 week)								

DEXA	X							X	
Gallbladder ultrasound	X							X	
Hematology[2]	X (1 week)							X	
Biochemistry[1]	X (1 week)							X	
Urinalysis[3] (dipstick)	X (1 week)							X	
Plasma and urine collection for biomarkers	X (1 week)							X	
400MW test	X (no earlier than 48 hrs before Day 0)							X	
Inclusion/ Exclusion criteria	X								
Randomization		**X**							
CIRS		X							
SF-MNA		X							
6 MWT		X						X	
Stair Climb Power Test		X						X	
Grip strength		X						X	
Knee extension (optional)		X						X	
SF-36		X		X		X		X	
PAT-D		X				X		X	
SarQoL		X		X		X		X	
TSD-OC		X		X		X		X	
Deliver investigational treatment		X	X	X		X			

Collect used treatment & record compliance to study intervention			X	X		X		X	
Actimetry*		Provided	X	X				collected	
General safety questions			X	X	X	X	X		X
AEs review and evaluation		X	X	X	X	X	X	X	X
Diabetes/ prediabetes questions							X		X
POP-PK sampling (optional)		X (1 day after Day 0)						X	
eCRF completion	X	X	X	X	X	X	X	X	X

Date of each next visit should be calculated back on Day 0 visit (baseline) in order to not exceed the total duration of 26 weeks of treatment (capped exposure).

*Actimetry is continuously recorded from Day 0 to M6.

[£] Reconsent based on the COVID-19 outbreak and the next planned visit of the participant

1 Biochemistry: sodium, potassium, chloride, bicarbonate, urea, uric acid creatinine, albumin, glucose, cholesterol (total cholesterol, LDL, HDL fractions), triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bone-specific alkaline phosphatase, lipase, amylase, gamma glutamyl aminotransferase, bilirubin (total, indirect, direct), creatine phosphokinase and mb-creatine phosphokinase, lactate dehydrogenase, total protein, and eGFR calculation;

2 Hematology: haemoglobin, HbA1c, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume; Coagulation: activated partial thromboplastin time, prothrombin time, and international normalized ratio.

3 Urinalysis: a midstream urine sample will be collected for urinalysis by dipstick for glucose, protein, and occult blood.

2 INTRODUCTION

2.1 STUDY RATIONALE

We aim to perform this phase 2, interventional study in Europe and USA in order to evaluate the clinical benefits, safety and tolerability of the investigational drug, BIO101. BIO101 will be administered orally for a six-month (26 weeks) duration to community dwelling men and women aged ≥ 65 years (living at home and able to walk outside from time to time. Homes can include living communities that may or may not offer optional services for the convenience of the residents. Older adults living in nursing homes or in medicalized residences where caretaker services are mandatory are not eligible) suffering from age-related sarcopenia (including sarcopenic obesity) and at risk of mobility disability.

This double-blind, placebo-controlled clinical trial will collect and analyze data on physical performance and body composition and will specifically focus on the change of one functional measurement: the gait speed measured during the 400MW test plus the change on a highly standardized PRO, the PF-10 sub-score of the SF-36 auto-evaluation questionnaire Together, they will estimate the efficacy of BIO101 in preventing mobility disability in the target population.

TARGET INDICATION

Age-related sarcopenia is a geriatric condition characterized by a progressive loss of muscle mass and muscle function, with development beginning at the fifth decade and contributing to an increased risk of falls and fractures later in life[3]. Sarcopenia occurrence increases with age and may lead to mobility disability and physical dependence of the older person. In October 2016, the Center for Disease Control and Prevention established an ICD-10-CM code, M62.84, for age-related sarcopenia therefore, providing its recognition for a separate reporting and data collection[4]. According to the Aging in Motion coalition, this new code designation for the disease has the potential to affect sarcopenia research and treatment in a number of ways, including the allowance for clearer establishment of clinical guidelines for diagnosis and treatment of sarcopenia and opening new avenues for development of novel therapeutics by researchers and approval by the United States Food and Drug Administration (FDA). Of note, the FDA organized a public consultation meeting to gather the point of view of patients suffering from sarcopenia in April 2017[5].

Depending on the definition used, sarcopenia prevalence in 60-70 years old is reported as 5 to 13% while the prevalence for people >80 years old ranges from 11 to 50%. The number of people around the world aged ≥60 years was estimated at 600 million in the year 2000, a figure that is expected to rise to 1.2 billion by 2025 and 2 billion by 2050. Even with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million in the next 40 years[6]. According to the World Health Organization (WHO) in 2009, the estimated direct healthcare cost attributable to sarcopenia in the United States of America in 2000 was $18.5 billion USD.

Many definitions can be considered for sarcopenia diagnosis. First, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a low muscle mass index in

participants (moderate sarcopenia is 8.51-10.75 kg/m^2 in men, and 5.76-6.75 kg/m^2 in women) with a walking speed of <0.8 m/s, or a normal walking speed and low muscle strength (<20 kg for women and <30 kg for men)[7]. Subsequently, the FNIH developed a data-driven definition based on a meta-analysis of 11 clinical studies and 26,725 participants (mean age of 75.2±6.1 years in men and 78.6±5.9 years in women). This definition takes into account the prevalence of low gait speed (≤0.8m/sec) and weakness (grip strength of <26 kg for men and <16 kg for women) in older individuals (≥ 65years) and is defined by low lean mass expressed as ALM <19.75kg in men and <15.02kg in women, or as ALM adjusted for body mass index (BMI), ALM/BMI, <0.789 for men and <0.512 for women[2]. This last definition of sarcopenia integrating the BMI was derived from a sensitivity analysis, and it allows for better appraisal of obese (sarcopenic) individuals. In fact, sarcopenic obesity (SO) represents a subgroup of sarcopenia characterized by the loss of muscle mass and function and a concomitant increase of fat mass. It is mainly affecting older obese individuals. A higher rate of functional decline has been reported in participants with SO. Indeed, lipid infiltration in muscle tissues seems to exacerbate sarcopenia, since accumulation of lipids prevents incorporation of amino acids, reduces protein synthesis and induces a chronic inflammation in the muscle[8-10]. The progressively increasing cohort of older people with SO are at particular risk of negative health impact such as loss of independence, increased disability and increased morbidity and mortality[11].

Establishing a consensus definition of SO is challenging since most of previous studies specifically focused on body composition (gain of fat mass and loss of muscle mass) and not on physical function[10]. The problem of the SO definition is also revealed by its wide range of prevalence (4-84% in men and 4-94% in women depending on body composition measurement methods used)[12]. The lack of a consensus definition as well as the imprecision in its prevalence hampers SO recognition as a specific geriatric condition and has also led to its under-diagnosis. Thus, despite SO's high relevance, appropriate clinical studies including both body composition and physical function measurements will contribute to better understanding of SO's prevalence and clinical importance in the ageing population. In that regard, the definition of Batsis et al.[13] that integrates the cut-off points for sarcopenia by the FNIH and a percentage of body fat mass of >25% in men and >35% in women, will be applied in this study.

The pathogenesis of SO, adapted from Donini et al.,[14] is described in Figure 1.

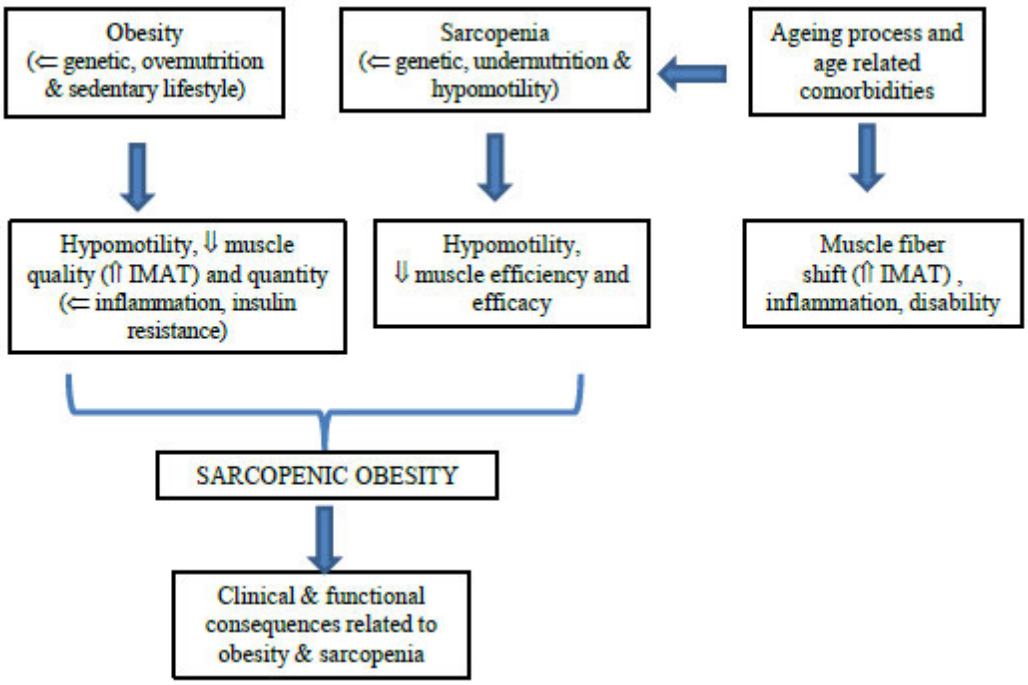


Figure 1: Pathogenesis of Sarcopenic Obesity

In the LIFE clinical trial, it has been shown that in older adults with a sedentary lifestyle and low SPPB score at baseline, the Physical Activity (intervention) group had better lower extremity performance (SPPB score), compared with the Health Education group, over the course of the trial[15]. These effects were more pronounced in lower functioning participants (SPPB <8)[16], with the greater benefit and difference between groups visible at as early as 6 months. The observed benefit was mostly explained by the chair stand component of the SPPB, while the balance test and the 4-meter gait speed were only slightly modified.

In Europe, the SPRINT-T clinical trial has started to test the effects of a multicomponent treatment strategy (focused on structured physical activity as well) in 1,500 physically frail older participants (the frailty status being operationalized by SPPB ≤9 or ≤7) and sarcopenia (defined by low ALM/BMI or low ALM, according to the two subsets of criteria by the FNIH. In fact, the ALM and ALM/BMI cut-off points identified two relatively distinct subsets of sarcopenic individuals as only 16% of patients do actually meet both definitions[17]. This clinical trial population is theoretically expected to be at higher risk of mobility disability than the LIFE population because of the dual initial diagnosis of physical frailty (based on low function) and sarcopenia (based on body composition by DEXA scans).

The SARA-INT clinical trial population is intended to include those at risk of further loss of muscle functions even in the medium term (6 months), based on the very low physical performance at baseline (SPPB ≤ 8) and the coexisting sarcopenia criteria based on DEXA measurements.

Sarcopenia management requires not only acting on muscle mass but also on the muscle functions in order to prevent subsequent disabilities. Physical performance is mainly measured through the SPPB, grip strength, or walking tests like the 400MW test or the 6MWT.

Several strategies were developed for the management of sarcopenia and/or SO[18].These include monoclonal antibodies targeting myostatin, a negative regulator of muscle growth, or its receptor. Many products of different classes of molecules have been tested over the past decade in clinical studies of sarcopenic participants:

- Molecule substrates of protein synthesis which are amino acids or their metabolites (leucine, beta-hydroxy-beta-methylbutyrate, citrulline, ornithine), as well as rapidly digested proteins such as whey.
- Anabolic hormones like testosterone or selective androgen receptor modulators (SARMs), growth hormone, IGF-1, vitamin D, ghrelin or progranulin.
- Myostatin inhibitors (monoclonal antibodies, soluble receptors).
- Molecules targeting the renin-angiotensin system (RAS) such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists and angiotensin 1-7 (or agonists thereof).
- Some beta blockers (inhibitors of β-adrenergic receptors), e.g. espindolol[19].
- Various natural substances such as polyphenols (resveratrol, isoflavones), triterpenes (ursolic and oleanolic acid), or phytosteroids (brassinosteroids, phytoecdysones).

Pharmaceutical companies had developed drug candidates based on the above technologies, especially on the use of therapeutic antibodies that inhibit myostatin. They also tested other strategies, in particular the use of testosterone in combination with aromatase inhibitors or receptor SARMs, but the development of these drug candidates was stopped in Phase 2 because of side effects and associated cancer risks. Moreover, SARMs have shown no advantage over testosterone.[17]. Finally, clinical research centers specialized in aging have tested the benefit of ACE inhibitors to increase muscle quality and mobility of elderly patients treated for hypertension, and the initial results were promising[20].

Regarding clinical research on myostatin inhibition for targeting sarcopenia, two main strategies are used, either blocking the myostatin receptor (activin A/B) or directly blocking myostatin and therefore preventing its interaction with its receptor. Three products have completed Phase 2 studies. These are bimagrumab developed by Novartis, LY2495655 by Ely Lilly, and REGN1033 by Regeneron.

[redacted] using their Troponin activator (CK-2127107), continue to target sarcopenia as well. The latter study with the troponin activator was terminated due to a lack of efficacy determined during interim analysis.

Bimagrumab [redacted] is a human monoclonal antibody that binds to myostatin receptor. The phase 2 clinical trial in patients with sarcopenia showed no change in bimagrumab treated group versus placebo. Only a subsequent analysis of the clinical data revealed that sarcopenic participants with slow walking speed showed statistically significant improvements in gait speed and in the 6MWT compared to placebo[21]. However, these results from very limited cohorts did raise concerns regarding correlation between muscle size and function[22].

The anti-myostatin antibody, LY2495655, in a phase 2 study on older, weak fallers for 24 weeks[23], induced a significant difference in appendicular lean body mass of 0.43 kg (95% CI 0.192 to 0.660; p<0.0001) but did not show any significant difference compared to placebo with regards to physical performance (stair climbing, chair rise with arms and fast gait speed).

REGN1033 or Trevogrumab a fully human mAb targeting myostatin was studied in sarcopenia, including disuse atrophy, chronic disease, changes in food and nutritional intake. The treatment induced an increase of total lean body mass of 2.29 % compared with placebo at the highest dose. However, this gain was not translated to statistically significant improvements over the placebo group in strength and function assessments including the 6MWT[24]. Clinical studies with REGN1033 seem to be discontinued.

To our knowledge, none of the products has concomitantly showed in Phase 2 meaningful effects on lean body mass and physical function. There is still an unmet need for new drugs for sarcopenia. Along with drug treatment, an ideal management would likely combine daily physical exercise to help strengthen muscle mass, adequate nutrition to avoid protein deficiency and drug therapy to limit the cardiovascular risk.

Biophytis has developed BIO101 as an investigational drug candidate for treating age-related sarcopenia, including sarcopenic obesity, and prevent mobility disability in at-risk older adults.
The overall clinical development of this innovative oral treatment currently conducted by Biophytis in age-related sarcopenia and SO is called “SARA” which stands for SARcopenia and sarcopenic obesity in patients Aged ≥ 65 years.

SARA clinical development program includes 3 steps:

1. SARA-PK: a phase 1 clinical trial evaluating the safety and pharmacokinetics of BIO101 administered by oral route in young and older healthy volunteers (completed).

2. SARA-OBS: an observational trial characterizing sarcopenia, including sarcopenic obesity, in community-dwelling older adults complaining about a loss of physical function and considered at risk of mobility disability. This is a 6-month observational study without any therapeutic intervention (completed).

3. SARA-INT: a phase 2 double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of two oral doses of BIO101 in study participants ≥ 65 years complaining of a loss of physical function, suffering from sarcopenia, and considered at risk of mobility disability.

The SARA program is supported and hosted by SARA-Data, an innovative platform for a novel approach of clinical trials management. This includes an electronic Case Report Form (eCRF) electronically administered Patient Reported Outcomesas well as a continuous physical activityy recorded through a wearable actimetry device. All of this is performed within a different-source-data integrated environment[25].

