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NEW THERAPEUTICS FOR AGING DISEASES

THE BIOTECH SPECIALIST IN AGING DISEASES

SARA-OBS, an observational study dedicated to characterize age related sarcopenia population suitable for interventional studies

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1-3 March 2018

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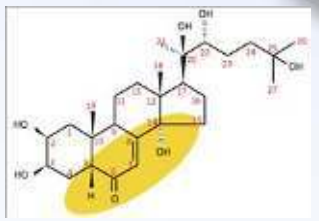
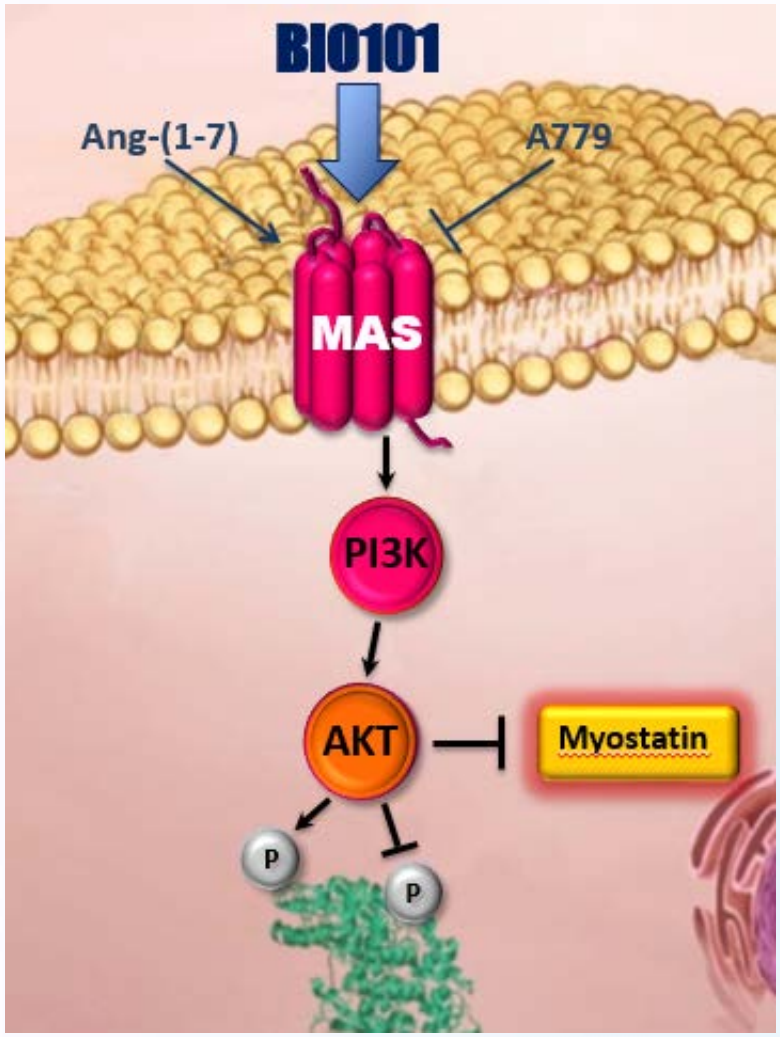
Clinical Development Director

About Sarconeos (BIO101)



- BIO101 is an investigational drug containing the active substance 20-hydroxyecdysone (20E) at 97%.
- 20E is a triterpene, member of the phytoecdysones family.
- BIO101 is manufactured through multiple steps of purifications, from the edible plant *Stemmacantha Carthamoides.*
- BIO101 is part of a pipeline which includes hemisynthetic products belonging to the same chemical family (Posters N° 112 & 113).
- BIO101 is intended to target:
  - Age-Related Sarcopenia
  - Hip fracture (post surgery)
  - Duchenne Muscular Dystrophy

Mechanism of action: Mas receptor activation



Plasma membrane receptor – GPCR receptor

- *7 hydrophobic trans-membrane domains*
- *Endogenous MAS ligand: Angiotensin-(1-7)*
- *Selectively inhibited by A779*
- *Activation of AKT/mTOR pathway*

