Ruvembri™ (20-hydroxyecdysone) in Sarcopenia: towards Phase 3 program

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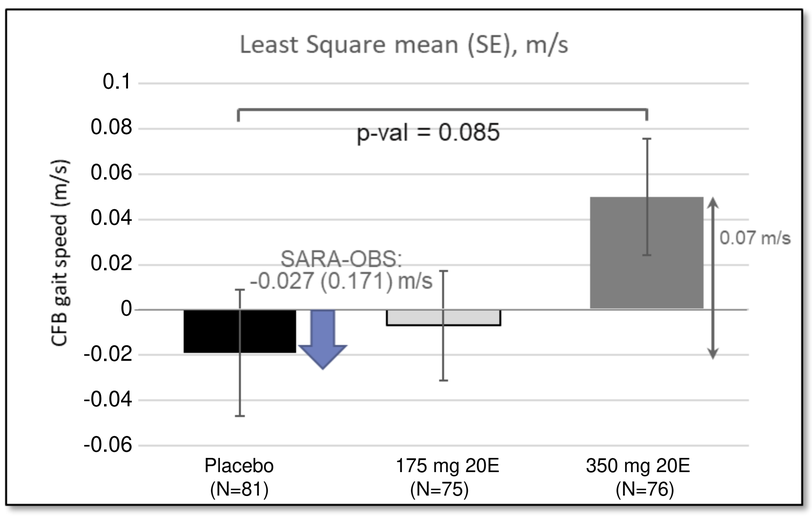
Introduction

Sarcopenia is characterized by the loss of muscle mass and muscle strength leading to a global muscle functional impairment and physical disability. Biophytis has developed the drug candidate Ruvembri™, purified at 97% of 20-hydroxyecdysone (20E), from the plant *Cyanotis sp.* 20E has a potential to improve muscle quality and function in *in vitro* and *in vivo* models and accelerates differentiation and enhances mitochondrial function in skeletal muscle cells (Serova et al., 2024). Following the promising results from the SARA-INT phase 2b trial on community-dwelling sarcopenic subjects in Europe and USA, aged ≥ 65 years, 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.

Rationale

Physical performance → Hard endpoint

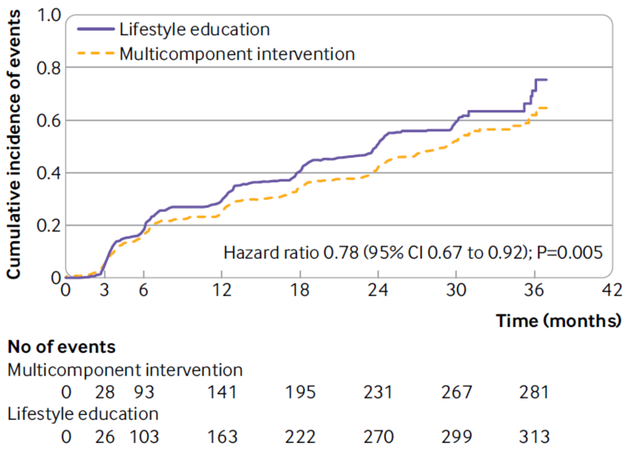
400MWT gait speed in SARA-INT Phase 2b trial



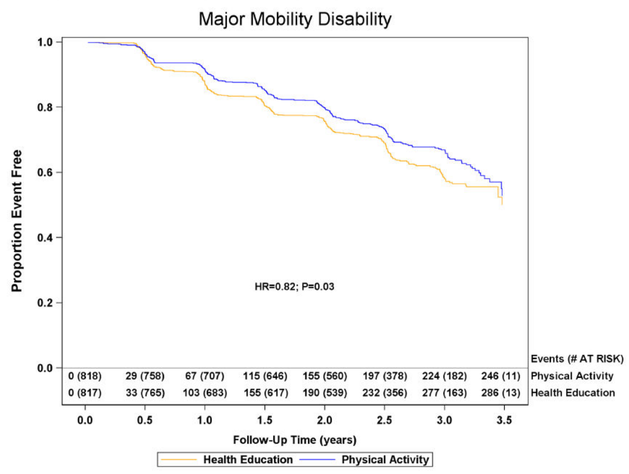
✓ Secondary statistical analysis of Change From Baseline (CFB) in 400MWT gait speed based on Multiple Imputation for subjects without on-site visit data at M6 and adj. Bayesian Imputation for non completers at M6 in the FAS population.