2.2 BACKGROUND

THE INVESTIGATIONAL PRODUCT

BIO101 active ingredient is 20-hydroxyecdysone (20E) [redacted]

The investigational product is formulated as 175 mg oral capsules, contained [redacted]

[redacted]

According to the FDA guidance for estimating starting doses in initial clinical trials (2005), [redacted]

On this basis, the starting dose of 100 mg and the range of doses from 100 to 1,400 mg/day were selected for the single ascending doses of BIO101 phase 1, first-in-human study in young and elderly healthy volunteers.

[redacted]

[redacted]

Based on these new evidences, an extended treatment of 3 additional months for participants missing the efficacy assessments at Month 6 visit is proposed. This would allow for additional data on safety and efficacy for the final analysis.

Based on all the data presented above, the 700 mg dose was set as the maximum daily dose [redacted]

The safety and pharmacokinetics of BIO101 were evaluated in SARA-PK, a phase 1, double-blind, placebo-controlled, randomized clinical trial combining a single oral administration in both young and older healthy volunteers and a 14-day multiple oral administration in older healthy volunteers, with the overarching objective of SARA-PK was to establish the range of oral doses suitable to be administered and evaluated in phase 2 clinical trials. The two clinical parts of the study started on August 2016 and were completed on December 2016[27].

In the Single Administration Dose (SAD) part, 2 cohorts of young healthy volunteers (18-55 years) in fasting state were dosed at 100, 350, 700 and 1,400 mg/day and one cohort of elderly healthy volunteers (65-85 years) was tested at 1,400 mg/day. Food effect was evaluated at 700 mg by comparing safety and pharmacokinetics in fed and fasted administration in the same cohort of young healthy volunteers (18-55 years). Age effect was evaluated at 1,400 mg/day by comparing safety and pharmacokinetics in the young healthy volunteer group to the elderly healthy volunteer group (65-85 years).

No serious adverse events (SAEs) were observed up to 1,400 mg/day in young or elderly cohorts. Adverse events (AEs) were mild and were reported at the doses of 350 mg and 1,400 mg in the young study participants and at 1,400 mg for the elderly study participants. Most frequently reported AEs were gastrointestinal disorders, nervous system disorders (headache) and musculo-skeletal-and-connective tissue disorders. No meaningful treatment-emergent laboratory, ECG or vital sign abnormalities were reported.

After a single administration in fasted conditions, BIO101 was rapidly absorbed with a median time to Cmax between 2 and 3.5 hours. BIO101 plasma concentrations increased less than dose proportionally between 100 and 700 mg, and dose proportionally between 700 and 1,400 mg. After single (fasted) oral administration of 100, 350, 700 and 1400 mg it was observed a Cmax of 141, 317, 399 and 710 ng/mL, respectively. The AUC was 797, 1,946, 2,658 and 4,283 ng.h/mL respectively. The mean half-life was short; between 2.4 and 4.9 hours.
No age effect was observed on the pharmacokinetic profile of BIO101; the comparison of young healthy volunteers and elderly healthy volunteers at 1,400 mg/day in SAD did not show a meaningful difference in the Cmax (710 vs 552 ng/mL) or in the AUC (4,283 vs 3,630 ng.h/mL).
In addition, no food effect was observed on the pharmacokinetic profile of BIO101; the comparison of healthy young volunteers dosed at 700 mg in fasted or fed conditions did not show a meaningful difference in the Cmax (399 ng/mL vs to 505 ng/mL) or in the AUC (2658 vs 3294 ng.h/mL). It was therefore decided to use the fed condition in the Multiple Ascending Doses (MAD) part.
Overall, BIO101 was well tolerated in doses ranging from 100 to 1,400 mg in a single oral administration. Cmax observed at 350 mg and 700 mg/day (399 and 505 ng/mL respectively) corresponds to the [redacted]
Both doses of 350 mg and 700 mg were therefore retained to be tested in the 14-day MAD part under fed condition.

Based on the relatively short half-life observed under single administration conditions, it was decided to compare, sequentially, 350 mg once a day and 350 mg b.i.d. Subsequently, based on the good safety profile observed, a higher dose was also tested at 450 mg b.i.d.

In the MAD part, three cohorts of elderly healthy volunteers (65-85 years) were administered 350 mg q.d., 350 mg b.i.d. and 450 mg b.i.d. during 14 days. No SAEs were observed. Reported AEs were either mild or moderate (the latest limited to 450 mg b.i.d.). The highest number of study

participants with treatment related AEs was reported in the cohort of 450 mg b.i.d., in 5 study participants. Treatment related AEs were reported in at most 1 subject each in the 350 mg q.d. and the 350 mg b.i.d. cohorts. None of the observed treatment-emergent laboratory, ECG or vital sign abnormalities were considered clinically significant and none were reported as AEs. Overall, 350 q.d. and 350 b.i.d. were equally safe.

Administration of 350 mg q.d. generated a Cmax of 346 ng/mL on day 1 and 388 ng/mL on day 14. From day 2 to day 12, the mean pre-dose concentrations ranged from 7.33 ng/mL to 7.73 ng/mL. At 350 mg b.i.d., Cmax corresponded to 453 ng/mL on day 1, and 506 ng/mL on day 14. From day 2 to day 12, the mean pre-dose concentrations ranged from 105 to 126 ng/mL. After repeated daily administrations of 350 mg for 14 days (i.e., on Day 14), BIO101 Cmax and $AUC_{0-\tau}$ were higher (increase of about 30% for Cmax and 16% for $AUC_{0-\tau}$), on average, in study participants administered 350 b.i.d. (506 ng/mL; 2768 ng.h/mL) than those administered q.d. (388 ng/mL; 2389 ng.h/mL). The b.i.d. administration was therefore selected as it allowed continuous pre-dose plasma concentrations close to the pharmacologically active dose of 140 ng/mL during the whole 14-day MAD period.
Administration of 450 mg b.i.d. generated a Cmax of 524 ng/mL on day 1 and 560 ng/mL on day 14. From day 2 to day 12, the pre-dose concentrations ranged from 109 ng/mL to 151 ng/mL. AUC0- τ was 2,429 ng.h/mL on day 1 and 3,203 ng.h/mL on day 14.
No accumulation of BIO101 was observed after q.d. administration of 350 mg BIO101 for 14 days (mean Rac= 1.14) whereas a slight accumulation was observed after b.i.d. administrations of BIO101 at 350 mg and 450 mg for 14 days (mean Rac= 1.31 in both panels).
Median Tmax was the same (i.e., 3 h) in all dose groups and after the first and last doses. Mean BIO101 half-life was short with values approx. 2.8 and 4.4 h in all cohorts. At 350 mg and 450 mg b.i.d., after the day 14 morning administration, mean Cmax and AUC0-τ increased by about 1.11-fold and 1.16-fold for a 1.29-fold dose increase (from 350 mg to 450 mg), so less than dose-proportionally. Based on the above results, no clinically meaningful accumulation is expected over the 26-week administration.
Based on the pharmacokinetic parameters, both 350 mg and 450 mg did show interesting profiles. On this basis, the b.i.d. administration was confirmed to be used for the next development phase of BIO101.

[redacted]

[redacted]

In conclusion, [redacted] the administration of 350 mg b.i.d. was selected as the highest dose to be tested in the phase 2 study. This dose was well tolerated as it generated few numbers of AEs with mild severity. The dose of 350 mg b.i.d generated a Cmax of 346 ng/mL [redacted] The dose of 175 mg b.i.d. was selected as a second dose for the phase 2 study. This dose being lower than 350 mg b.i.d., is anticipated to be safe and well tolerated. The 175 mg b.i.d. was not evaluated during the MAD part. [redacted]

Refer to the Investigator's Brochure (IB) for more details.

SCIENTIFIC RATIONALE FOR DESIGNING SARA-INT CLINICAL TRIAL

Study population

SARA-INT will enroll older persons living at home and encountering objective limitation of physical functions as defined by a low score at SPPB (SPPB≤8). A similar reasoning has been applied to the SPRINT-T[16] clinical trial (SPPB≤9 with a quota of patients scoring ≤7), an approach consistent with recent recommendations by the European regulators (ICFSR Philadelphia, 2016). According to published data, lower performers are in a state of disease in which therapeutic interventions such as a structured physical activity can produce a significant improvement on various parameters like gait speed or chair stand. We have therefore targeted participants that combine objective criteria for sarcopenia, as measured by DEXA, with evidence of reduced mobility.

The main difference, between SARA-INT and SPRINT-T, is that SPRINT-T tests the impact of exercise. It is possible, that individuals who improve with exercise only, will not require an addition of a drug intervention. This is why, in this study, we are including only participants with an SPPB score of ≤8, and excluding those with a score of 9, like those who were included in the SPRINT-T study and were considered to be potentially more stable, and may respond well to exercise treatment only.

Study Endpoints

Designing and implementing an adapted set of investigations to accurately and efficiently describe the progressive decline of physical function in at-risk older individuals is also a challenge. In fact, there is no final consensus on the most sensitive and specific primary endpoints, even though there is a general convergence on low gait speed as the key physical function related to an increased risk for mobility disability, falls, loss of independence and mortality[28,29].

The LIFE study, and its preparatory LIFE-P clinical trial, extensively evaluated the 400MW test in a population of community dwelling men and women aged 70-89 years with a sedentary lifestyle

and an SPPB ≤ 9. The 400MW test was used as a dichotomous test, with failure being defined as the inability to walk 400 meters without sitting and without help within 15 minutes. The incident rate of failure in the LIFE control group (n= 817) with no specific therapeutic intervention, was 35.5% (290 out of 817 study participants) and permanent mobility disability occurred in 19.8% over a mean follow-up duration of 2.6 years. Interestingly, majority of mobility disability events were observed in the subgroup with SPPB <8, with 177 out of 378 study participants or 46.8% with incident disability[15]. Transition rate from success to failure with the 400MW test over 6 months had been 6.9% in LIFE-P. However, this outcome was more efficient as compared to the 4-meter walk, or the SPPB itself[30].

The 6MWT has been initially validated and extensively used mostly in respiratory and cardiovascular conditions[31]. This test can be analyzed as a continuous variable, although a threshold value of 50 m improvement has been used as a dichotomous test.

However, in a recent clinical trial on the effects of testosterone treatment in older men aged ≥ 65 years, relatively stable values of 6MWT were observed over 6 months in the control group (n=196), as well as in the active treatment group (n=191), and there was no significant difference between the two groups[32]. Several reasons can be considered to explain the lower than expected effect of the tested intervention, among these: a) the selection of a relatively preserved population in terms of motor function (i.e. gait speed≤1.2 m/s) and b) the choice of a minimum clinically important difference of 50 m (although this threshold was previously validated in different patients populations, e.g. total and knee arthroplasty or chronic lung disease; see methods in Snyder et al, 2014 ClinTrials[33]).

The LIFE study used the 400MW test as a dichotomous variable and a proxy for mobility disability. The same methodological approach was adopted in the case of SPRINT-T. Overall, the choice of this kind of primary endpoint is particularly onerous in terms of study and intervention duration; LIFE participants were treated for two and a half years and SPRINT-T has an expected treatment duration of two years in order to detect a meaningful difference between treatment groups[15].

Santanasto et al performed additional prespecified analyses on LIFE results with the objective of identifying earlier changes that could anticipate later mobility disability or possibly focus on functional improvement and stabilization of muscle functions[16]. Interestingly, both the gait speed measured during the 400MW test and the chair stand sub-score of SPPB did show a visible and statistically significant improvement at six months, followed by a relative stabilization or decline. In general, gait speed decline has been strongly correlated to major outcomes like incident mobility disability, hospitalizations and lower life expectancy.

For these reasons, it was decided to define the 400MW test **gait speed** as the primary endpoint for SARA-INT.

In terms of PROs, both the US FDA and the European Medicine Agency (EMA) recently emphasized the importance of accompanying physical function objective measurements by an auto-evaluation questionnaire to estimate the corresponding improvement in the daily life activities (ICFSR Philadelphia, 2016; FDA Patient-Focused Drug Development Public Meeting for Sarcopenia April 6, 2017). The SF-36 is one of the most widely used, validated measures of health-related

quality of life and has been shown to discriminate between study participants with different chronic conditions and between study participants with different severity levels of the same disease[34,35]. The SF-36 has also demonstrated sensitivity to significant treatment effects in a variety of patient populations. Population-based normative data on the SF-36 is available for the US and other countries as well.

This instrument addresses health concepts that are relevant to the patient's perspectives. There is no single overall score for the SF-36, instead, it generates 8 subscales and two summary scores. The PF-10, which measures the role limitations due to physical problems, will be a key secondary endpoint for SARA-INT. PF-10 has been tested in numerous clinical trials and is considered a simple and effective measure of mobility disability and for epidemiological studies[36]. Climbing one flight of stairs (no change versus decline of two levels, two-point difference) or walking a block (no change versus two levels decline) exemplifies a substantial meaningful change, as appreciated by patients[33,36].

Data from the recently completed SARA-OBS study could be used to corroborate these hypotheses.

COVID-19 pandemic

Safety of study patients and investigators should be the priority during COVID-19 outbreak. Only ePROs (SF36, SARQoL, TSD-OC and Pat-D will be assessed during this period until further guidance. An extension of the treatment period for a total period of 9 months of intervention will enable the full assessment of the safety and efficacy of the investigational product for a significant part of the population randomized in this study, while staying in compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks are related to the long-term administration of an investigational drug to participants suffering from multiple chronic diseases.

[redacted]

[redacted]

BIO101 was well tolerated in healthy elderly volunteers receiving up to 450 mg b.i.d. for 14 days. Based on non-clinical safety (26-week studies [redacted], safety pharmacology and phase 1 results, both immediate and long-ranging risks can be considered as low.

The active ingredient in BIO101, 20E, may become a restricted substance, which is not allowed to be used in sport competitions. The reason is that there is a tendency to use it as an anabolic agent. Since BIO101 contains a high concentration of 20E at a dose that is much higher than the one that appears in nutritional supplements, there is concern that non-sarcopenic individuals may want to use BIO101 illicitly. Participants in this study will be warned and instructed to not allow anyone to gain access to their medication and to use only according to the medication instructions provided in the drug kits.

In addition, [redacted] its putative mechanism of action through activation of the MAS receptor and potential impact on the renin–angiotensin–aldosterone system (RAS) requires attention. A special surveillance and precaution will be taken with events that could theoretically indicate presence of orthostatic hypotension (OTH), including dizziness and presyncope related to orthostatic changes and actual measurements. In addition, events that comply with the clinical definition of OTH (i.e. decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position) will require special attention even without symptoms.

There are limited risks linked to the execution of the functional tests, e.g. falling during a test. The investigational site staff will put in place adapted surveillance, adequate prevention including cancellation or postponing of a planned test, and adapted emergency care in order to prevent, limit and appropriately and timely treat possible adverse events.

All AEs will be reported as per standard pharmacovigilance procedures (Section 8.4).

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefit of BIO101 has been demonstrated in several *in-vitro* and *in-vivo* studies, as described in the investigator's brochure and mentioned in section 2.2. This justifies testing the potential benefit of this drug in participants with age-related sarcopenia.

Elderly participants suffering from initial loss of physical function are expected to improve their motor ability based on observed BIO101 non-clinical effects on muscles and muscle cells.

All patients will undergo several nonspecific exams that could contribute to earlier diagnosis of unknown diseases.

A further potential and indirect benefit is that all participants will be closely followed-up with their physical activities continuously reported through the wearable actimetry device and this could allow earlier diagnosis of a concomitant condition or of worsening of the mobility impairment.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Overall, potential benefits of participating in the study are expected to outweigh the potential risks.

