SARA PROGRAM: THE USE OF BIO101, A MAS RECEPTOR AGONIST, FOR THE TREATMENT OF SARCOPENIA

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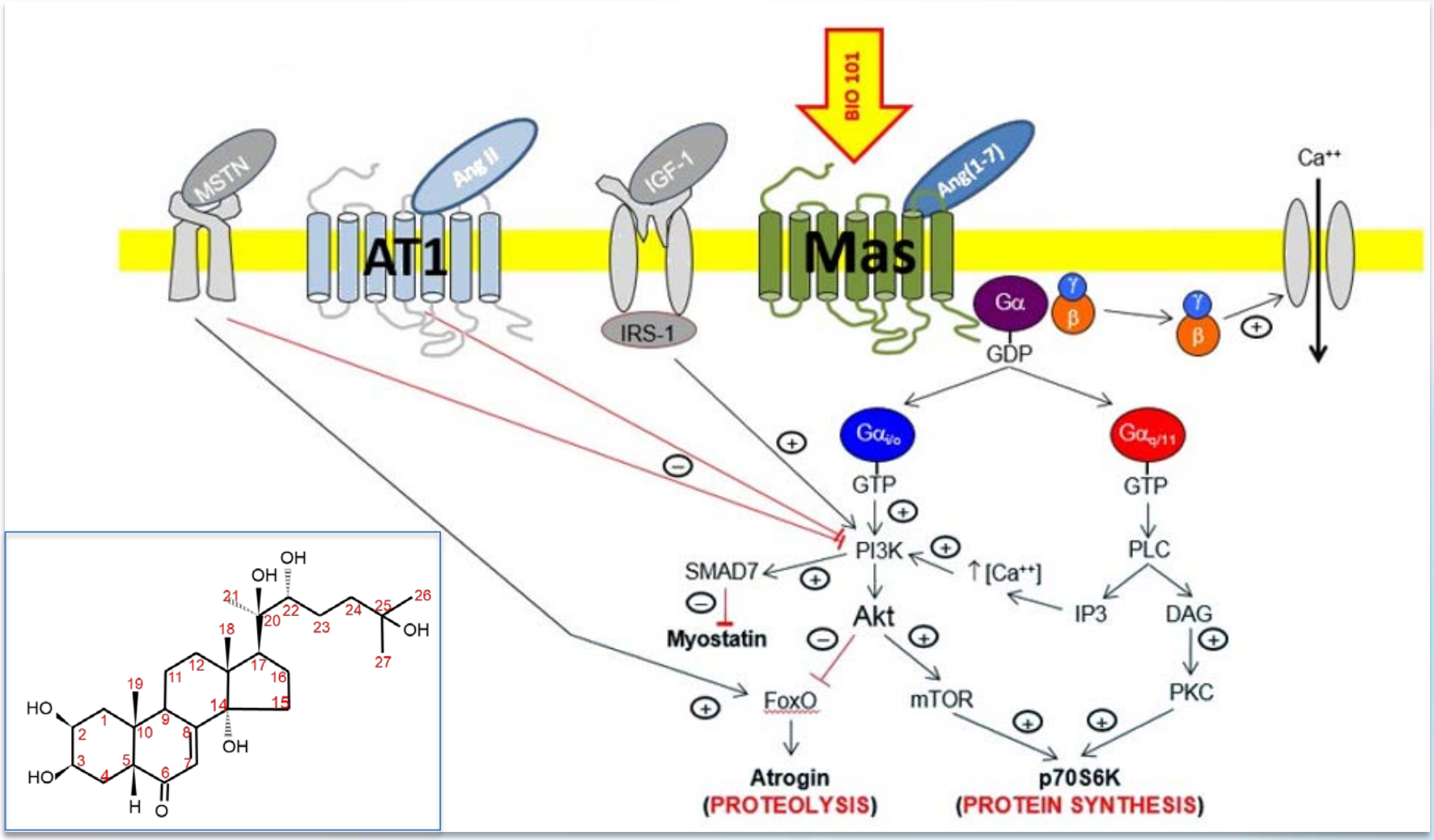
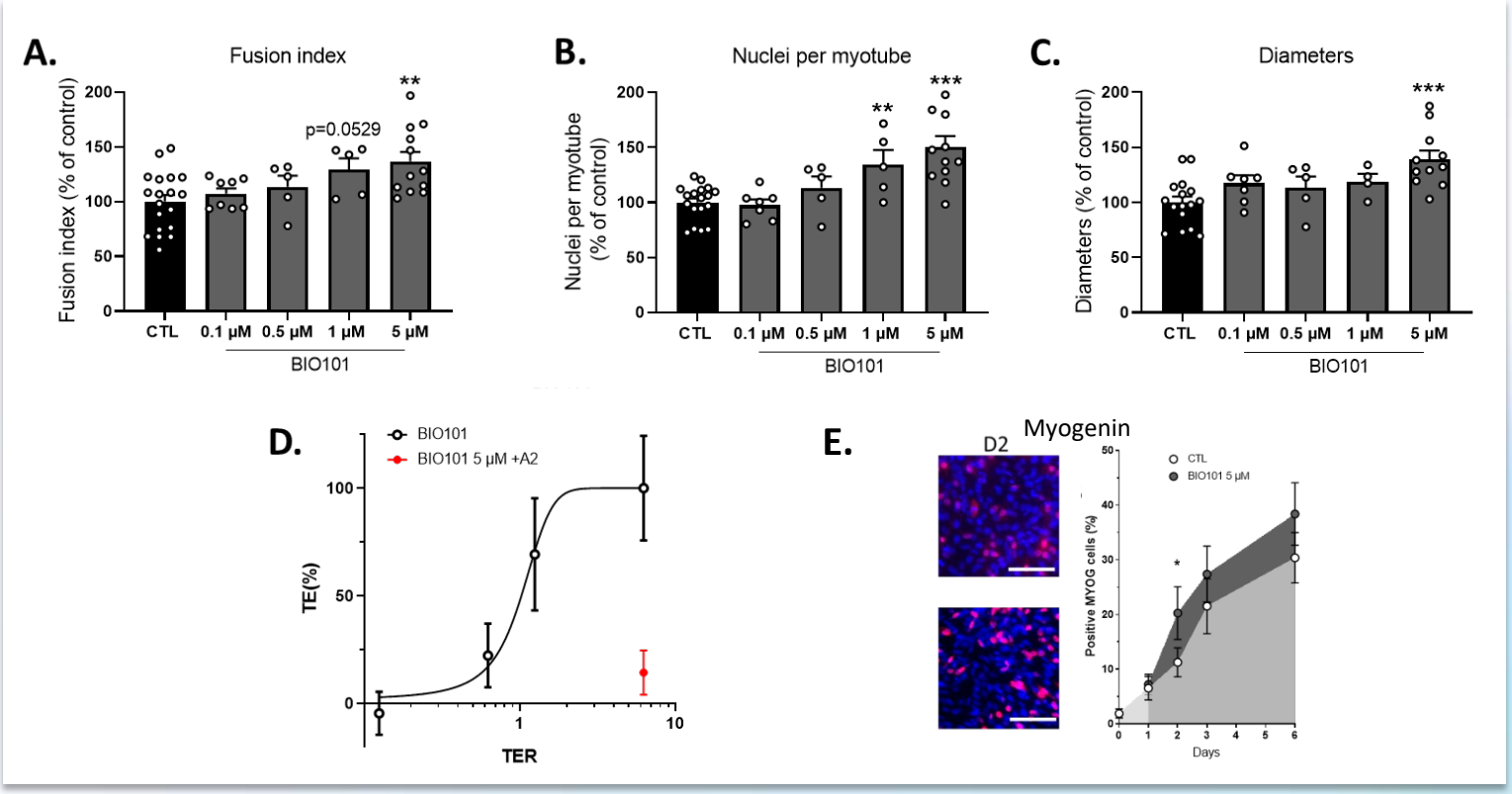
BIO101: MECHANISM OF ACTION