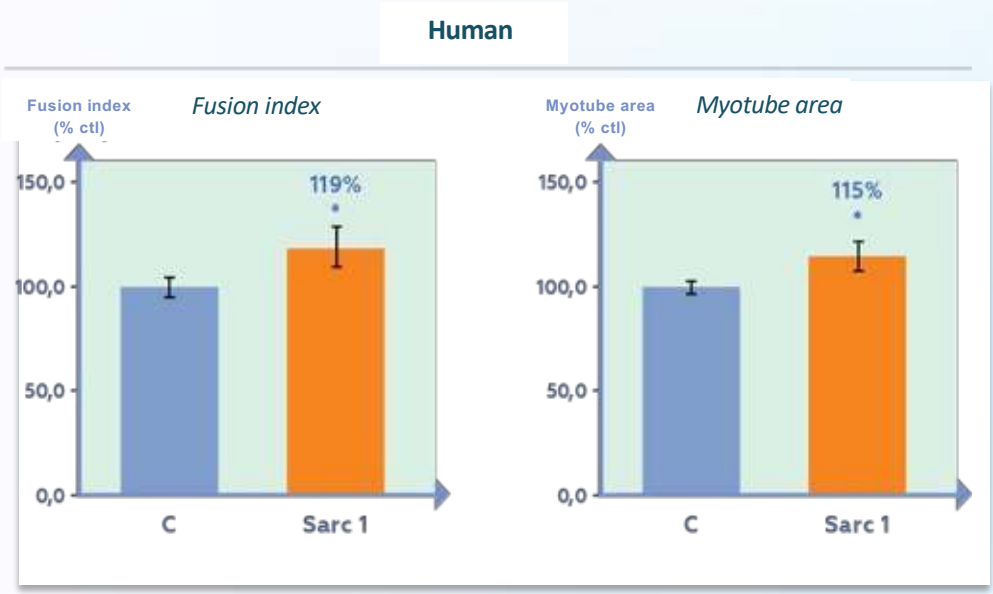
→ BIO101 inhibits myostatin gene expression in a dose-dependent manner

→ Mas activation by Sarconeos (BIO101) was demonstrated by pharmacological and gene interference approaches

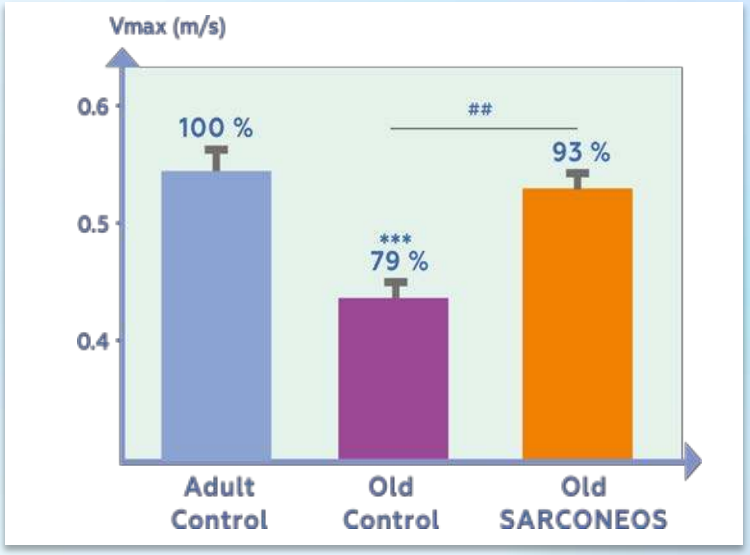
Sarconeos (BIO101) effects *in vitro* and *in vivo*

SARCONEOS (BIO101) demonstrates hypertrophic effects of human muscle fiber and activates protein synthesis

SARCONEOS (BIO101) compensates effect of ageing on muscle functionality and on mobility; stimulates anabolism in muscles