Immediate and long-term risks are considered low based on phase 1 safety evidence and non-clinical studies. The scientific information collected during this clinical trial will allow the assessment of the safety and efficacy of a novel drug that could be useful in the future to prevent the consequences of a geriatric condition like age-related sarcopenia.

2.3.4 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS DURING THE COVID-19 PANDEMIC

The main risk for participants is the exposure to COVID-19 virus and infection if clinical visits continued. The measure taken on March 20th 2020, therefore, was to cancel all on-site visits for participants active in the study.

As a consequence of this measure, it is impossible to conduct most of the safety and efficacy assessments, putting the completeness of the data that is collected during the study at risk. The lack of information from participants during this period may hamper the global analysis of the full dataset of the study, to the extent that the whole study may become nullified. To mitigate this risk, and based on the safety profile of recently available pre-clinical data, an extension of the participation of these subjects under treatment is proposed up to a total of 9 months of intervention. This will allow the collection of safety and efficacy data at the end of the COVID-19 outbreak based on the updated projections from national/federal, state and local governments on the restrictive measures for travel and daily activities of participants and trial staff.

All study activities are impacted by the restrictions on physical interactions (such as physical distancing and stay-at-home orders) due to the COVID-19 outbreak, which could lead to an early termination of participation of individuals in the study. The sponsor will rely on the contingency plans of each vendor

involved in the trial, including a monitoring visit mitigation plan, contingency plan for IP production and shipment.

3 OBJECTIVES AND ENDPOINTS

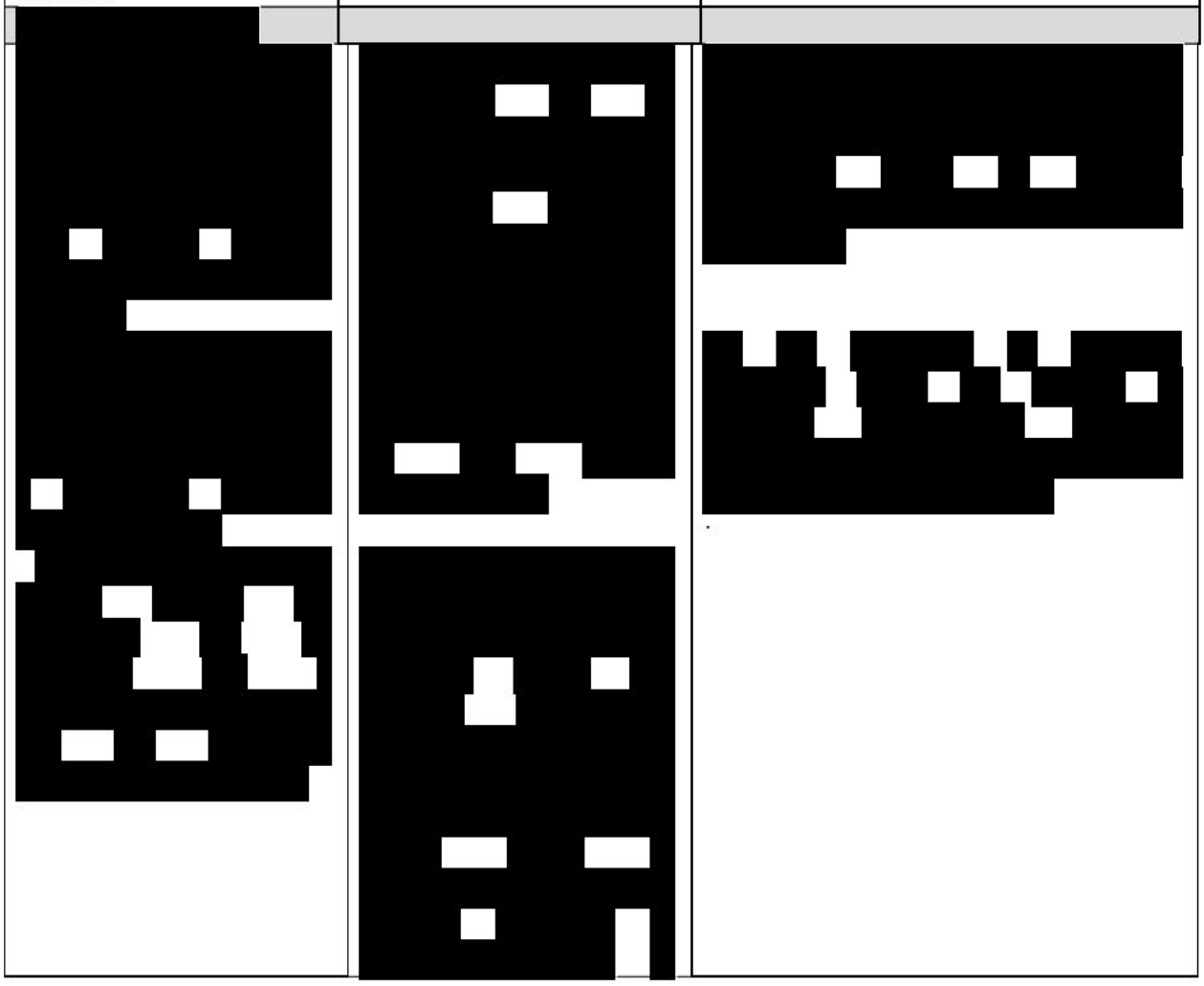
The overarching objective of the SARA-INT clinical trial is to evaluate the efficacy and safety of BIO101 26-week oral administration on the prevention of mobility disability in at-risk, community dwelling older adults (≥ 65 years) reporting a loss of physical function over the last 6-12 months. In particular, this trial aims to:

a. Estimate treatment effect on improvement of physical functions after a six-month treatment versus placebo in the target population.
b. Estimate treatment effect on decrease of risk of mobility disability after a six-month treatment versus placebo in the target population.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the effects of two daily doses of BIO101 versus placebo on mobility functions as measured by the gait speed during the 400MW test.	The primary endpoint is the 400MW test **gait speed**: the change from baseline to month 6/month 9 will be compared between groups of treatment (each dose versus placebo). The absolute change from baseline in meters per second observed in each treatment group at M6 /M9 will be compared to the one observed in the placebo group. A minimum clinically significant benefit is set at 0.1 m/s in the mean difference between groups.	This endpoint was chosen because it is a continuous variable that reliably expresses the grade of residual (lower limbs) muscle functions in older adults. The 400MW test gait speed was shown to improve after 6months of structured physical activity (Santanasto et al, 2017[16]). This test could also be applied as a dichotomous variable but this would necessitate a much longer observation period not corresponding to the phase 2 operational requirements. The 400MW test gait speed change following a 6-month intervention has been demonstrated as a good predictor of mobility disability progression or improvement during the LIFE study according to Santanasto et al., 2017[16]. A change of 0.05 m/sec was considered a minimal clinically meaningful change to patients, according to Perera et al, 2006[36], and is well adapted to a phase 2 design. In addition, with our analysis of a similar study population in our phase 2a, observational study, (SARA-OBS), a decline of 0.05 m/s over the 26-week period was detected. Therefore, this observation allows an increase of an additional 0.5 m/s for the expected

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		difference between the treatment groups and hence 0.1 m/s was chosen as the minimal clinically meaningful change for this study. A change of 0.1 m/sec will also be considered as a substantial clinically meaningful change to patients[36], and will be used for (individual) responders analysis.
Key Secondary:		
1) To evaluate the effect of BIO101 on physical function from the study participants' perspective using an adapted PRO. 2) To evaluate the effect of BIO101 on muscle strength using the handgrip strength test.	1) The PF-10 sub-score of the SF-36: the change from baseline to month 6/month 9 will be compared between groups of treatment (each dose versus placebo). Additionally, a responder analysis will be performed with a responder definition of "patient with an improvement of PF10 greater or equal to 2 points versus baseline", at an individual level. 2) Handgrip strength test: the change from baseline to month 6/month 9 will be compared between groups of treatment, each dose versus placebo; a minimal clinically significant benefit is set at 2 kg of difference between groups.	The SF-36 is a validated measure of health-related quality of life, sensitive to significant treatment effects, addressing health concepts that are relevant to the patients' perspectives. Specifically, the PF-10 has been used in numerous clinical trials and is considered a simple yet effective measure of mobility disability and also for epidemiological studies[36]. Climbing one flight of stairs (no change versus decline of two levels, two-point difference) or walking a block (no change versus two levels decline) exemplifies a substantial meaningful change, as appreciated by patients[36]. Change in muscle strength is directly related to the expected mechanism of action of the investigational drug and needs to be assessed. Assessment of muscle strength using the handgrip strength test is commonly used in interventional studies targeting muscle loss in older adults[21,23]
Other secondary		
1. To assess changes in body composition and specifically on appendicular lean body mass, which is an expression of sarcopenia. 2. To estimate the change of 400MW test as a dichotomous variable, for possible use in further studies. 3. To evaluate the effects of two daily doses of BIO101 versus placebo on	Change from baseline of ALM and other parameters of body composition based on DEXA measurements. The rate of success for completing the 400MWtest after the 6-month treatment versus placebo. Change from baseline of the distance during the 6 MWT. Change from baseline of muscle strength based on the knee extension and the SCPT.	Change of body composition and specifically the lean body mass as a proxy for change of muscle mass is an important parameter to measure with respect to the expected mechanism of action of the investigational drug, although many confounding factors can limit the use of this endpoint in a clinical trial. Change in muscle strength is directly related to the expected mechanism of action of the investigational drug and need to be assessed.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
mobility functions as measured by the distance measured during the 6 minutes walking test. 4. To estimate the effect on muscle strength. 5. To assess the overall change of the SPPB total score as a cumulative expression of the physical frailty status. 6. To assess muscle functions using a simplified function test, i.e. the change in time needed to complete the chair stand test. 7. To estimate the effect using a sarcopenia-specific PROs, in preparation of future studies.	Change from baseline of the SPPB total score. Change from baseline of the time for five chair stands as part of the SPPB assessment. Change from baseline using the SarQol, PAT-D and TSD-OC auto-evaluation questionnaire.	High variability and several confounding factors can limit the use of this endpoint in a clinical trial, as for the previous parameter. Change from baseline of SPPB will provide an estimate of the overall clinical impact of treatment on the burden of physical frailty. Improvement of the SPPB observed in the active intervention group in the LIFE study[16] was mostly explained by the chair stand test, while the balance test and 4-meter gait speed were only slightly modified. Change in SarQol PAT-D and/or TSD-OC will provide an estimate of the clinical impact of treatment on sarcopenia related symptoms from the participants' (subjective) perspective.



OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	[redacted]	

4 STUDY DESIGN

4.1 OVERALL DESIGN

SARA-INT is a 3-arm (2 doses versus placebo), randomized, double-blind, placebo-controlled parallel design phase 2 clinical trial. This comparative clinical trial evaluates the effects of a 6-month treatment duration, based on the hypothesis that physical function of sarcopenic, older patients with an initial degree of mobility disability (SPPB≤8) will be meaningfully improved after 6 months of oral treatment with BIO101 (in at least one of the two tested doses) with respect to placebo.

SARA-INT is a multi-site study that aims to enroll 231 community dwelling, older adults (men or women ≥ 65 years), reporting a loss of physical function over the previous 6-12 months, and at risk of mobility disability, to undergo screening tests for inclusion in the study. Included participants will be randomized in a 1:1:1 ratio, for one of the 3 arms of treatment in a blinded manner. The randomization will be stratified by gender and by center. Bias are minimized by the use of identical therapeutic units whose number is automatically assigned via an eCRF embedded algorithm after the Investigator confirms randomization of a participant. All included participants will complete the inclusion visit and start a 6 to 9-month treatment and observation, with the main evaluation at the end of the study duration. Based on non-clinical safety considerations, the investigational drug exposure is capped at 39 weeks. The complete Schedule of Activities is provided in Section 1.3.

An interim analysis will take place however, the number of completers, based on which it will be conducted, will be determined once restrictions are lifted and it is clear, how many participants dropped out before the end-of-study assessments.

[redacted]

[redacted]

[redacted]

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Study population

As stated in the introduction, we are including older adults who are still living independently in the community and who have encountered objective limitation of physical function as defined by a low SPPB score (SPPB≤8). A similar reasoning was applied to the SPRINT-T[17] clinical trial (SPPB≤9 with a quota of patients scoring ≤7) which is an approach consistent with recent recommendations by the European regulators (ICFSR, Philadelphia, 2016). In fact, prespecified analyses from the LIFE study clearly showed a better response in lower performers and raised the possibility of limited benefits in treating more robust individuals as compared to the lower functioning individuals.

Study Endpoints

Designing and implementing an adapted set of investigations to accurately and efficiently describe the progressive decline of physical function in at-risk older individuals is a challenge. There is currently no consensus on what is the most sensitive and specific primary endpoint, however, there is a general convergence on low gait speed being the key physical function related to an increased risk for mobility disability, falls, loss of independence and mortality.

The LIFE study, and its preparatory LIFE-P clinical trial, extensively evaluated the 400MW test in a population of community dwelling men and women aged 70-89 years old with a sedentary lifestyle and an SPPB ≤ 9. The 400MW was used as a dichotomous test with failure being defined as the inability to walk 400 meters without sitting and without help within 15 minutes. The incident rate of failure in the LIFE control group (n= 817) with no specific therapeutic intervention was 35.5% (290 out of817 study participants), and permanent mobility disability occurred in 19.8% over a mean follow-up duration of 2.6 years. An interesting fact is that the majority of mobility disability events were observed in the subgroup with SPPB<8, in 177 out of 378 study participants or 46.8%, for incident disability[15]. Transition rate from success to failure with the 400MW test over 6 months was 6.9% in LIFE-P. However, this outcome was more efficient as compared to the 4-meter walk, or the SPPB itself[30].

The 6MWT was initially validated and extensively used mostly in respiratory and cardiovascular conditions[31]. This test can be analyzed as a continuous variable, although a threshold value of 50 m improvement has been used as a dichotomous variable.

However, in a recent clinical trial on the effects of testosterone treatment in old men aged ≥ 65 years, relatively stable values for the 6MWT were observed over 6 months in the control group (n=196) and in the active treatment group (n=191) with no significant differences between the two groups[32]. Several reasons can be considered to explain this lower-than-expected effect of the tested intervention: a) the selection of a relatively preserved population in terms of motor function (i.e. gait speed≤1.2 m/s) and b) the choice of a minimum clinically important difference of 50 m although this threshold was previously validated in different patient populations that included those with total and knee arthroplasty or chronic lung disease (see methods in Snyder et al, 2014 ClinTrials[33]). The LIFE study used the 400MW test as a dichotomous test and as a proxy

for mobility disability. The same methodological approach was adopted in the case of SPRINT-T. Overall, the choice of this kind of primary endpoint can be particularly onerous in terms of study and intervention duration: LIFE participants were treated for two and a half years and the expected treatment duration for SPRINT-T is two years in order to detect a meaningful difference between treatment groups.

Therefore, Santanasto et al[16] performed additional prespecified analyses on LIFE results with the objective of identifying earlier changes that could anticipate later mobility disability or possibly focus on functional improvement and stabilization of muscle functions.

Interestingly, both the gait speed measured during the 400MW test and the chair stand sub-score of the SPPB showed a visible and statistically significant improvement at six months, followed by relative stabilization or decline. In general, gait speed decline has been strongly correlated to major outcomes like incident mobility disability, hospitalizations and lowered life expectancy.

For these reasons, the 400MW test **gait speed** was chosen as the primary endpoint for SARA-INT.