MAS receptor activation



TARGET ENGAGEMENT STUDIES *IN-VITRO*

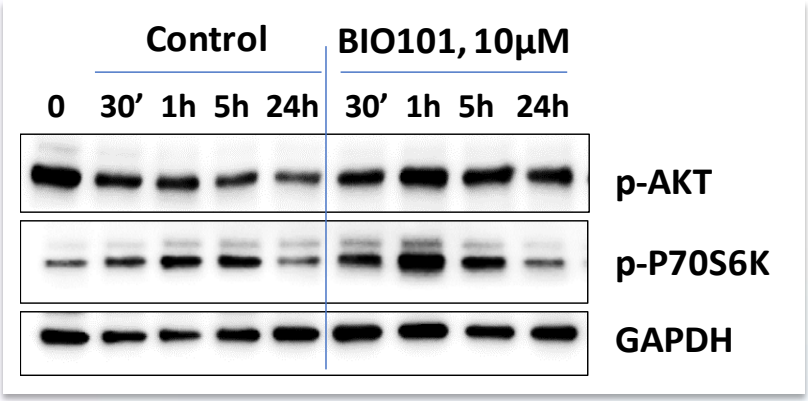
Myoblast differentiation



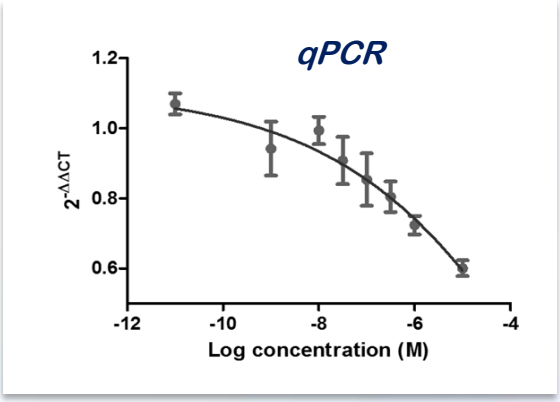
⇒ Dose-dependent effect of BIO101 on myoblast differentiation, based on effects observed on fusion index, number of nuclei per myotube and myotube diameter, as well as Myogenin protein expression.

TARGET ENGAGEMENT STUDIES *IN-VITRO*

AKT signaling pathway

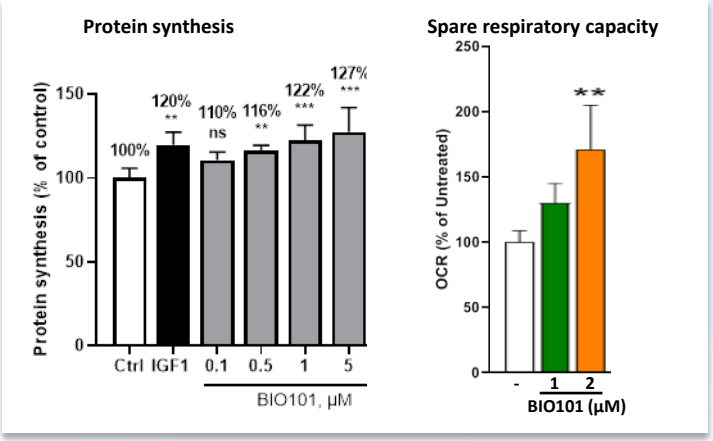


Myostatin gene expression



=> BIO101 stimulates AKT signaling pathway and inhibits myostatin gene expression

Myoblast protein synthesis and mitochondrial respiration



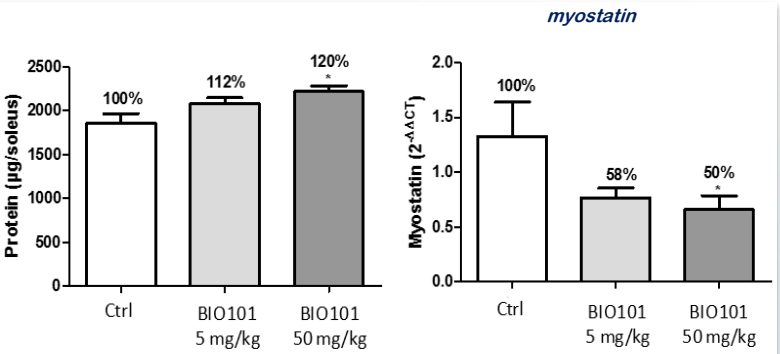
⇒ BIO101 is responsible for a significant increase in protein synthesis in differentiated muscle cells.