Hypertrophic effect on human muscle fibers



Increase in running speed in old mice

The SARA Clinical Program

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

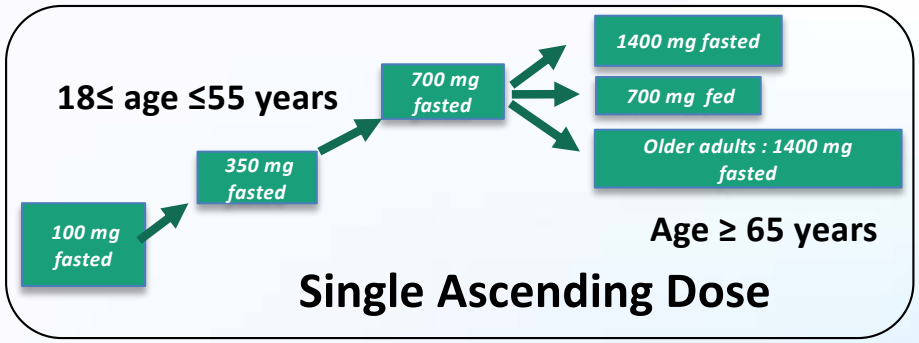
SARA clinical program is based on three main studies:

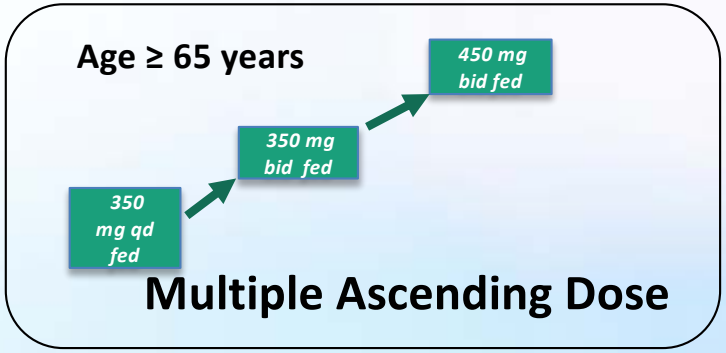
- **SARA-PK,** the completed Phase 1 study that showed safety and pharmacokinetic profiles of BIO101 in older adults and allowed the selection of doses for SARA-INT.
- **SARA-OBS,** the observational study to better characterize the target population and main parameters of SARA-INT.
- **SARA-INT**, the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

SARA clinical program is hosted by the SARA Data infrastructure (Poster N° 110)