In terms of PROs, both the US FDA and the EMA recently emphasized the importance of accompanying physical function objective measurements by an auto-evaluation questionnaire estimating the corresponding improvement in the daily life activities (ICFSR Philadelphia, 2016; FDA Patient-Focused Drug Development Public Meeting for Sarcopenia April 6, 2017). The SF-36 is one of the most widely used, validated measures of health-related quality of life and has been shown to discriminate between subjects with different chronic conditions and between subjects with different severity levels of the same disease[35]. The SF-36 has also demonstrated sensitivity to significant treatment effects in a variety of patient populations. Population-based normative data on the SF-36 is available for the United States and other countries as well.

This instrument addresses health concepts that are relevant to the patient's perspective. There is no single overall score for the SF-36, instead, it generates 8 subscales and two summary scores. The PF-10 sub-score that measures role limitations due to physical problems, will be the key secondary endpoint for SARA-INT. PF-10 has been tested in numerous clinical trials and is considered as a simple yet effective measure of mobility disability and also for epidemiological studies[36]. Climbing one flight of stairs (no change versus decline of two levels, two-point difference) or walking a block (no change versus two levels decline) exemplifies a substantial meaningful change, as appreciated by patients[33,36].

Data from the recently completed SARA-OBS study could be useful to corroborate these hypotheses.

<u>COVID-19 pandemic</u>

Safety of study patients and investigators should be the priority during COVID-19 outbreak. Only ePROs (SF36, SARQoL, TSD-OC and Pat-D will be assessed during this period until further guidance. An extension of the treatment period for a total period of 9 months will enable the full assessment of the safety and efficacy of the investigational product for a significant part of the population randomized in this study, while staying in compliance with good clinical practice (GCP) and minimizing risks to trial integrity during the COVID-19 pandemic.

4.3 JUSTIFICATION FOR DOSE

Based on the pharmacokinetics and safety parameters of the SARA-PK phase 1 MAD part, the administration of 350 mg b.i.d. was selected as the highest dose to be tested in the phase 2b study. This dose was well tolerated as it generated few numbers of AEs with mild severity. The dose of 350 mg b.i.d. generated a C_{max} of 346 ng/mL [redacted] of BIO101 [redacted] The dose of 175 mg b.i.d. was selected as a second dose for the phase 2 study. This dose, being lower than 350 mg b.i.d., is anticipated to be safe and well tolerated. The 175 mg b.i.d. was not evaluated during the MAD part. [redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last on-site visit that includes all the safety and efficacy assessments and the post-intervention phone call or the last scheduled procedure for an end-of-study visit as shown in the SoA, Section 1.3.

The end of the study is defined as a completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

231 community dwelling older adults (men or women ≥ 65 years) living at home and reporting a loss of physical functions over the last six-twelve months and considered at risk of mobility disability will be included in this randomized, interventional clinical trial, with 64 patients per treatment group and a treatment period of 26 to 39 weeks. 39 additional participants will be randomized to allow a 20% of non-evaluable withdrawals or lost to follow-up for a total of 231 older adults included in the US and the EU.

It is expected, that due to COVID-19 related restrictions, that the number of non-evaluable withdrawals will be higher than 20%. However, reassessment of the sample size, will take place, as a part of the interim analysis, that will take place after restrictions are lifted.

A predefined subgroup efficacy analysis will also be performed in a number of pre-identified, at- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated **informed consent form**
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. **Male or female aged ≥ 65 years, living in the community** (living at home, able to walk outside from time to time. Homes can include living communities that may or may not offer optional services for the convenience of the residents. Older adults living in nursing homes or in medicalized residences where caretaker services are mandatory are not eligible) **and reporting a loss of physical functions over the last 6-12 months**
4. **SPPB score ≤ 8**
5. **ALM/BMI < 0.789 in men and 0.512 in women, or ALM < 19.75kg in men and <15.02kg in women, as measured by DEXA scan**
6. Ability to take oral medication and willingness to adhere to the study intervention regimen (see section 6)
7. Agreement to adhere to the Lifestyle Considerations (see section 5.4) throughout the study duration
8. In the US, women and members of minority groups should not be excluded, in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects

5.2 NON-INCLUSION CRITERIA

An individual who meets any of the following criteria will not be included in this study:

1. In France, non-affiliation to compulsory French social security scheme (beneficiary or right-holder)
2. In France, being under tutelage or legal guardianship

5.3 EXCLUSION CRITERIA AND TEMPORARY EXCLUSION CRITERIA

An individual who meets any of the following exclusion criteria will not be eligible to participate in this study. An individual who meets any of the following temporary exclusion criteria may be re-screened after 3 months.

Exclusion criteria:

1. Current use of anabolic drugs (e.g. testosterone); current use of Erythropoietin; current use of corticosteroid agents (except for local administration routes, such as eye drops or dermatologic formulations)
2. Non-menopaused women (however, ongoing hormonal replacement treatment is not an exclusion criterion if started at least 3 months before screening)
3. Known allergic reactions to sourcing components of the investigational drug [redacted]
4. Treatment with another investigational drug or other interventions within three months
5. Unable to understand and perform the functional tests, as judged by the Investigator
6. Inability to complete the 400MW test within 15 minutes
7. Clinical conditions:
    a. Current diagnosis of major psychiatric disorders
    b. Alcohol abuse or dependence
    c. Severe arthritis
    d. Cancer requiring active treatment (study participants with cancer previously treated with chemotherapy and/or radiotherapy, or study participants currently on remission is not an exclusion criterion)
    e. Lung disease requiring regular use of supplemental oxygen
    f. Inflammatory conditions requiring regular use of oral or parenteral corticosteroid agents
    g. 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)
    h. Parkinson's disease or other progressive neurological disorder
    i. Renal disease requiring dialysis, or known renal insufficiency (moderate or severe reduction in eGFR≤30 ml/min/1.73 m2, using Cockroft & Gault (CG) formula)
    j. Chest pain, severe shortness of breath, or occurrence of other safety concerns during the baseline functional test (the 400MW test)
    k. History or active signs or symptoms of gallbladder/biliary disease (e.g. previous episodes of cholestasis/biliary tract obstruction, cholelithiasis, cholecystitis, etc.). Of note, history of cholecystectomy and no active biliary signs or symptoms, is not an exclusion criterion
8. Current physical/rehabilitation therapy (except for passive physical therapy. However, this should not be initiated the week before an evaluation visit and once started, it should be maintained over the study duration)

<u>Temporary exclusion criteria:</u>

1. Uncontrolled hypertension (systolic blood pressure >200mmHg or diastolic blood pressure >110 mmHg)
2. Uncontrolled diabetes with recent weight loss, diabetic coma, or frequent hypoglycemia

3. Stroke, hip fracture, hip or knee replacement, or spinal surgery in the past 6 months
4. Heart arrhythmic disorder, e.g. third-degree heart block, uncontrolled arrhythmia, new Q waves within the past 6 months or ST-segment depression (>3mm) on the ECG. Of note, a current pace-maker implant is not an exclusion criterion
5. Myocardial infarction, major heart surgery (e.g., valve replacement or bypass surgery), deep vein thrombosis, or pulmonary embolus in the past 6 months
6. Febrile illness within 7 days
7. Recent introduction of hormone replacement therapy in menopaused women (less than 3 months before screening)

5.4 LIFESTYLE CONSIDERATIONS

During the SARA-INT 6-month treatment phase, all participants are asked to avoid a sedentary lifestyle and to try to perform at least 30 minutes of physical activity per day, at least 5 days per week. Physical activities can consist of walking, going for groceries, gardening, housekeeping, and light exercise (at home or outdoors) but only if the participant is already used to performing them on a routine basis.

Of note, walking and other physical exercise will be automatically recorded via a wearable actimetry device for later analyses. With this aim, all participants will be requested to wear the actimetry device most of the time as a wrist watch, including at night. They are expected to remove it only during showers and/or baths.

A structured physical exercise program should not be started during the study treatment phase.

During this study, participants are also asked to maintain a healthy diet and to avoid excessive or low food intake. A brochure reminding participants of simple rules for a healthy, nutritional diet will be provided to all participants.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failures) because of a temporary exclusion criterion may be re-screened after 3 months. These re-screened participants should be assigned the same participant number from the initial screening. Investigational sites are allowed to rescreen a participant who had borderline results for an eligibility criterium (*i.e*. SPPB=9) 6 to 12 months after their first screening, if the subject complains from a decline in his.hr physical abilities. These rescreened participants should be assigned with a new participant number compared to the first screening. Participants can only be screened twice.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

Mass mailings, posters or videos in the hospital/clinic waiting rooms, presentation of the SARA-INT study in local newspapers, on TV, radio broadcasting or on social media by the PI and

Investigators are all strategies that will be considered, made available and implemented/adapted according to the local policies and regulations. In addition, app-based tools could also be utilized.

A dedicated website to present the study to the general public is available online (https://mysara.eu/#/) and could be referenced by institutional websites.

Transportation vouchers could be provided to participants according to local policies and legislation.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The investigational product BIO101 is prepared in accordance with Good Manufacturing Practice (GMP) as required by Good Clinical Practice (GCP).

The BIO101 active principle ingredient is 20E, [redacted]

[redacted]

Placebo was prepared in accordance with GMP as required by the current GCP [redacted]

A Certificate of Analysis (CoA) is included in the CMC IMPD (Chemistry, Manufacturing and Controls Investigational Medicinal Product Dossier).

6.1.2 DOSING AND ADMINISTRATION

Three doses are tested in this study: 175 mg b.i.d. of BIO101, 350 mg b.i.d. of BIO101 or placebo b.i.d. A rationale for the doses selected of the study drug is provided in section 4.3.

Administered daily dose is the same throughout the whole treatment period.

All therapeutic units (175 mg BIO101 b.i.d. or 350 mg BIO101 b.i.d. or placebo b.i.d.) are identical in compliance with the double-blind process.

Study participants are instructed by the investigator or the investigation center staff to start the treatment the day after randomization; e. g. if the participant is randomized on Friday, he/she will start the investigational treatment on Saturday morning.

Each administration is made of two capsules, to be taken by oral route, swallowed with water or fruit juice or other common soft drinks. Capsules should be taken twice a day: once in the morning and once in the evening. Those can be taken with a meal such as breakfast or dinner,

approximately 12 hours apart. If the participant forgets or is not able to take the capsules at the appointed time, he/she should be instructed not to make up for the missed pills; i.e. to not take more capsules later in the day or the day after.

The four capsules to be taken daily is the same across the entire 6-month treatment period.

Important note: Date of each next visit should be calculated back on Day 0 visit (baseline) in order to not exceed the total duration of 26 weeks of treatment.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

In the US, all Therapeutic Units (TUs) will be distributed to the clinical centers by [redacted] will ensure all logistical steps including repository, physical management of TU packages and TU delivery to investigation centers in the US.
In Europe, all TUs will be distributed to the clinical centers by [redacted]). [redacted] will ensure all logistical steps including repository, physical management of TU packages and TU delivery to EU investigation centers.
The order to deliver the initial stock and further reorders of individual investigation centers will be given by the contract research organization, [redacted] according to the center's actual enrollment rate.

Return of expired TUs or unused TUs will be ordered by Biophytis.
Detailed information on TU handling will be provided in a Manual of Procedures (MOP).

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

BIO101 is formulated as a [redacted] capsule that includes 175 mg of the active principle ingredient, 20E, [redacted] Placebo is manufactured as an identical size 1 opaque capsule containing [redacted]

Capsules containing BIO101 and placebo are opaque and identical in appearance. The matching placebo capsule [redacted] Stability was tested following ICH regulations. In order to be fully compliant, the drug substance and the excipients are controlled according to the FDA and European pharmacopeia.

The study drug is packaged in [redacted] The study drug was labelled according to local law and regulatory requirements. All TUs had to be stored as specified at delivery and in the original packaging. In case of a deviation in storage conditions, the clinical site cannot dispense the affected study drug and have to notify Biophytis right away. Utmost care will be taken to correctly dispense the study drugs as assigned by the randomization system embedded within the eCRF.

TUs are made up of [redacted] The [redacted] is called a kit. Each kit is individually numbered.

Each [redacted] box, [redacted] contains [redacted] capsules, which is presented in [redacted] columns. [redacted]

[redacted]

[redacted] The actual capsule combinations correspond to daily doses of 175 mg b.i.d., 350 mg b.i.d. or placebo.

[redacted]

The box is conceived to be elderly friendly (US and EU), and child proof (for US only). Each individual study participant will receive a total of [redacted] over the 6-month period, released to the study participant according to the timeline of the study: [redacted] at randomization /baseline visit; [redacted] at the Month 1 visit , and [redacted] at the Month 3 visit.

Detailed information on TU dispensing will be provided in a MOP.

A representative labeling of the drug product is presented below:

Clinical Study Number: BIO101-CL03
Study treatment: "BIO101, or placebo"
Batch Number: #
[redacted] **capsules of BIO101 (175mg capsule) or placebo, per box**
Oral route, 4 capsules per day (two on the morning and two on the evening)
To be swallowed entirely without opening the capsules
Expiration Date: #

Kit Number: #

Patient ID *(to be completed at the center before supplying the patient)*
Investigator Name *(to be completed at the center before supplying the patient)*
Visit Number *(to be completed at the center before supplying the patient)*
Date dispensed *(to be completed at the center before supplying the patient)*

Store at [redacted] *away from light and humidity*
CAUTION: New Drug--Limited by Federal (or United States) law to investigational use
Drug for investigational use – keep out of the reach of children
Please return non-used capsules and empty boxes to your center at the end of the study

Sponsor: Biophytis, 14 avenue de l'Opéra – 75001 Paris – FRANCE
telephone: [redacted]

6.2.3 PRODUCT STORAGE AND STABILITY

Based on the available stability data of the Drug Product, Biophytis currently certifies a shelf life of [redacted] at room temperature and protection from light and humidity. For more details please also see the IMPD.

6.2.4 PREPARATION

All treatment packages are delivered ready to be given directly to the participants. No further preparation is needed by the study Staff.

Study participants should be instructed to take 4 capsules per day everyday in a specific order: the first two [redacted] in the morning and the second two [redacted] in the evening.

If a dosing administration is skipped, study participants should start a [redacted] the day after and should not take the skipped capsules.

Important note: **Date of each next visit should be calculated back on Day 0 visit (baseline) in order not exceeding the total duration of 26 weeks treatment (capped exposure)**

6.2.5 SHIPMENT

Following GCP guidance on the situation of the public health emergencies, the core consensus guidelines for clinical trial management and the study DSMB recommendation, the safety of study patients and investigators is the priority during this COVID-19 outbreak. No on-site visit is allowed during the COVID-19 outbreak. Therefore, during this period and until further guidance, participants will receive their IPs at home with direct shipping/delivery from the study sites. The boxes are shipped to the participants' homes only after the site investigator/staff(s) have completed reviewing of all relevant safety study assessment resultsfrom the the scheduled calls. Shipment to the participant's homes are carried out based on a predefined and specific process to guarantee the proper shipment conditions that ensure study drug integrity. For intake of the drug, all participants have already been educated during previous on-site visits by the study staff and will already know the proper method and schedule for drug intake.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will be stratified by center and by gender. Randomization is performed online at the time of the inclusion visit for each study participant fulfilling all the inclusion and non-inclusion criteria, according to the appropriate ratio. The randomization procedure is embedded within the eCRF, which is based on the [redacted] by [redacted] a 21CFR Part 11 compliant system.

Each treatment kit will show a pre-printed kit number affixed on the primary, secondary and tertiary containers. The kit number will be assigned via the eCRF after a patient qualifies and is randomized. Neither the Investigator, the staff or the Sponsor will be aware of the treatment that corresponds to the kit number. The assigned treatment cannot be retrieved from the system unless a specified **unblinding** procedure is engaged by the investigator. Unblinding can only occur when it is deemed necessary by the responsible physician of the investigation center in the context of a severe or serious adverse event.

The randomization list will be provided by [redacted] to the manufacturer and to the eCRF identified responsible person. The randomization list will not be available to the Sponsor staff, study participants, investigators, monitors or employees of the clinical site involved in the management of the study before unblinding of the data (after database lock), except in case of emergency.