✓ Similar trends are observed with other gait speed assessment: 4-m gait speed from SPPB, 6MWD.

Incident mobility disability in sarcopenic population



SPRINTT study, Bernabei et al., 2022



LIFE study, Pahor et al., 2014

➢ Towards using Major Mobility Disability (MMD) as Primary parameter of SARA Phase 3 program
Major mobility disability 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 objectives

Primary objectives:

- To evaluate the efficacy of 20E 350 mg b.i.d. administered orally 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 wet and novel potential biomarkers of sarcopenia and of drug activity, with the hazard of mobility disability and physical function changes over the study.

Target population

Community dwelling males and females (65+) with 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

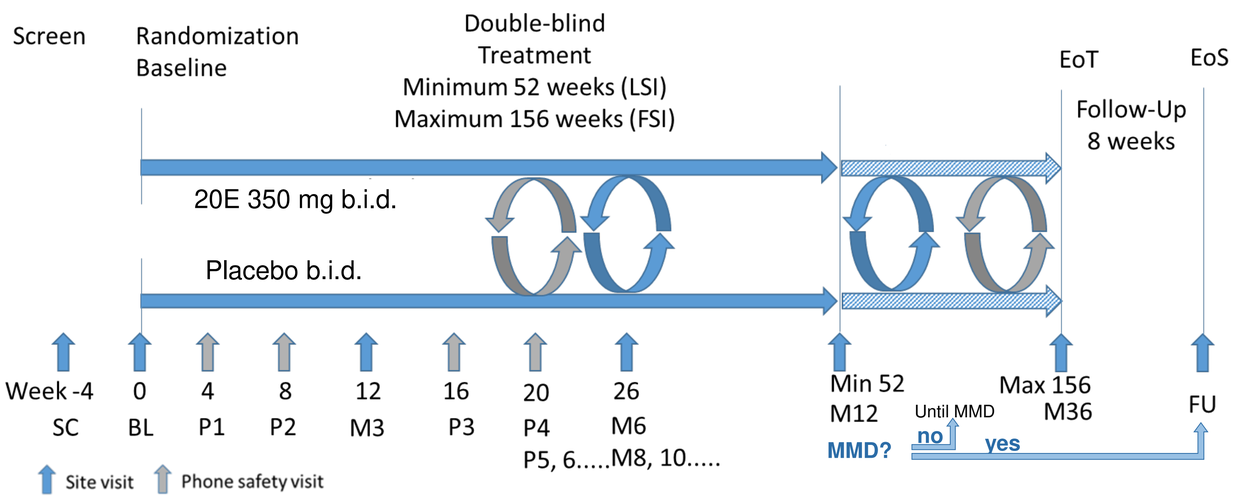
Handgrip strength < 16 kg for females, < 35.5 kg for males (from SDOC, Cawthon et al., 2020), based on correlation with similar distant outcomes.

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

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

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 events. Planned subgroup analyses include sarcopenic obesity and chair stand sub-score ≤2 from SPPB.

Conclusions

With the use of MMD as primary parameter, this trial ensures a clinically relevant assessment of 20E efficacy in sarcopenia patients.

The clinical trial protocol was submitted to competent authorities in USA and Europe (Belgium) and approved. While interactions are still ongoing with competent authorities and ethics committees, the protocol may still be amended with the expansion to other countries in Europe and rest of the world.

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