BIO101, a drug candidate to counter-act age-related sarcopenia: towards Phase 3 program

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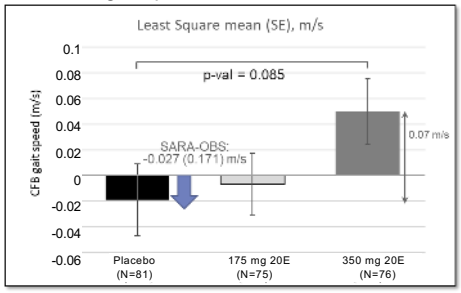
Introduction

Age-related sarcopenia is a progressive generalized loss of muscle mass and function associated with negative outcomes such as falls, fractures, and mortality. Lean body mass preservation may reduce the negative outcomes especially in subjects with obesity. Biophytis targets the Renin Angiotensin System with 20-hydroxyecdysone (20E), a MAS receptor activator, in the SARA program investigating its efficacy in sarcopenia through SARA-PK phase 1, SARA-INT phase 2 and the upcoming confirmatory phase 3 studies. Following the promising results from the SARA-INT phase 2b trial on community-dwelling sarcopenic subjects in Europe and USA, Biophytis designed a phase 3 program to assess the efficacy and safety of 20E administered 1-3 years in a sarcopenic population at risk of functional decline and mobility disability.

From the SARA-INT Phase 2 to the SARA-31 Phase 3 trial in age-related sarcopenia

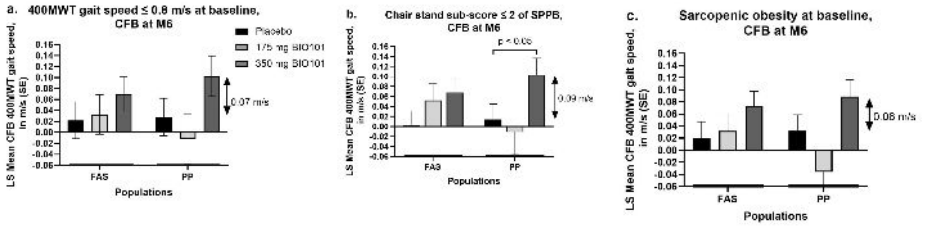
Physical performance

400MWT gait speed in SARA-INT Phase 2b trial



SARA-INT

Subgroup analysis for 400MWT gait speed

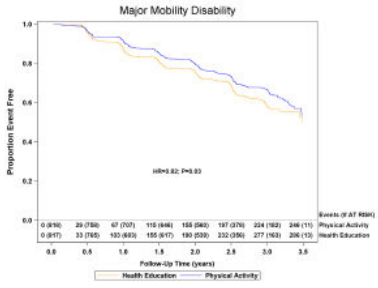


✓ Secondary statistical analysis of Change From Baseline (CFB) in 400MWT gait speed based on Multiple Imputation for subjects without on-site visit data at M6 and adj. Bayesian Imputation for non completers at M6 in the FAS population.
✓ Similar trends observed with other gait speed assessment: 4-m gait speed and 6MWD.

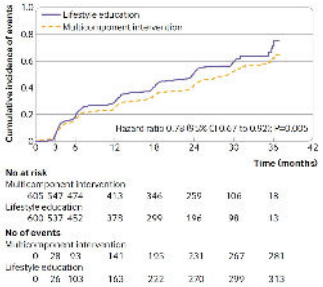
✓ A nominally significant treatment effect vs placebo in the CFB for 400MWT gait speed in subpopulations:
✓ Chair stand sub-score ≤2 of the SPPB (p-val = 0.0037 in PP population at M6)
✓ Slow walkers (p-val = 0.0154 in PP population at M6),
✓ Patients with obesity (p-val = 0.0037 in PP population at M6),