The Clinical Research Organization (CRO) team from [redacted] performing the data management and statistical activities will receive a copy of the randomization list after database lock.

A specific unblinding procedure will be made available in the eCRF for the investigator to perform emergency unblinding of a given patient for documented reasons. An unblinding procedure can only be engaged in an emergency situation where the Investigator considers it essential to know what treatment the subject was receiving. The monitor shall be notified promptly if unblinding is performed. It is recommended that the Investigator contacts the [redacted] medical monitor before unblinding, if possible. The investigator will document the date, time, and reason for the unblinding in the patient's medical records.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the remote system in case of emergency. The investigator will inform the subject how to contact his/her backup in case of emergencies when he/she is unavailable.

Should the code be (intentionally or unintentionally) broken by the Investigator or by a clinical staff, whether the subject could remain in the study or not should be judged by the Investigator

according to the subject's best interest. The event will be immediately reported to the Sponsor and to [redacted] and dealt with as a major protocol deviation.

The subject's clinical data will not be analyzed in the per protocol set.

6.4 STUDY INTERVENTION COMPLIANCE

During the COVID-19 outbreak, all participants will be asked to send back all used and unused boxes containing the investigational study drug. These returns are carried out based on the same predefined and specific process as the one applied for the shipment from site to participants home. Adherence to the protocol will be assessed by the Investigator staff by counting the full and empty blisters.

A participant study drug log will be completed (to be kept in the source documents) and recorded into the eCRF. An algorithm will automatically calculate the adherence based on visit dates.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and supplements.

The following medications are not allowed during the study:

1. Anabolic drugs e.g. testosterone, growth hormone, etc. (replacement hormonal treatment for menopause is allowed if started at least 3 months before randomization without dose changing)
2. Anabolic supplements, e.g. branched-chain amino acids, anabolic treatments, or treatments containing 20E
3. Herbal treatments containing [redacted]
4. Erythropoietin
5. Corticosteroid agents chronically administered per oral or parenteral route (except local administration route such as eye drops or dermatologic formulations; except emergency parenteral administration for acute conditions like asthma, allergic reactions, etc.)
6. Chemotherapy
7. Radiotherapy
8. Androgen suppressant treatments (e.g. finasteride); estrogen suppressant treatments (e.g. tamoxifen)

Should a participant need or report the use of these drugs during the study due to treatment for an AE, the physician will make the decision to withdraw or to keep the patient in the study according to the patient's best health interest.

6.5.1 RESCUE MEDICINE

There is no specific rescue medicine for BIO101. Standard medical measures should be taken in case of an accidental or deliberate overdose of BIO101.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The Investigator should discontinue study intervention and specifically ensure that a participant stops taking the investigational drug if the bioanalytical results at Month 1 or Month 3 shows the following changes:

1. Confirmed 3-fold or greater elevations above the Upper Limits of Normal (ULN) of [redacted]

These stopping rules for discontinuation are established based on [redacted].

Discontinuation from investigational oral treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to, changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

The data to be collected at the time of study intervention discontinuation will include the following:

- AE complete follow-up (if the treatment is stopped following an AE)
- Last investigational medication administration date and time

The physician can decide to re-introduce the investigational treatment if it was stopped because of a concomitant acute condition he/she considers unrelated to the treatment.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participating in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy: however, in principle, only menopaused women are eligible in this protocol
- Significant study intervention non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive oral treatment for more than 4 weeks

The list above is provided as considerations to guide the investigators and the decision to discontinue or withdraw a participant is up to the investigator's discretion. A study participant is allowed to continue in the study, given his/her own choice, even if he/she needs to stop the study drug intervention.

The reason for participant discontinuation or withdrawal from the study will be recorded in the eCRF. Based on the number of study participants enrolled in each center, study participants who signed the informed consent form and are randomized but do not receive the study intervention may be replaced. Study participants who signed the informed consent form were randomized and received the study intervention, but subsequently withdrew, or are withdrawn or discontinued from the study, will not be replaced.

In any case, each subject needs to be randomized via the eCRF procedure, and already assigned TUs cannot be manually assigned to a new participant.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for all remaining scheduled visits and is unable to be contacted by the investigation site staff.

The following minimum actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant (and at default his/her proxy when available) and reschedule the missed visit within 2 weeks. The site will counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (a minimum of 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- If previously agreed by the participant, the study staff can decide to visit him/her at home in order to collect important medical information, and if applicable, perform a minimum functional assessment (i.e. SPPB).
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 PARTICIPANT DISCONTINUATION DURING THE COVID-19

During the COVID-19 pandemic, participants may not be willing to continue their participation in the SARA-INT study. Consent withdrawal due to the COVID-19 outbreak will be identified and recorded specifically in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The following tests will be used in SARA-INT. The specific timing of procedures/evaluations to be done at each study visit can be found in Section 1.3, Schedule of Activities.

Cumulative Illness Rating Scale (CIRS)

The Cumulative Illness Rating Scale (CIRS)[38,39] rates 13, conceptually valid, body systems (supporting content validity) on a five-point (pathophysiologic) severity scale. It has been slightly adapted to form the CIRS-G (CIRS geriatric), for which guidelines to enhance reliability have been formulated. Criterion validity has been confirmed by showing high correlation coefficients when comparing CIRS scores based on autopsy (the gold standard) with those based on health histories and chart reviews[40,41]. The CIRS was correlated with four other measures of comorbidity. Three out of five correlation coefficients exceeded 0.40, supporting concurrent validity. There is little evidence to support predictive validity. Small to fair positive correlations in the anticipated directions have been found for other variables, such as medication usage, ADL, IADL, and age, supporting construct validity[41]. Interrater and test-retest reliability are good.

In the present protocol, the CIRS is compiled by a medical doctor, on the basis of the physical examination and patient's clinical history. It will provide an estimation at baseline of the overall burden of disease.

Short Physical Performance Battery (SPPB)

In SARA-INT (and in SARA-OBS), the low physical performance is assessed first and defined by a low score as SPPB≤ 8. It is imperative to perform the SPPB at the beginning of the screening period, ahead of the DEXA or the ultrasound scans. The SPPB is a series of tests designed to examine physical movements[1]. The first test examines balance (without the assistance of a cane or walker) with the feet placed in 3 different orientations. The second test examines gait speed and the third test involves standing from a chair a number of times to test leg strength.

The SPPB, originally developed for the Established Populations for the Epidemiologic Study of the Elderly (EPESE), is a brief performance battery based on timed short distance walk, repeated chair stands and balance test[1, 29]. The battery is administered by trained examiners. The measurement goal for this battery is to assess lower extremity functional limitations, which indicates functional abilities and is a strong measure of risk for future disability. This test takes about 10-15 minutes to administer and can be done in the home or the clinic setting. The battery has an excellent safety record. It has been administered to over 20,000 people in various studies and no serious injuries are known to have occurred. The components of the battery are as follows:

- **Walking speed.** Walking speed is assessed by asking the participants to walk at their usual pace over a 4 m course. Participants are instructed to stand with both feet touching the starting line and to start walking after a specific verbal command.

Participants are allowed to use walking aids (cane, walker, or other walking aid) if necessary, but not the assistance of another person. Timing begins when the foot starts to move across the starting line and the time in seconds needed to complete the entire distance is recorded. The faster of two walks is used to compute walking speed.

- **Chair stands.** The repeated chair stands test is performed using a straight-backed chair, which is placed with its back against a wall. Participants are first asked to stand once from a sitting position without using their arms. If they are able to perform the task, they are then asked to stand up and sit down five times, as quickly as possible. The time to complete the task is recorded.

- **Standing balance**. For the test of standing balance, participants are asked to maintain balance in three positions, characterized by a progressive narrowing of the base support: with feet together (side by side position), the heel of one foot beside the big toe of the other foot (semi tandem position), and the heel of one foot in front of and touching the toes of the other foot (tandem position). For each of the three positions, participants are timed to a maximum of 10 seconds. Scores are summed for the measure of balance for a range of 0 to 30 seconds.

- **Summary performance score**. Each of the three performance measured is assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. For the test of balance, participants are assigned a score of 1 if they can hold a side-by-side standing position for 10 seconds but are unable to hold a semi-tandem position for 10 seconds; a score of 2 is assigned if they can hold a semi-tandem position for 10 seconds, but are unable to hold a full-tandem position for 3 seconds; a score of 3 is assigned if they can stand in a full-tandem position for 3 seconds but less than 10 seconds; a score of 4 is assigned if they can stand in a full tandem position for 10 seconds.

  Four categories are computed for walking speed and chair stands, according to cut-off points that are based on quartiles of the time to perform each task assessed in the EPESE. The time of the faster of two walks is scored as follows: > 8.7 sec = 1; 6.21 to 8.70 sec = 2; 4.82 to 6.20 sec = 3; < 4.82 sec = 4; a score of 0 is assigned to participants unable to perform the test. The time required to perform five chair stands is scored as follows: ≥ 16.70 sec = 1; 13.70 to 16.69 sec = 2; 11.20 to 13.69 sec = 3; ≤ 11.19 = 4. A score of 0 is assigned to participants unable to perform the task. A summary score ranging from 0 (worst performers) to 12 (best performers) is calculated by adding sub-scores from the walking speed, chair stands and balance tests.

The SPPB test will be performed during screening, at M3 and then at M6 or the end-of-study visit. During screening, it will allow evaluation of the patients' lower extremities physical function impairment and to measure loss of physical function.

The instructions for performing the SPPB test as well as for how to score each component will be standardized through the participating centers before the beginning of the study.

Dual Energy X-ray Absorptiometry (DEXA)

In SARA-INT, the definition of the muscle mass component of sarcopenia is based on the operational criteria proposed by the FNIH initiative[2]. FNIH reports triggered a re-appraisal of existing operational definitions of sarcopenia, such as the one from the EWGSOP, that were mostly based on experts' consensus. The new findings of the FNIH relied on a meta-analysis of eleven clinical trials with men and women ≥ 65 years. Applying the Classification and Regression Tree (CaRT) statistical model allowed for testing of several variables that best predicted low gait speed and weakness which are the two functional consequences of age-related sarcopenia.

The FNIH project report recommended two alternative gender-specific measures to be used to define low muscle mass[2]. The first FNIH definition, ALM-to- BMI ratio or ALM/BMI, is the one recommended by the FNIH project, while the second definition using the ALM alone is proposed as an alternative.

DEXA scan examination should be performed during the later phase of the screening period after the SPPB assessment. This should be performed only if most of the screening procedures, with the exception of the ultrasound and the 400MW test, have passed the inclusion criteria.

DEXA is a simple, quick and non-invasive examination. DEXA scans can provide accurate measurements of body composition, recording fat and lean mass distribution throughout the entire body. Radiation exposure for the participant is relatively low, approx. 0.0042 mSv for an adult scanned on the Hologic Discovery A device[42].

DEXA exams will be standardized through the study participating centers.

400 Meter Walk (400MW) Test

The 400MW test is a measure of how long it takes a participant to walk a distance of 400 meters. In addition, the need for each participant to stop and rest (yes/no) and the ability to complete the test at all (yes/no) are factored in as variables. Since the gait speed measured during the 400MW test is defined as the primary endpoint, it is imperative to perform the 400MW test as the last test during the screening period, on Day 0 (prior to randomization) or within 48 hrs of Day 0, in order to ensure data accuracy.

The test will be performed at the study centers. Study participants will receive instructions to walk 400 m on a 20 m walking course (20 laps of 20 m) following a 2-min warm-up with standard encouragement from the study team. Instructions will be to walk at the usual pace. (For precise instructions and to obtain the script to be followed, please refer to the study handbook and/or the SARA portal digital version of the instructions and script).

Non-disabled participants are defined as participants who are able to walk 400 m within 15 minutes without sitting, leaning against the wall, or assistance of another person or walker.

During the study, the onset of major mobility disability will be defined as the inability to complete the 400 m walk within 15 min without sitting, leaning against the wall, or assistance of another person or walker, and will be the primary study outcome assessed.

The time needed to perform the 400 m walk as well as whether or not the study participant performed the test without any assistance (i.e. successful test or onset of mobility disability) will be reported in the eCRF.

The inability to complete the 400MW test during the screening period is an exclusion criterion.

If the participant is unable to complete the 400 m, the actual distance reached and the time spent before suspending the test will be reported.

The instructions to perform the test as well as to evaluate it (including timing) will be standardized throughout the study center teams.

The choice of **gait speed** measured using the 400MWtest as a **primary** outcome in SARA-INT is justified by its prevalent use in similar study populations (LIFE-P[30], LIFE[15], SPRINT-T[17], VIVE2, etc.). Gait speed, a continuous variable, is well adapted to a phase 2 study for assessing dose ranges. Specifically, Santanasto et al[16], have demonstrated the sensitivity of the test to a 6-month structured physical activity regimen versus an educational intervention in the LIFE study population.

This test also provides a dichotomous result (i.e., capacity/incapacity to complete the task) that accurately reflects a specific and clinically relevant condition, which is mobility disability[1]. The ability to walk 400 m is a proxy for mobility within the community and independent living[16]. As opposed to walking tests aimed at measuring the reserve capabilities of an individual (e.g. 6MWT), the 400MW test is very safe and does not need to be performed as fast as possible. On the other hand, the relatively long distance walked allows identification of those individuals with mobility limitation but who may appear to be well functioning during shorter tests (e.g., 4 meters). The 15-minute time limit of the 400MW test is indeed there to differentiate the mobility efficiency of the individual. The inability to complete the 400MW test has already been used as the defining criterion for mobility disability in major clinical trials, in particular the LIFE-P and full-scale projects[15,30]. It has been demonstrated that the capacity of the 400MWtest to predict major negative health-related events (including disability and mortality) is independent of comorbidities.

A difference of change from baseline of 0.1 m/s is determined to be the minimal clinically meaningful change between treatment groups based on preliminary analysis of the SARA-OBS participants, and a change of 0.1 m/sec will also be considered as a substantial clinically meaningful change to patients, according to Perera et al, 2006[36].

6 Minute Walking Test (6MWT)

The 6MWT is a test for functional exercise capacity and involves measuring the distance a participant can cover within the allotted time of 6 minutes.

The 6MWT has gained importance in the assessment of functional exercise capacity in patients with chronic respiratory disease. It has been used in many studies with elderly people. The 6MWT has proved to be reliable, inexpensive, safe and easy to apply[43,44]. In addition, it correlates well with important outcomes including death[45,46]. Considerable variability was observed in the

distance walked in the 6MWT in studies performed by healthy volunteers[46,47]. The study performed with healthy elderly study participants aged 50-85 years[47] showed that the 6MWT distance ranged from 383 to 820 m. On average, the distance was 631 ± 93 m. An important part of the variability in 6MWT was explained by height, gender, age and weight as dependent variables.

The rationale behind the choice of 6MWT is guided by several points. First, this is a continuous assay that can be used to evaluate the percentage of decline over a period of time as well as the average speed in 6 minutes. Second, walking tests and endurance tests share many characteristics in common and there is a good correlation between the 6MWT and the VO2max[46,48,49]. Third, from a functional point of view, the 6MWT can be used to assess the physical fitness and exercise capacity of individuals with poor physical condition, heart disease or advanced age as described in several studies[1,49].

The 6MWT should be performed indoors in a long (approximately 100 m), flat, straight, enclosed corridor with a hard surface. The walking course could be 30 m in length; with length marked every 3 m. The turnaround point should be marked with a cone and a starting line should be marked with brightly colored tape.

The test should be stopped at the onset of any of the following:

- Chest pain
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale/ashen appearance

Further information on required equipment, patient preparation, measurements and safety issues are available in the Guideline for the Six-Minute Walk Test[31]. The distance walked in the 6MWT will be measured at Day 0 and at M6 and will be reported in the eCRF.