⇒ BIO101 increases significantly the mitochondrial spare respiratory capacity in differentiated C2C12

TARGET ENGAGEMENT STUDIES *IN-VIVO*

Mouse soleus, 6 weeks oral treatment

Muscle protein content

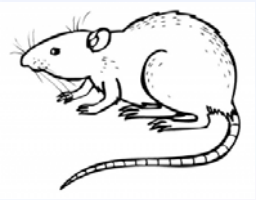


Gene expression

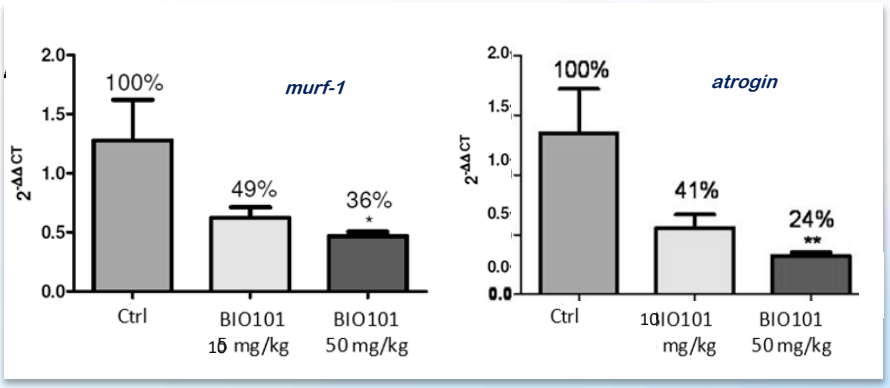
BIO101 causes an increase in muscle protein content in treated mice.

BIO101 administration cause a partial inhibition of myostatin gene expression.

Rat tibialis anterior, 12 weeks oral treatment



Gene expression

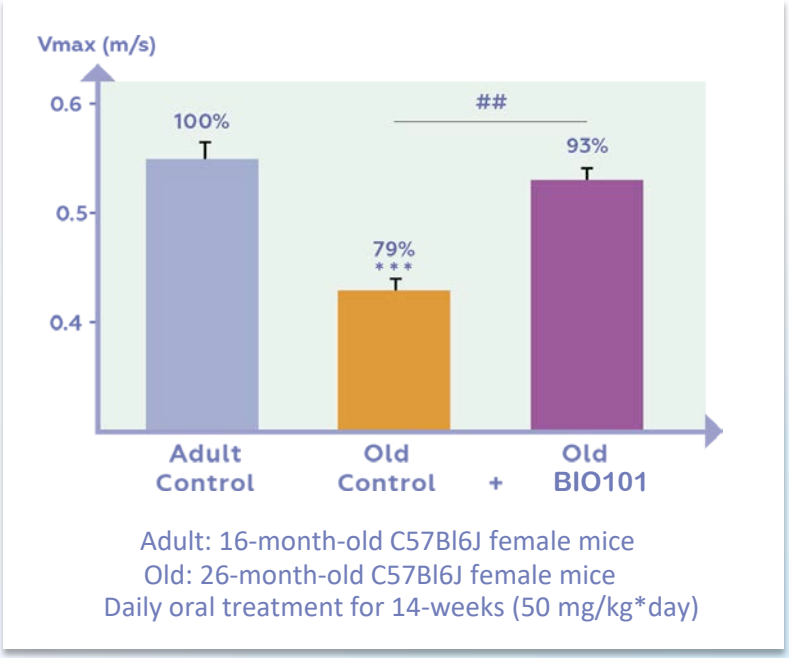


Chronic BIO101 treatment causes a dose-dependent gene expression inhibition of two important regulators of ubiquitin-mediated protein degradation in skeletal muscle (Murf-1 and Atrogin).

=> BIO101 has a dose-dependent effect in the target tissue with a chronic treatment

PROOF OF CONCEPT

Age-related muscle wasting and loss of function



Adult: 16-month-old C57Bl6J female mice
Old: 26-month-old C57Bl6J female mice
Daily oral treatment for 14-weeks (50 mg/kg*day)

⇒ Significant protection against muscle function loss during ageing

THE SARA CLINICAL PROGRAM

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

SARA-PK

- Phase 1 study
- Safety and pharmacokinetic profiles of BIO101 in older adults
- Selection of doses for SARA-INT

SARA-OBS

- An observational study to characterize the target population and main parameters of SARA-INT

SARA-INT

- A phase 2 interventional trial to evaluate the safety and efficacy of BIO101 after 6-month administration in sarcopenic patients on mobility function

SARA-OBS: AN OBSERVATIONAL CLINICAL TRIAL

Characterizing Sarcopenia and sarcopenic obesity in patients Aged 65 years and over, at risk of mobility disability

Objectives:

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

Main endpoints:

- Primary endpoint: gait speed of the 400MW test
- Co-primary endpoint: The Physical Function Domain (PF-10) of the Short Form Health Survey (SF-36)
- Key secondary endpoint: Hand grip strength
- Other secondary endpoints: 6 MWD, completion of 400MW Test, SPPB, SPPB sub-score of sit-stand, stair climbing Power Test, PROs (SF36; SarQoL; TSD-OC) knee extension strength, DXA measurements
- Safety and tolerability

Main inclusion criteria:

- Men and women aged ≥ 65 years, living in the community, and reporting loss of physical function
- Short Physical Performance Battery (SPPB) score ≤ 8
- 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

WHAT WE LEARNED FROM SARA-OBS

Mobility of the SARA population has naturally decreased within 6 months

	Baseline	Month 6	change	p-value
Gait speed from 400MWT (m/s)	0.866 ±0.255	0.835 ±0.243	-0.027 ±0.171	0.064
6MWT distance (m)	297.561 ±93.040	284.841 ±98.723	-16.655 ±76.841	0.006

None of the muscle strength assessments showed a significative difference between baseline and M6, nor ePROs

Ongoing analysis

- Sub-group analysis
- Actimetry

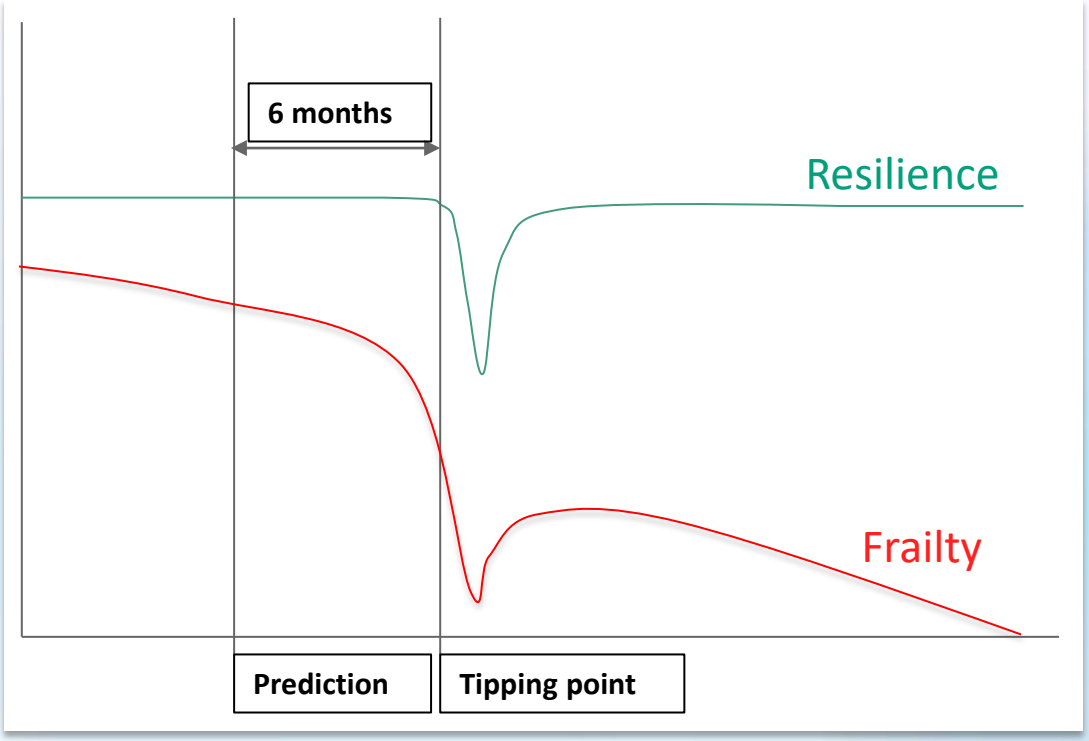
WHAT WE LEARNED FROM SARA-OBS

Mobility of the SARA population has naturally decreased within 6 months

⇒ **Exclusion of individuals with SPPB = 9 is the main difference between the SARA program and previous sarcopenia studies.**