Hard endpoint

Incident mobility disability in sarcopenic population



LIFE study, Pahor et al., 2014

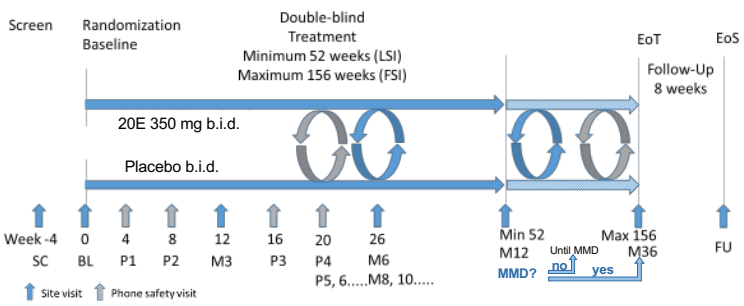


SPRINTT study, Bernabei et al., 2022

✓ Major Mobility Disability (MMD) is used as Primary parameter of SARA 31 Phase 3 program.
✓ MMD is defined as the inability to complete a 400-meter walk (400MWT) test within 15 minutes, without sitting, help from another person or use of a walker.
✓ MMD is considered as the most proximal hard endpoint in the cascade of falls, fractures, hospitalization, institutionalization and death in sarcopenic patients.

SARA-31

Clinical study design



Approximately 50 study sites internationally are planned. 932 subjects (466 subjects per group) will be randomized. This is an event driven trial with a target of 330 MMD events.
Planned subgroup analyses include sarcopenic obesity and chair stand sub-score ≤2 from SPPB.

Objectives

Primary objective: To evaluate efficacy of oral 20E 350 mg b.i.d. versus placebo on the hazard of mobility disability in non-disabled older people suffering from sarcopenia.

Secondary objectives

- To assess the efficacy of 20E treatment versus placebo for minimally 52 weeks and maximally 156 weeks on relevant health-related outcomes in non-disabled older subjects suffering from sarcopenia and at the end of the Follow-Up period. These include physical performance, quality of life, frequency of falls, frequency of bone fractures, healthcare resources utilization, mortality.
- Assess the safety and tolerability of 20E (TEAEs, ECG, vital signs, clinical laboratory).

Exploratory Objectives

- To explore pharmacokinetics of 20E and metabolites in a subset of patients.
- To document disease burden and patient perception of treatment efficacy during exit interviews in a subset of patients and caregivers.
- To explore the correlation of potential biomarkers with sarcopenia and drug activity.

Target population: Community dwelling males and females (≥65 years old) with the following criteria:

low SPPB score
3 ≤ SPPB score ≤ 7: population likely to experience MMD within 12 Months (23% at 12 Months on average, almost half of participants of the SPRINTT study over 24 months)

low gait speed
4-m gait speed (SPPB) ≤ 0.8 m/s, as low gait speed predicts major negative health-related events

low muscle strength
Handgrip strength < 16 kg for females, < 35.5 kg for males (from SDOC, Cawthon et al., 2020), based on correlation with similar distant outcomes.

Reporting a loss of motor function over the last year: population at high risk of a deterioration to be assessed with objective criteria, closer to the onset of mobility disability.

Key endpoints

- Primary: Time to onset of Major Mobility Disability.
- Key secondary: Quality of life (SarQol).
- Muscle strength (handgrip strength), 4-m Gait speed (from SPPB).
- Exploratory:
  - PK/PD parameters, frequency of falls and injurious falls, physical performance, PGI- and CGI- status and change.
- Health care resource utilization and mortality. Safety (TEAEs, SAEs AESIs).

Conclusions

SARA-31 Phase 3 trial ensures a clinically relevant assessment of 20E efficacy in sarcopenia patients with the use of MMD as primary parameter.

The clinical trial protocol was approved by competent authorities in USA and Europe (Belgium) and interactions are still ongoing with competent authorities and ethics committees.

Biophytis approach with phase 2 and phase 3 remains the way to evaluate BIO101 effect in age-related sarcopenia and a proposed path for drug approval in this indication.

References

R. Bernabei *et al.*, "Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project)," *BMJ*, vol. 377, p. e068788, May 2022, doi: 10.1136/bmj-2021-068788.

M. Pahor *et al.*, "Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults: The LIFE Study Randomized Clinical Trial," *JAMA*, vol. 311, no. 23, Art. no. 23, Jun. 2014, doi: 10.1001/jama.2014.5616.

P. M. Cawthon *et al.*, "Putative Cut-Points in Sarcopenia Components and Incident Adverse Health Outcomes: An SDOC Analysis," *J Am Geriatr Soc*, vol. 68, no. 7, Art. no. 7, Jul. 2020, doi: 10.1111/jgs.16517.