Repeated negative results in similar population studies, however, failed to validate the use of the 6MWT as a primary endpoint in sarcopenia. For these reasons, we will apply it as a secondary endpoint and a benchmark towards previously investigational treatments.

Stair Climb Power Test (SCPT)

Locomotion on stairs is among the most challenging and hazardous activities of daily living for older individuals. This is evidenced by the reports that stair falls account for more than 10% of fatal fall accidents[50]. Moreover, stairs require greater range of motion from the joints of the lower limb and greater muscle strength, with the demands on the joints and muscles differing between stair ascent and descent. Stairs are a more advanced activity of daily living and thereby may demonstrate functional difficulties more readily than walking tests[51]. All the features render the ability to climb one of the key markers of functional independence in older adults[52]. However, there is still a great need for a better characterization for stair negotiation (stair climbing and descent) as this activity has been identified as a major limitation in functional assessment in

several reviews[53]. Stairs also have the benefit of being able to measure multiple systems and highlight the limiting factors between the musculoskeletal, neurological, and cardiorespiratory systems. This makes the test even more valuable for assessing elderly or frail populations who may have multiple limitations. Stairs are currently increasingly being used in clinical practice as both an assessment tool and as part of exercise programs[54]. The benefit of the SCPT is that stairs are readily available, convenient, and cheap to use. The SCPT has been considered as a clinically relevant measure of leg power impairment as the results are consistent with more complex techniques for measuring leg power (double leg press at 40 and 70% of the one-repetition maximum) and performance (SPPB with components of gait speed, chair stand time and standing balance)[54].

The SCPT measures the ability to ascend and descend stairs and tests lower body strength and balance and measures time (in seconds) taken to ascend and descend a flight of stairs (10 steps with a 20 cm step height; a handrail is recommended). Step heights should be suitable (between 16 and 20 cm). Measurements will be performed at Day 0 and at the M6 visit, and will be recorded in the eCRF.

Handgrip Strength Test

Handgrip strength will be measured using a Jamar dynamometer handle. The width of the dynamometer will be adjusted for each participant separately for optimal fit. Participants will be instructed to stand upright and with the dynamometer beside them but not against their body. Strength will be measured 3 times for both hands and will be recorded in kilograms. The highest value of all 3 attempts will be kept for further analysis. If the participant reports current flare-up of pain in the dominant wrist or hand, or has undergone fusion, arthroplasty, tendon repair, synovectomy, or other related surgery of the dominant hand or wrist in the past 3 months, it is o.k.to have only the other hand tested. The same dynamometer will be used in all study centers and it should be calibrated regularly.

Handgrip strength is a commonly used measure of upper body skeletal muscle function and has been widely used as a general indicator of frailty with predictive validity for both mortality and functional limitation[55,56]. Other than possible temporary discomfort during the test itself, there are no known risks for the participant.

The isometric handgrip test will be performed at Day 0 and at M6 visit or the end-of-intervention visit.

At Day 0 it will allow the evaluation of the patients' strength or weakness and characterization of loss of muscle strength in the context of low physical performance and sarcopenia.

The instructions to perform the test as well as how to score each component will be standardized through the study centers before the beginning of the study.

Knee Extension Test *(optional according to center feasibility)*

Strength can be measured isometrically or isokinetically, the latter being a closer reflection of muscle function in everyday activity. Isometric strength testing of maximal voluntary contractions

can be measured with relatively simple custom-made equipment. It is usually measured as the force applied to the ankle, with the subject seated in an adjustable straight-back chair, the lower leg unsupported and the knee flexed to 90°[57].

The knee extension measurement will be performed using protocols described in several publications[57], and using preferably the Biodex System isokinetic dynamometer. Isometric knee extension torque will be measured with a knee extension dynamometer chair. The participants will be positioned in an upright position, with straps to affix the hips to the chair and the ankle to a force or torque transducer at the knee angle of 90°. Lever arm length will be recorded as the distance between the knee axis of rotation and the middle of the pad. After 3 warm-up trials at 50 and 90% of self-perceived maximal strength, 3 trials will be conducted to measure maximal voluntary contraction (MVC) force of the knee extension muscle. For each attempt, maximal force or torque will be recorded by the transducer and saved on the computer. Each assay will be separated by a 1 minute rest period. Knee extension torque will be obtained either directly or by multiplying recorded peak force with the lever arm length. The assay with the highest torque output will be taken for analyses.

PATIENT REPORTED OUTCOMES:

Short Form-36 (SF-36)

The SF-36 is one of the most widely used, validated measures of health-related quality of life and has been shown to discriminate between study participants with different chronic conditions and between study participants with different severity levels of the same disease[34,35]. The SF-36 has also demonstrated sensitivity to significant treatment effects in a variety of patient populations. Population-based normative data on the SF-36 is available for the United States and other countries as well.

This instrument addresses health concepts that are relevant to the patient's perspective. There is no single overall score for the SF-36, instead, it generates 8 subscales and two summary scores. The 8 subscales are: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems, and mental health. The two summary scores are the physical component summary and the mental component summary. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the more disability; the higher the score the, less disability (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

The physical function sub-score of PF-10, role limitations due to physical problems, will be a key secondary endpoint of SARA-INT. PF-10 has been tested in numerous clinical trials and is considered a simple and effective measure of mobility disability and is also often used in epidemiological studies (Syddall, 2009[35]). Climbing one flight of stairs (no change versus decline of two levels) with a 2-point difference) or walking a block (no change versus two levels decline) exemplifies a substantial meaningful change, as appreciated by patients (Perera, 2006[36]).

In SARA-INT, SF-36 will be auto-administered, either electronically or by filling out a paper booklet manually as provided by the clinical center .

Pepper Assessment Tool for Disability (PAT-D)

The Pepper Assessment Tool for Disability (PAT-D) is a disability questionnaire that was developed to assess difficulty with functioning in both discrete tasks and social/role functioning. The PAT-D has been widely used in randomized controlled trials and observational studies in a variety of chronic health conditions[58]. There are three domains: mobility, activities of daily living, and instrumental activities of daily living. This questionnaire asks respondents how much difficulty they have had with a range of activities in the past month due to their health. For each item, respondents answer on a 5-point Likert-type scale whether they experience: (1) no difficulty, (2) a little difficulty, (3) some difficulty, (4) a lot of difficulty, or (5) unable to do. For each item there is also a 'not applicable' option if the respondent usually did not do that activity for reasons other than disability. The PAT-D produces a score for each of the three domains as well as a total score, with higher scores indicating greater disability.

This questionnaire will be administered by the clinical center personnel at Day 0 and M6.

Sarcopenia Quality of Life (SarQoL)

The SarQoL is a sarcopenia-specific, self-administered, quality of life questionnaire designed for community-dwelling elderly study participants aged 65 years and older[59]. The questionnaire will be provided to study participants in the appropriate language. The questionnaire contains 22 questions, which takes approximately 10 minutes to complete. The questionnaire covers 7 domains: physical and mental health; locomotion; body composition; functionality; activities of daily living; leisure activities; and fears. Most questions are answered on a 4 point Likert scale.

This questionnaire will be auto-administered, electronically or filling a paper booklet provided at the clinical centre.

Test SIO Disabilità Obesità Correlata (TSD-OC)

The TSD-OC is considered a reliable and valid instrument for measuring self-reported disability in obese subjects[60]. The questionnaire is a set of multiple questions in 7 dimensions to measure pain; stiffness; function and autonomy in daily activities, housework, outdoor activities, occupational activities, and social life. Each question is scored by the subject from 0 (best) to 10 (worst). Each dimension score is calculated and then all dimension scores are added together for a total TSD-OC score.

8.2 SAFETY AND OTHER ASSESSMENTS

Several procedures and evaluations in SARA-INT clinical protocol will be performed to monitor the study intervention's safety. Some of those are necessary for other purposes (e.g., screening, eligibility, and enrollment).

- **Physical examination:** a standard medical exam of all organ systems to detect possible concomitant conditions that could represent an exclusion criterion (e.g. food ulcer, lower limbs arterial insufficiency, severe respiratory condition, etc.)

- **Anthropometry**: includes height and weight, subcutaneous tissue thickness (with the help of a plicometer) and various circumference measurements
- **Short Form -Mini Nutritional Assessment (SF-MNA):** this is a 6-question short form of the MNA that can be completed in 5 minutes or less. The MNA has been validated in international studies with a broad range of HCPs in a variety of settings. Currently, this instrument is administered by healthcare professionals to determine patients' nutritional status (Huhmann et al, 2013)[61]
- **Vital signs** (pulse and blood pressure) are measured at screening, M1, M3 and M6 (or end-of-study) visits. These are measured twice, in lying or sitting and standing positions
- **Electrocardiograms (ECGs)**: this is performed for screening purposes only. It will be read locally, in order to exclude any underlying cardiac diseases that could represent an exclusion criteria. Meaningful abnormalities will be reported on the eCRF. The original will be kept in the source documents. This should be conducted prior to the start of any physical functional assessments (e.g. the 400MW test) for the safety of the study participants
- **Radiographic or other imaging assessments:** 1) DEXA scan in SARA-INT is mostly devoted to assess body composition in terms of appendicular lean body mass, at screening visit and M6 (or end-of-study visit). DEXA scans could be performed up to 8 weeks before randomization and enrollment. 2) Gallbladder ultrasound: this is required during screening to exclude previous or active hepatobiliary diseases (e.g. cholestasis/biliary tract obstruction, cholelithiasis, cholecystitis, etc.), and is repeated at the end of the treatment (M6 visit) to assess any emergent hepatobiliary abnormalities
- **Biological specimen collection and laboratory evaluations:** Blood samples will be collected by venepuncture or via indwelling cannula at screening, M1, M3 and at M6 visits for biochemistry and analyses. In case of previous abnormalities or new symptoms, a blood sample can be collected at M5

    a. **Hematology**: hemoglobin, HbA1c, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume

    b. **Biochemistry**: sodium, potassium, chloride, bicarbonate, urea, uric acid creatinine, albumin, glucose, cholesterol (total cholesterol, LDL, HDL fractions), triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bone-specific alkaline phosphatase, lipase, amylase, gamma glutamyl aminotransferase, bilirubin (total, indirect, direct), creatine phosphokinase and mb-creatine phosphokinase, lactate dehydrogenase, total protein, and GFR estimation based on Cockroft & Gault calculation

    c. **Coagulation**: activated partial thromboplastin time, prothrombin time, and international normalized ratio.

    d. **Urine analysis**: A midstream urine sample will be collected for urinalysis by dipstick for glucose, protein, and occult blood

All study analyses will be performed by a centralized laboratory. The Investigator must review the laboratory report, document this review, and record any changes occurred during the study. Laboratory values outside the normal ranges will be flagged and their clinical relevance will be assessed by the Investigator. **See also Exclusion criteria based on lab results and stopping rules in Section 5.3** Exclusion criteria and temporary exclusion criteria and **Section 7.1** discontinuation of study intervention, respectively.

- **Counseling procedures, including any dietary or activity considerations***: see section 5.4 Lifestyle considerations*
- **Assessment of study intervention adherence**: see Study Intervention Compliance, section 6.4
- **Administration of the PROs**: see Efficacy Assessments, Section 8.1
- **Assessment of AEs:** At each visit, participants will be explicitly asked to report any new symptoms or any newly observed abnormality since the previous study visit. An unsolicited AE is one reported without any prompting or in response to a general question such as "Have you noticed anything different since you started the study, since you began the study intervention and etc.". A solicited AE is one that is specifically solicited such as "Have you noticed any falls since you started the study medication?". Ongoing AEs/SAEs will be followed up until resolution or clinical stabilization. See also Section 8.3.4, Time Period and Frequency for Event Assessment and Follow-Up.

Participants will be provided with the results of their ECG and laboratory analyses.

Due to the COVID-19 situation and safety concerns over viral transmission, every investigational visit within the protocol is now be performed remotely (e.g. by phone) for all participants still active in the study by the investigational site staff. The investigational site will continue to monitor the health status of the participants by collecting information on general health status, Concomitant Medication and Adverse Events.

M7.5 and M10.5 phone calls include a pre-diabetic questionnaire as recommended by

the DSMB committee.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity:

- **Mild** – Events that require minimal or no treatment and do not interfere with the study participant's daily activities
- **Moderate** – Events that result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning
- **Severe** – Events that interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious"

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to the study intervention assessed by the clinician who examines and evaluates the study participant based on the temporal relationship between the occurrence of the AE and the study drug administration and based on his/her clinical judgment. The degree of certainty about any causality will be graded using the categories below. In a clinical trial, the study product must always be suspected.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "potentially related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

For any reported AE, the study investigator will report the relationship to study intervention in the eCRF.

8.3.3.3 EXPECTEDNESS

The DSMB will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

The expectedness determination will take place during periodic reviews, or exceptional reviews, as needed.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits, during interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by

those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

A SAE follow-up includes a prompt blood sampling for PK analyses, if deemed applicable by the Investigator or by his/her staff. Any medical condition that is present at the time that the study participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates while performing any physical assessments at any time after signing the ICF (including the screening period), it will be recorded as an AE. Unanticipated problems (UPs) will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

For the purposes of this study, AEs will be recorded from the time of informed consent until the completion of the study or at the end-of-study visit. However, AEs occurring prior to randomization will not be included in the analysis of the reports of events so it will not be part of the risk-benefit assessment in relation to the study intervention.

All ongoing AEs should be followed up for 30 days after the end-of-study visit.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor of any SAEs, whether or not considered study intervention related, including those listed in the protocol or investigator brochure, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar

days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

All SAEs must be reported by the Investigator within 24 hours to the [redacted] mail box:

[redacted]

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to [redacted] within one day as described above. For a non-serious AE that becomes serious but which is not fatal or life-threatening, a complete clinical report should be received within 5 days.

The following variables will be recorded for each AE: verbatim AE description, time and date for AE start and stop, maximum intensity, seriousness, causality rating, whether or not the AE caused the patient to discontinue, and the outcome.

All SAEs have to be reported, whether or not considered causally related to the study procedures. All SAEs will be recorded in the eCRF. The investigator is responsible for informing the IEC/IRB of the SAE based on local requirements.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

In this study, **falls and injurious falls as well as orthostatic hypotension** are considered events of special interest.

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

Unexpected in terms of nature, severity, or frequency given:

- The research procedures that are described in the protocol-related documents, such as the IEC/IRB-approved research protocol and informed consent document
- The characteristics of the participant population being studied
- The event is related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- The suggestion that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

This study will use the OHRP definition of UP.

In this study, in which tests an investigational drug in older adults, and applies well established diagnostic tests and procedures, all precautions will be taken for prompt detection and reporting of UPs.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report all medically relevant UPs to [redacted]. [redacted] will report to the lead principal investigator (PI), Sponsor, the DSMB and the reviewing IRB.
The UP report will include the following information:

- Protocol identification information including protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 24 h of the investigator becoming aware of the event
- Any other UPs will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the problem

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 15 days of the IRB's receipt of the report of the problem from the investigator

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The main hypothesis to be tested in this study is the superiority of at least one dose of active versus placebo on the change from baseline of the 400 m gait speed criterion after 6 months of treatment.

In order to deal with the multiplicity issue due to the two doses, a Hochberg procedure will be used for testing the main hypothesis.

Full details of the analysis and the procedure will be given in the statistical analyses plan (SAP) of the study.

9.2 SAMPLE SIZE DETERMINATION

Originally, the sample size was calculated for a comparison test at a 0.05 two-sided significance level, a power of 80%, to detect a difference of 0.05 m/s (minimal clinically important difference) between active groups and placebo on the change from baseline in the 400 m gait speed at 6 months, with a standard deviation of 0.13 (estimated from the VIVE2 trial, Fielding et al, 2017[62]).