SARA-PK: Phase 1 Clinical Trial

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

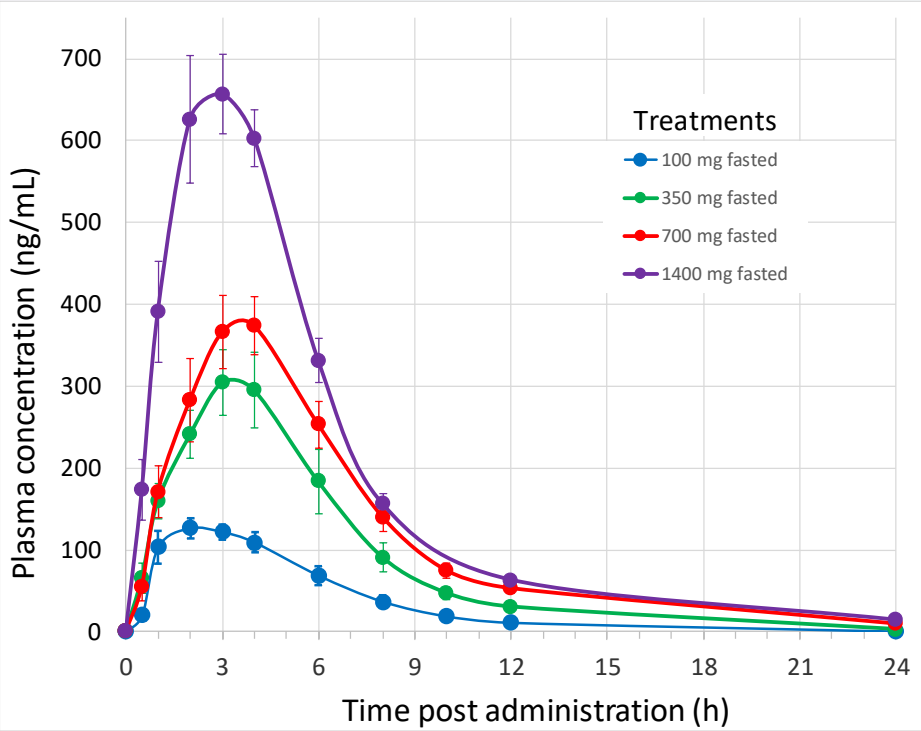




- Oral administrations of BIO101 were safe and well tolerated in SAD up to 1400 mg and in MAD up to 450 mg b.i.d.
- No deaths, Serious Adverse Events or TEAEs leading to treatment discontinuation were reported.
- No abnormal clinical vital signs were reported as TEAE. No clinical laboratory parameters reported as TEAE.
- All TEAEs were mild or moderate in severity and were resolved by the end of the study.

SARA-PK: Phase 1 Clinical Trial

BIO101 plasma concentration increased with the dose



- C_{max} and AUCs increased, but less than dose-proportionally.
- Slight plasma accumulation after b.i.d administrations (350 mg and 450 mg) mean R_{ac}: 1.31 in both cohorts.
- Short half-life (3-4 h) and steady-state reached on day 2 post administration.
- **Similar pharmacokinetic profile in older vs younger adults: 22% Cmax decrease.**

SARA-OBS
Characterising SARcopenia and sarcopenic obesity in patients Aged 65 years and over, at risk of mobility disability.
An OBServational Clinical Trial (SARA-OBS)

SARA-OBS Main Objectives

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

- Prepare phase 2 SARA-Data infrastructure

Diagnosis and criteria for inclusion

Sarcopenia according to FNIH criteria and SPPB

1. Men and women aged ≥ 65 years, living in the community, and reporting loss of physical function
2. Short Physical Performance Battery (SPPB) score ≤ 8
3. ALM/BMI < 0.789 in men and 0.512 in women, or ALM <19.75 kg in men and <15.02 kg in women by DXA

Target Population:

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

SARA-OBS Endpoints

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

SARA-OBS Enrollment Status

Country	Prescreened	Eligible to screen	Screened	Included	Screened vs Prescreened	Screened failure
USA	869	395	326	36	37%	89%
EUROPE	318	182	159	45	50%	72%
Total	1187	577	485	81	41%	83%

- 59% of the prescreened patients are not retained.
  - Absence of mobility issues and conditions in SARA-OBS exclusion criteria.
- High screening failure: 17 % of screened patients are included. This is also observed in other sarcopenia clinical trials (Fielding et al., 2015; Fielding et al., 2017).
  - SPPB>8 (57%).
  - ALM/BMI > 0.789 or > 0.512 and ALM > 19.75 kg or > 15.02 kg (40%)
  - Other reasons including pending screening issues

SARA-OBS Baseline characteristics

- **Demographics & Body composition**

Variable	Mean	Standard Deviation
Age	78.47	7.87
BMI	30.10	7.29
Women/Men	48/33	NA
Appendicular Lean Mass (ALM)	16.53	4.67
Men	19.52	4.96
Women	14.44	3.37
ALM/BMI	0.57	0.14
Men	0.66	0.16
Women	0.51	0.10

- Average BMI is high.
- 43% of included patients have a BMI≥ 30 and are obese.
- 59% of patients are women.

