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

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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

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

SARCOMEOS (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

- \(C_{\text{max}}\) and AUCs increased, but less than dose-proportionally.
- Slight plasma accumulation after b.i.d administrations (350 mg and 450 mg) mean \(R_{\text{ac}}\): 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\% \(C_{\text{max}}\) 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; aldosterone; 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

<table>
<thead>
<tr>
<th>Country</th>
<th>Prescreened</th>
<th>Eligible to screen</th>
<th>Screened</th>
<th>Included</th>
<th>Screened vs Prescreened</th>
<th>Screened failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>869</td>
<td>395</td>
<td>326</td>
<td>36</td>
<td>37%</td>
<td>89%</td>
</tr>
<tr>
<td>EUROPE</td>
<td>318</td>
<td>182</td>
<td>159</td>
<td>45</td>
<td>50%</td>
<td>72%</td>
</tr>
<tr>
<td>Total</td>
<td>1187</td>
<td>577</td>
<td>485</td>
<td>81</td>
<td>41%</td>
<td>83%</td>
</tr>
</tbody>
</table>

- 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

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

- 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

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

- 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

### Mobility pattern of SARA-OBS patients at baseline

- Very low mobility %: 8.8%
- Low mobility %: 4.7%
- Medium mobility %: 25.9%
- High mobility %: 4.2%
- Very high mobility %: 56.4%

<table>
<thead>
<tr>
<th>Index</th>
<th>Activity level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low mobility %</td>
<td>Lying</td>
</tr>
<tr>
<td>Low mobility %</td>
<td>Sitting</td>
</tr>
<tr>
<td>Medium mobility %</td>
<td>Standing with low activity</td>
</tr>
<tr>
<td>High mobility %</td>
<td>Walking low cadence</td>
</tr>
<tr>
<td>Very high mobility %</td>
<td>Walking high cadence</td>
</tr>
</tbody>
</table>

- 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

- **SARA Clinical Team**
  - Susanna DelSignore
  - Waly Dioh
  - Gianluca Zia
  - Cendrine Tourette
  - Carole Margalef

- **Research Team**
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  - Pierre Dilda
  - Maria Serova
  - Mathilde Latil
  - Sissi On
  - Blaise Didry-Barca

- **Operations and Non Clinical Team**
  - Philippe Dupont
  - Marie-Noelle Ly
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