After analysis of the preliminary data from our observational trial data (SARA-OBS, with approx. 105 completers), the following were learned:

- During the 6 months follow-up, this study population deteriorated as suggested by a decreased gait speed of 0.05 meter per second on the 400MW test, with a standard deviation of the change from baseline of 0.2
- The expected effect of BIO101 remains at 0.05 meter per second, as the change from baseline
- Together, this new information allows an increase of up to 0.1 m/s to be considered as a minimal clinically important difference of changes at the M6 visit from baseline between the treatment groups. Under these assumptions, a number of 64 patients/group is needed, giving a new sample-size of 192 patients for 3 arms, with a standard deviation of 0.20 (estimated from SARA-OBS preliminary data).

Taking into consideration this increased expected difference between treatment arms, a formal interim analysis will be performed by the DSMB when half subjects reach their month 6 visit (See section 9.4.6). Once half study participants complete their End-of intervention study visit, an unblinded 'promising zone' interim analysis will take place and determine if there is a need to increase the sample size based on the complete efficacy data.

Based on current calculation and given a limited 20% provision for premature withdrawals or lost-to-follow up, a total number of 231 participants will be included in the study.

It is expected, that due to COVID-19 related restrictions, that the number of non-evaluable withdrawals will be higher than 20%. However, reassessment of the sample size, will take place, as a part of the interim analysis, that will take place after restrictions are lifted.

9.3 POPULATIONS FOR ANALYSES

The following analysis populations will be considered:

- The safety population consists of all patients randomized in the study for whom there is any evidence that they used study medication and for whom any follow-up information is available.
- The Full Analysis Set (FAS) population consists of randomized study participants, potentially excluding a few participants who failed to take at least one dose of trial medication and had a very early withdrawal (first week after randomization) definitely not related to study medication and lacked any post randomization data (CPMP/ICH/363/96).
- The Per Protocol (PP) population will exclude FAS patients with major protocol deviations that are related to drug administration (e.g. a long interruption period, see section 7.1) that may impact the efficacy analysis. The exclusion of patients from the PP population will be determined in a blinded data review meeting that will be held prior to the disclosure of the randomization list. Reason(s) for exclusion will be provided for each patient.

The safety population (all the included patients having taken the product at least once) will be the set for the safety analyses.

Concerning the main endpoint and the key secondary endpoints, the FAS population will be the population of interest (main population). However, for sensitivity purpose, the corresponding analyses (mixed models and logistic regression models) will also be fitted on the PP population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The SAP will be finalized & signed-off before database lock and unblinding.

All inferential tests will be two-tailed and with a 5% alpha risk, unless otherwise specified.

Descriptive statistics (mean, standard deviation, 95% confidence interval for mean, minimum, median, maximum, and number of observations and missing cases) will be used for quantitative variables, and frequencies and percentages will be used for categorical variables. The descriptions will be broken down by treatment group.

A Hochberg procedure will be used to deal with the multiplicity concern on the main endpoint and the key secondary endpoints. Other multiplicity concerns (relative to secondary endpoints) are kept under control by the pre-specification of key-secondary endpoints and a low number of secondary endpoints and analyses.

Due to the quantitative form of the endpoints (gait speed PF10 and handgrip strength test) and the large number of patients, the normal assumption for the residuals of the mixed models will be assumed. However, if found necessary, additional non-parametric approach could be added and detailed in the SAP of the study.

The covariates included in the models are the stratification factors (gender and center) and the baseline score of the parameter if available. No interactions will be included by default in the models, however, in case of interesting findings in the subgroup analyses, further analyses would be conducted.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

A Mixed Effect Model Repeat Measurement (MMRM) model with fixed factors in treatment, in centers, the baseline score and the stratification factor (gender) will produce an estimate of the contrast at M6 in the change from baseline of the 400MW test gait speed between each active arm and the placebo group (after adjustment by the Hochberg procedure).

The MMRM model will give a correct estimation in presence of missing data, under the Missing at Random (MAR) assumption. This analysis will provide an estimand of the efficacy of the tested product in the population that stayed in the study for the entire 6 months. Additional sensitivity analyses may be added in the SAP during the blind-review meeting if the number of missing data is important (more than 10%).

The same model will be also fitted in the Per Protocol population to give an estimand of the efficacy of the product in the population with good compliance.

Alternative methods to adjudicate missing data for the primary endpoint like the Bayesian Multiple Imputation (MI) methods could be considered and adopted before to finalize the SAP. Chen at al (2017) demonstrated the interest of applying Bayesian MI method to 400MW non-completers in the LIFE study[63].

Additionally, a responder analysis will be provided, using a logistic regression (with the same fixed factors as the mixed model) to model the chance to be a responder for the 400MW test (improvement of 0.1 m/s or more). The odds ratio of each active group versus placebo will be provided with a 95% confidence interval (CI).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The key secondary endpoints (handgrip strength and PF-10 sub-score of the SF-36) will be analyzed with the same strategy as the primary endpoint (i.e. using a repeated measures mixed model to estimate the contrast at M6 of the difference of each active group versus placebo).

Missing data will not be replaced in these analyses but the MMRM model on observed data is known to perform well under a MAR hypothesis.

Additional sensitivity analyses may be added in the SAP during the blind-review meeting if the number of missing data is important (more than 10%).

Concerning the responder endpoints:

1. for the PF-10 sub-score of the SF-36, a responder analysis will be performed with a responder definition of "patient with an improvement of PF-10 greater or equal to 2 points versus baseline", at an individual level.
2. for the handgrip strength test: a responder definition is equal to the minimal significant benefit set at least 2 kg of improvement versus baseline, at an individual level.

The rate of responders (according to the predefined definitions provided in the corresponding endpoint sections) will be provided in each group of treatment at M3 and M6 visits for the PF-10 sub-score and at the M6 visit only for the handgrip strength test. Participants without any assessment for a parameter at a visit will be considered as non-responder for the corresponding parameter.

A logistic regression model with treatment group, gender and center as fixed effects will be used to compare each active group versus placebo at M6. The odds-ratio comparing groups will be provided as well as its 95% confidence interval. The multiplicity issue due to the two doses of active treatment will be addressed using the Hochberg procedure.

The other secondary and exploratory endpoints will be analyzed only in the FAS population.

Details and exploratory endpoints analyses will be provided in the SAP.

9.4.4 IMPACT OF THE COVID-19 OUTBREAK

Due to the COVID-19 outbreak, an updated strategy for the final analysis will be implemented, to account for the missing data on safety and efficacy which will have impact on the final analysis This will include sensitivity analyses comprising before/during/after COVID_19 outbreak. This will be detailed in an updated version of the SAP.

In addition, sample-size reassessment, will take place, based on an interim analysis, which will take place once the COVID-19 restriction is lifted, to account for additional non-evaluable withdrawals and other considerations, based on reduced activity of participants due to restrictions.

9.4.5 SAFETY ANALYSES

Safety variables will be summarized/analyzed by groups of treatment, on the Safety population.

Vital signs, biochemistry and hematology parameters will be described by descriptive statistics, for the entire period of the study and at each timepoint.

Usual tables (by SOC and preferred term) will be produced for AEs (falls, injurious falls and orthostatic hypotension will be tabulated separately) after coding with the MEDRA terms.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

The disposition of study participants at each visit will be described, by treatment groups and overall, as well as the number of premature discontinuations and their main reasons.

Demographic and baseline characteristics of the patients will be presented overall and by treatment arms with descriptive statistics (mean, standard deviation, median, range and number of missing cases for quantitative parameters and percentages and number of missing cases for the qualitative parameters).

Compliance will also be described and compared by treatment groups. Details of the calculations will be provided in the SAP of the study.

9.4.7 PLANNED INTERIM ANALYSIS

The primary endpoint is the gait speed measured during the 400MW test. The group-sequential design consists in one interim analysis, which was originally planned to take place when 50 participants have finished their participation. Due to the COVID-19 restrictions, this analysis is postponed. The timing of this analysis will be defined once restrictions are lifted and will take into account, COVID-19 related non-evaluable withdrawals and reduction of activity.

The sample size increase will use the 'promising -zone' method of Mehta and Pocock (Mehta, 2011)[64] for an interim analysis. This approach ensures that the sample size is only increased in case the interim results are promising, in which case the overall type-I error is not inflated by use of the conventional Wald statistic. More specifically, this 'promising zone' is defined in terms of the conditional probability of rejecting the null-hypothesis at final analysis, given the estimated difference at interim ('conditional power') and assuming that this estimated difference is the true underlying difference. Depending on the conditional power (CP) at interim analysis, we consider three different zones and anticipated actions:

1. Unfavorable zone

The interim results are so disappointing that it is not worth to increase the sample size to retrieve CP and the original sample size is retained. This zone will be defined for a sample size reassessment at 50% information fraction and a maximal increase in sample size 100 additional

participants. Note that in case the observed gait speed difference at interim below the threshold defined in the SAP, the study would stop for futility.

2. Promising zone:

If the CP is below the originally planned 0.80, the sample size will be increased to the maximal sample size of 330.

3. Favorable zone

The conditional power is at least 0.80. In this zone, the interim results are sufficiently favorable for the trial to continue to the original sample size without the need to adaptively increase the trial size.

The DSMB will be responsible for reviewing accumulated safety and efficacy data at intervals throughout the study.

In particular, the DSMB will evaluate the results of a formal pre-planned interim futility analysis and sample size reassessment. The DSMB will recommend to the Sponsor whether to continue, modify or stop the clinical trial based on futility but also on safety issues or other considerations not related to efficacy or safety. In case the study continues and the original sample size is retained, the DSMB will not communicate to anyone whether this is due to unfavorable or favorable results.

9.4.8 SUBGROUP ANALYSES

A predefined subgroup efficacy analysis will be performed in a number of pre-identified, at-high risk of worsening, subpopulations:

- Low gait speed
- Sarcopenic obesity
- Study participants with a chair stand sub-score of ≤2 of the SPPB
- Study participants who experience a deterioration in their ALM/BMI as measured by the DEXA scan in the M6 visit compared to the baseline measurement

The subgroup analyses based on these factors will be performed in order to better characterize treatment benefits in patients with increased risk of mobility disability. Results will be presented in forest-plots graphs, for both the primary endpoint and the 2 key secondary endpoints. Parameters of low gait speed (4-meter walk with a gait speed $\leq$0.8 m/s) and sarcopenic obesity (having a percentage of body fat mass of >25% in men and >35% in women) will be used as stratification factors, as well as important demographics or baseline characteristics such as gender, age, country, etc.

9.4.9 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual data listings will be provided in the annex 16 of the study report.

9.4.10 EXPLORATORY ANALYSES

Exploratory analyses description will be provided in the final statistical plan.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

The investigator will ensure that this study is conducted in full conformity with applicable regulations, the Declaration of Helsinki, GCP and ICH E6.

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing the study intervention, study procedures, and risks in detail are given to the participant and a written documentation of informed consent is required prior to start of intervention/administration of study intervention. The following consent materials are submitted with this protocol.

I. General Informed Consent for participating in SARA-INT clinical trial and secondary research on data
II. Separate Informed Consent for Biobank sample storage and DNA tests
III. Separate Informed consent for the Population PK sub-study.

Due to the COVID-19 outbreak, the following measures have been taken:

IV. A specific letter of information has been sent to every participant still active in the study, providing the measures taken during the COVID-19 outbreak and all related modifications of their participations (e.g. replacement of on-site visits by phone calls, IP home delivery).
V. An addendum to the general informed consent during the COVID pandemic has been provided.

Participant will consent to an addendum to the current version of the ICF, that includes the modification of the schedule of activity, the IP delivery, and the option of an extension of the treatment period for an additional 3 months, with the entire treatment period totaling up to 9 months. To avoid any on-site visit for the reconsent, investigational sites will contact the trial participants via phone or video-calls to obtain oral consents supplemented with email/mail confirmation. Any consent obtained this way will be documented and confirmed by way of normal consent procedures with signatures at the earliest opportunity when the trial participants will be back at the regular sites.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in this study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB-approved and participants will be asked to read and review the document. The investigator will explain the research study to the participant and answer any

questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants should have the opportunity to discuss the study with their family or surrogates or time to think prior to agreeing to participate. Participants will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), along with the participant's signed signature on the form, before the participant can undergo any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The nature and purpose of the trial shall be fully explained to each patient in a form understandable to them; the investigator must confirm that the participant is able to understand the language of the ICF and Subject Information. The process of obtaining informed consent will be in compliance with relevant regulatory guidance, ICH requirements and local laws. The consent documents to be used for the trial shall be reviewed and approved by the appropriate IEC/IRB prior to use.

Signed and dated informed consent must be obtained from each study participant prior to any trial procedures being performed. The investigator or investigator's designee will provide background information on the trial, including the benefits and risks of study participation, scope of the study, procedures to be done at each visit, and responsibility of the subject (e.g. attendance at each visit, completion of all surveys/questionnaires). The investigator or investigator's designee will also encourage the prospective subject to ask questions about the trial and will provide the prospective subject with opportunity to consider whether or not to participate.

Original signed and dated ICFs must be filed in the investigator's site file at the site. A copy of the signed and dated consent with original signatures must also be provided to the subject, or to his/her legal guardian (should this becomes applicable over the study duration).

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, EC/IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Sponsor's decision based on not meeting realistic timelines and resources allocated to the clinical trial

Study may resume once concerns about safety, protocol compliance, and data quality were addressed, and satisfy the sponsor, IRB and/or the FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IEC or IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IEC/IRBs and institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the SARA Clinical Data Platform at Biophytis. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Biophytis research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Biophytis.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study (including DEXA raw data and actimetry records) will be analyzed and stored by the Sponsor. After the study is completed, the de-identified, archived data could be made available on demand based on previous agreement for use by other researchers or Consortia including those outside of the study. Permission to use and transmit de-identified data for secondary research will be included in the main ICF.

With the participant's approval and as approved by the local IRBs, de-identified biological samples will be stored at the Sponsor premises or at an independent Biobank (according to local legislation) with the same goal as the sharing of data. These samples could be used to research the causes of sarcopenia or sarcopenic obesity, its complications and other conditions for which individuals with sarcopenia or sarcopenic obesity are at increased risk, and to improve treatment. The third part will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Sponsor or the mandated Biobank.

With the participant's approval and as approved by local IRBs, genetic material from de-identified samples collected under this protocol may be used to study sarcopenia and sarcopenic obesity. DNA material will be kept for secondary research.