SARA-OBS Baseline characteristics

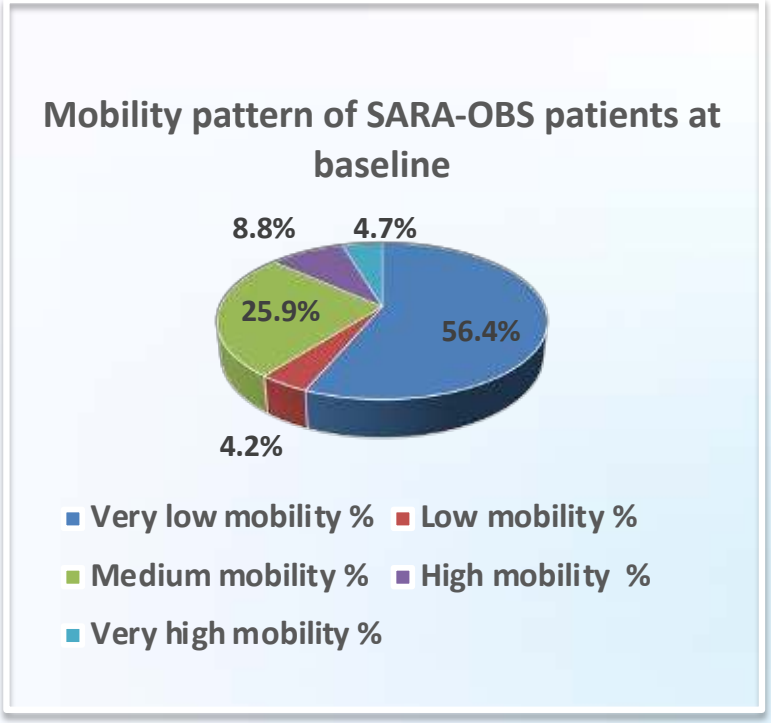
- **Physical performance & Plasma biomarkers**

Variable	Mean	Standard Deviation
400M (min)	7.10	3.74
Gait speed 400M (m/sec)	0.87	0.27
SPPB	6.46	1.63
Gait Speed in SPPB (sec)	0.74	0.18
Chair stand	1.55	0.77
6MWD	314.07	98.17
hsCRP (mg/L)	5.44	10.20
IL-6 (pg/ml)	6.33	4.10
VitD25OH (nmol/L)	81.82	36.85

- 400 m gait speed is similar to the Life study (0.83 m/s at baseline; Pahor et al., 2014).
- SPPB is low (6.46/12), corresponding to patients at risk of mobility disability and comparable to other sarcopenia studies (Life study with 7.4±1.6 in the physical activity group, Pahor et al., 2014).
- Gait speed SPPB is <0.8 m/s and fits to EWGSOP definition of sarcopenia.
- IL-6 and hsCRP plasma levels are slightly higher compared to values reported in healthy elderly people (70-90 years) by Wyczalkowska-Tomasik et al., 2016.

SARA-OBS Baseline characteristics

- **Physical activity measured by Connected Device**



Index	Activity level
Very low mobility %	Lying
Low mobility %	Sitting
Medium mobility %	Standing with low activity
High mobility %	Walking low cadence
Very high mobility %	Walking high cadence

- Subsample of patients that worn the connective device for at least 60 days.
- Patients did wear the device 83% of the measured period.

Next steps : SARA-INT

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

- Multicenter (US and EU), double-blind, placebo-controlled study
- Treatment: 2 Doses (175 mg BID or 350 mg BID) and placebo
- Population: 334 community dwelling adults ≥ 65 years
- At least 22 investigational centres
- Participant Duration: 26 weeks + screening (1 to 8 weeks)

Conclusions

- Preliminary observations in SARA-OBS confirmed recruitment opportunities in sarcopenia trials when using the FNIH criteria.
- Similarly to SPRINTT study, low performers at SPPB≤8/12 as an index of mobility disability risk were selected.
- Baseline characteristics are comparable to other sarcopenia studies (SPRINTT study and Life study, Pahor et al., 2014).
- SARA-OBS population is suitable for interventional studies in Age-Related Sarcopenia.
- SARA-INT clinical trial received all due authorisations from Competent Authorities in USA and Belgium.

Biophytis Research and Development Team

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- **Operations and Non Clinical Team**
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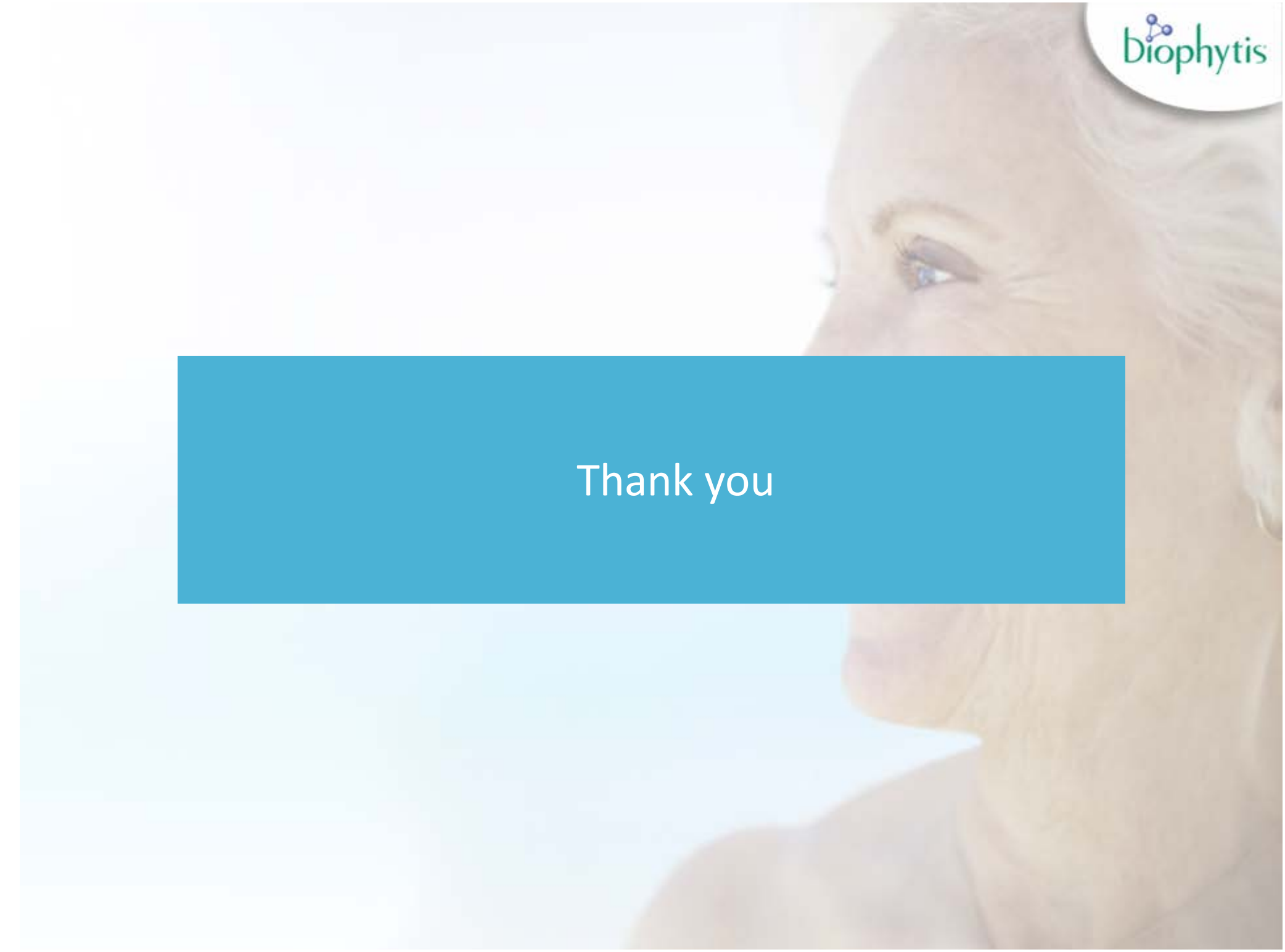
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Thank you

Main exclusion criteria

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