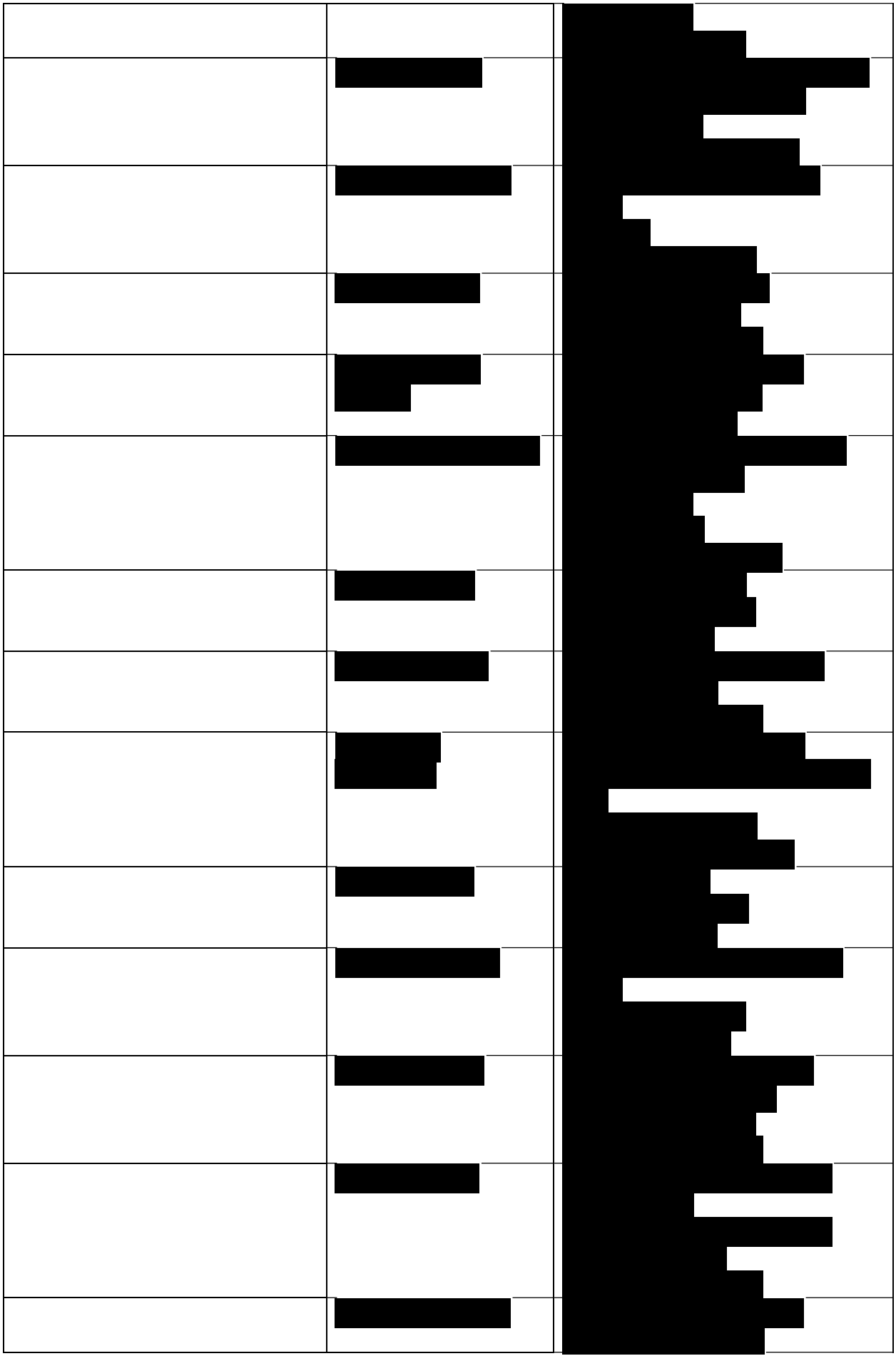
Storage: Access to stored samples will be limited. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. During the study, only investigators and laboratory personnel will have access to the samples. Both investigators and Biophytis/Biophytis representatives will have access to de-identified data.

Disposition at the completion of the study: all stored samples will be sent to a central storage facility. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

See also **Section 10.1.3, Confidentiality and Privacy** and **Section 10.1.9, Data Handling and Record Keeping**, for further information on future use of study records.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Role	Individual/Company Name	Contact Address
Principal Investigator	[redacted]	[redacted]
Investigators/Sites (US)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]



Investigators/Sites (Belgium)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
EU Clinical Coordinator	[redacted]	[redacted]
Sponsor	Biophytis S.A.	14 Avenue de L'Opera 75001 Paris, France
Clinical Research Organization	[redacted]	[redacted]
Information and Communication Technology (ICT)	[redacted]	[redacted]
eCRF and ePROs, online randomization	[redacted]	[redacted]
Centralized Laboratory and Biobank for Biochemistry, Hematology and Biomarkers	[redacted]	[redacted]
Centralized Laboratory and Biobank	[redacted]	[redacted]

Bioanalytics and BIO101 plasma quantification	[redacted]	[redacted]
Biostatistics for DSMB reviews	[redacted]	[redacted]
Therapeutic Units: Manufacturing, Primary packaging, technical release, stability warehouse	[redacted]	[redacted]
Therapeutic Units distribution in the USAOrganization	[redacted]	[redacted].

The overall organizational structure of the SARA-INT Clinical Trial will be organized and managed through the following bodies:

- SARA Managing Board (on behalf of the Sponsor)
- Steering Committee (independent)
- Plenum: all the study investigators (independent)
- Data Safety Monitoring Board (independent)
- Independent Scientific Advisory Board

This governance structure is meant to guarantee a high level of the scientific quality of SARA-INT.

The SARA Managing Board

The Managing Board is composed by two Biophytis representatives and the Principal Investigator. Main responsibilities include:

- Making and implementing strategic decisions as advised by the independent Committees
- Coordinating and optimizing the study resources
- Monitoring the progress of the SARA-INT activities with respect to its objectives
- Identifying possible issues and proactively proposing solutions
- Coordinating communication activities

It is envisioned that the Board will meet regularly, at least once every 3 months.
Any member of the Managing Board may participate in meetings of the Managing Board by teleconference, video-conference or any other technology that enables everyone participating in the meeting to communicate interactively and effectively with each other and as a group.
For major changes, the Managing Board will consult the Plenum, the SDMB, and the other leaders as applicable.

The Steering Committee

The Steering Committee is composed of four Members who are representatives of the two participating regions, the EU and US. The Steering Committee is chaired by the [redacted] are the EU representatives.
The Biophytis Chief Medical Officer will act as Secretary of the Steering Committee. The Steering Committee will be able to invite other experts from Biophytis and Biophytis subcontractors, e.g.

clinical operations, clinical development, etc. as deemed necessary for the purpose of the meetings.

The Plenum

The Plenum consists of all SARA-INT Investigators and will be chaired by the Coordinator. The Plenum can be asked to meet and advise on topics and issues related to the good implementation of the clinical operations, their possible improvements and/or opportune changes.
The Plenum will meet at least once a year to conduct a general project review and project outlook and will meet via teleconference in case an urgent decision has to be undertaken based on their advice.

The Data Safety Monitoring Board (DSMB)

The DSMB is periodically reviewing all safety data and raise alerts in case of negative or dangerous findings. Members of the DSMB will be selected based on their expertise by the SARA managing Board.
During the COVID-19 outbreak, the DSMB is meeting at least every other week to review its recommendation based on update of guidance from the national health agencies and local status.

The Adjudication Committee

The committee will specifically adjudicate the primary end -point, i.e. the 400MW test, in those cases where patients either did not show up or were not able to be tested after 6 months of treatment. Adjudication will be based on the medical dossier and, when available, on the results to a proxy of the 400MW test, e.g. the walking speed of the 4-meter test of SPPB, (for rules of conversion see MCDermott, 2007[58]) with a comprehensive individual case objective evaluation. Precise rules will be endorsed by the adjudication committee at the first meeting and will then made available in the study handbook and its digital version on SARA portal.
Any effort will be undertaken to contact and evaluate patients temporarily lost to follow-up, including home visits where feasible.

The Scientific Advisory Board (SAB)

This is an independent advisory committee, able to advise and discuss the overall study conduct and scientific basis in view of ongoing progress of knowledge within the scientific community. The SAB will meet yearly and may ask DSMB questions and recommend specific actions to the other governance committees.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including geriatrics, gerontology, clinical trial methodology, human and clinical nutrition, internal medicine, bioethics, data privacy and ethics of information technologies, information and communication technologies applied to health (e-health). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet quarterly to assess safety data of all study participants enrolled in the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Study Managing Board and will answer questions from the Steering Committee and the Scientific Advisory Board.

[redacted] the DSMB will review bioanalytical data and other relevant safety data each 3 calendar months once the 25th patient is randomized and starts the investigational drug administration. The DSMB can trigger interim PK analysis of collected blood samples by a third party in order to avoid the unblinding of the study.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by [redacted] staff
- On-site monitoring will be complemented by centralized remote monitoring. The first on-site visit will take place no later than 4 weeks after the start of clinical activities. Frequency will be adapted according to the center inclusion rate. Training on the study procedures, including the use of eCRF will be provided jointly by [redacted] and [redacted] before study start. Targeted review of critical data and targeted data verification of endpoints, safety and other key data variables will be specified in the Clinical Monitoring Plan (CMP)
- The Sponsor will be provided copies of monitoring reports within 10 days of visit
- Details of clinical site monitoring are documented in a CMP. The CMP describes in detail who will conduct the monitoring, at what frequency the monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports
- Independent audits could be conducted by the Sponsor or a mandated sub-contractor to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP

Planned Sponsor audits are postponed during the COVID-19 outbreak and will resume once permitted under national, local and/or organizational social distancing restrictions.

The investigator shall permit the Site Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The investigator shall access medical records for the Monitor so that the entries in the eCRF may be verified. The investigator, as part of his/her responsibilities, is expected to cooperate with [redacted] in ensuring that the study adheres to GCP requirements.

The investigator may not start recruiting study participants into the study until a sponsor/[redacted] monitor has conducted a visit to give a detailed review of the protocol and the eCRF. Alternatively, with the agreement of the sponsor, attendance at the investigator meeting can be in lieu of an on-site visit by the sponsor or CRO.

During the COVID-19 outbreak, no on-site visit is allowed. Remote monitoring is allowed when the system is CRFpart11 compliant. When no compliant system allows a full remote monitoring visit, alternative oversight is put in place, including the remote review of eCRF entries, collection of the list of participants who signed ICFs, protocol deviations with the identification of the COVID-

19 outbreak reason, and collection of the list of document items that will require onsite follow-up during the next onsite MV.

All the monitoring visits will resume once external visitors are allowed on investigational sites.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Biophytis shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and that the data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements. Specifically, for clinical operations, the SOPs of the CRO in charge, [redacted] will be applied.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The investigator should not deviate from the protocol without a formal protocol amendment approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat and legible manner to ensure accurate interpretation of data. Source data are all informational, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Electronic source data are data initially recorded in electronic form. Examples of source data include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

It is not acceptable for the CRF to be the only record of a participant's inclusion in the study. Study participation should be captured in a participant's medical record. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

Hardcopies of the study visit worksheets will be made available (as printable version of eCRF) and could be used in addition to standard medical records as source document worksheets for

recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a proprietary eCRF, a 21 CFR Part 11-compliant data capture system provided by the Sponsor ICT subcontractors. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

To obtain a high level of readability and easy data exchange between different systems, and to make statistical analysis easy, the following standards and dictionary will be used.

1. CDISC (Clinical Data Interchange Standards Consortium) CDISC ODM v.1.3.2.
2. CDISC (Clinical Data Interchange Standards Consortium) SDTM v.1.4 or more recent versions as applicable
3. MedDRA: Medical Dictionary for Regulatory Activities
4. WHO-DD: World Health Organization Drug Dictionary

This study will use a dedicated Information and Communication Technology (ICT) centralized infrastructure for clinical data capture, different data source integration (e.g., DEXA scan results, actimetry), PROs electronic entry, and secure data storage.

The collected information will be initially handled and stored by [redacted] and subsequently transferred and stored at Biophytis's SARA Clinical Data Platform.

The SARA Clinical Data Platform will allow to securely keep and access anonymized clinical data for the purpose of the clinical trial remote monitoring, managing, validation and result analyses.

The investigator shall be provided with standardized eCRF and shall ensure that all data from participant visits are promptly entered into the eCRF in accordance with the specific instructions given. The investigator must electronically sign each eCRF to verify the integrity of the data recorded. Further details will be provided in the MOP.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports.

For patients that are not able to use an electronic device (desktop, laptop, tablet or analogous device), a printed booklet will be made available to complete the PROs foreseen at the protocol. The PRO booklets should be considered to be a source data.

After the end of SARA-INT clinical trial, SARA Clinical Data Platform will continue operations and allow secondary research on the collected data.

10.1.9.2 STUDY RECORDS RETENTION

The investigator/institution should maintain the study documents as specified in the ICH guidelines of GCP and as required by the applicable regulatory requirements. The

investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or the GCP. Further details about the handling of protocol deviations will be included in the MOP.
The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

No changes from the final approved and signed protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and local competent authorities as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only non-substantial logistics or administration. Each investigator and the sponsor will sign the protocol amendment.

It is the responsibility of the Investigator to use continuous vigilance to identify and report all deviations to Biophytis and the local IRC/IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IEC/IRB requirements.

The sponsor expects that the COVID-19 situation will introduce more protocol deviations than normal. All protocol deviations will be accurately recorded and identified as deviations that incurred due to the COVID-19 outbreak and as reasons why the procedures were not performed according to protocol. They will be assessed and reported in the clinical study report, following ICH E3.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The sponsor shall retain the ownership of all data. When the study is complete, the sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory

authorities. All proposed publications based on this study must be subject to the sponsor's approval requirements.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate for their participation in the trial. The study leadership, in conjunction with Biophytis, will establish policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

The investigator will ensure that this study is conducted in full conformity with applicable regulations, the Declaration of Helsinki, GCP and ICH E6.

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC and IRB. The IEC and IRB shall be appropriately constituted and perform its functions in accordance with the FDA, ICH GCP and local requirements as applicable.

The IEC and IRB shall approve all protocol amendments (except for logistical or administrative changes), including but not limited to: written informed consent documents and document updates, participant recruitment procedures (e.g., advertisements), written information to be provided to the participants, available safety information, information about payment and compensation available to participants, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC, IRB and Regulatory Authority (Competent Authority) as applicable.

10.3 ABBREVIATIONS

20E	20-hydroxyecdysone
400MW	400-meter walk test
6MWT	6-minute (distance) walk test
ACE	Angiotensin Conversion Enzyme
AE	Adverse Event
ALM	Appendicular Lean body Mass
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BFM	Body Fat Mass
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CIRS	Cumulative Illness Rating Scale
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
COA	Certificate of Analysis
COVID-19	COronaVIrus Disease 2019
CRO	Contract Research Organization
DCC	Data Coordinating Center
DEXA	Dual-energy x-ray absorptiometry
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EPESE	Established Populations for the Epidemiologic Study of the Elderly
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
FNIH	Foundation of NIH
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HbA1c	Glycated Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICD-10	International Classification of Diseases- 10th Edition
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
ICT	Information and Communication Technology
IDE	Investigational Device Exemption
IGF-1	Insulin-like growth factor 1
IL-6	Interleukin 6
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LIFE	Lifestyle Interventions and Independence for Elders
LIFE-P	Lifestyle Interventions and Independence for Elders- Pilot study
LSMEANS	Least-squares Means
MAD	Multiple Ascending Dose (phase1)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
NYHA	New York Heart Association (class of congestive heart failure)
OHRP	Office for Human Research Protections
OHT	Orthostatic Hypotension
PAT-D	Pepper Assessment Tool for Disability
PF-10	10 item Physical Function domain at SF-36
PI	Principal Investigator
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
SAD	Single Ascending Dose (phase1)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARA	SARcopenia and sarcopenic obesity in patients Aged ≥ 65 years
SARA-OBS	SARA OBServational Study "Characterizing SARcopenia and sarcopenic obesity in patients Aged 65 years and over, at risk of mobility disability."
SARA-PK	SARA Pharmaco-Kinetics phase1 study
SARA-POP-PK	Phase2 population PK sub-study
SARM	Selective Androgen Receptor Modulator
SarQoL	Sarcopenia Quality of Life (questionnaire)

SF-36	Short Form-36 (quality of life questionnaire)
SF-MNA	Short Form Mini-Nutritional Assessment
SO	Sarcopenic Obesity
SOA	Schedule of Activities
SCPT	Stair Climb Power Test
SOC	System Organ Class
SOP	Standard Operating Procedure
SMC	Safety Monitoring Committee
SPPB	Short Physical Performance Battery
TSD-OC	Test SIO Disabilità Obesità Correlata (obesity disability questionnaire)
TU	Therapeutic Unit (individual patient packaged and labelled treatment)
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States
WHO	World Health Organisation

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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