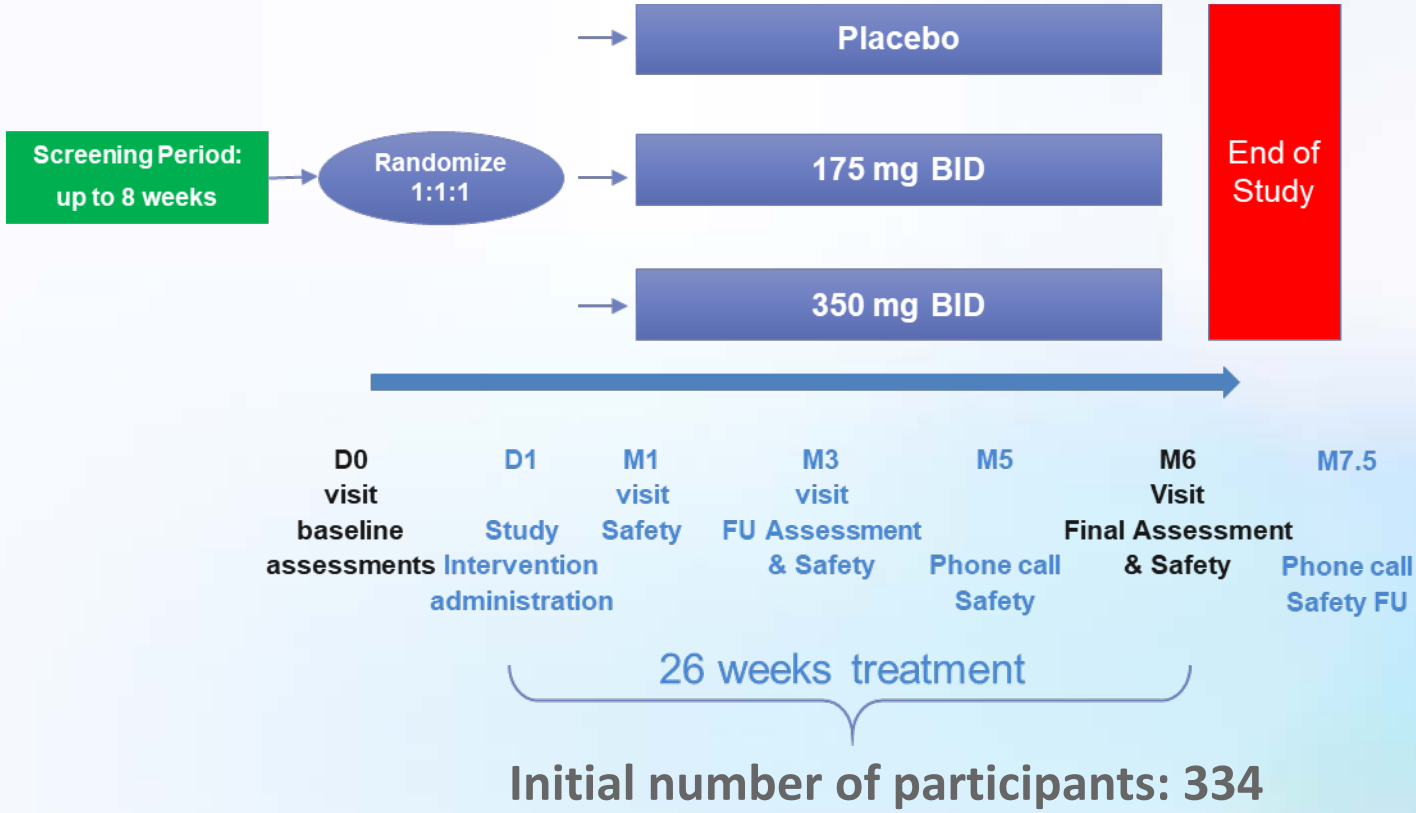
⇒ **This led to the selection of a more vulnerable population, which is closer to the 'tipping point'**

- In standard care, individuals with a chronic disease are often diagnosed when a bad thing happens. This is the **Tipping Point**
- The tipping point is an untoward medical event, from which the affected individual is not able to recover to their pre-event function
- **Resilience** indicates the ability of individuals to recover from untoward events. The opposite of resilience is **frailty**
- Sarcopenia is a significant cause for increased frailty and losing the ability to complete the 400-meter gait task. 400MW test is a measure that is associated with loss of resilience



SARA-INT: A PHASE 2 INTERVENTIONAL STUDY

Following the same outline as that of the SARA-OBS study



Initial number of participants: 334

Main differences from SARA-OBS:

- Participants must perform the 400MWT within 15 minutes
- Exclusion of individuals with an active biliary-tract disease

SARA-INT: LESSONS FROM SARA-OBS

Mobility of the SARA population has naturally decreased within 6 months

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Disease progression and its impact on the sample size

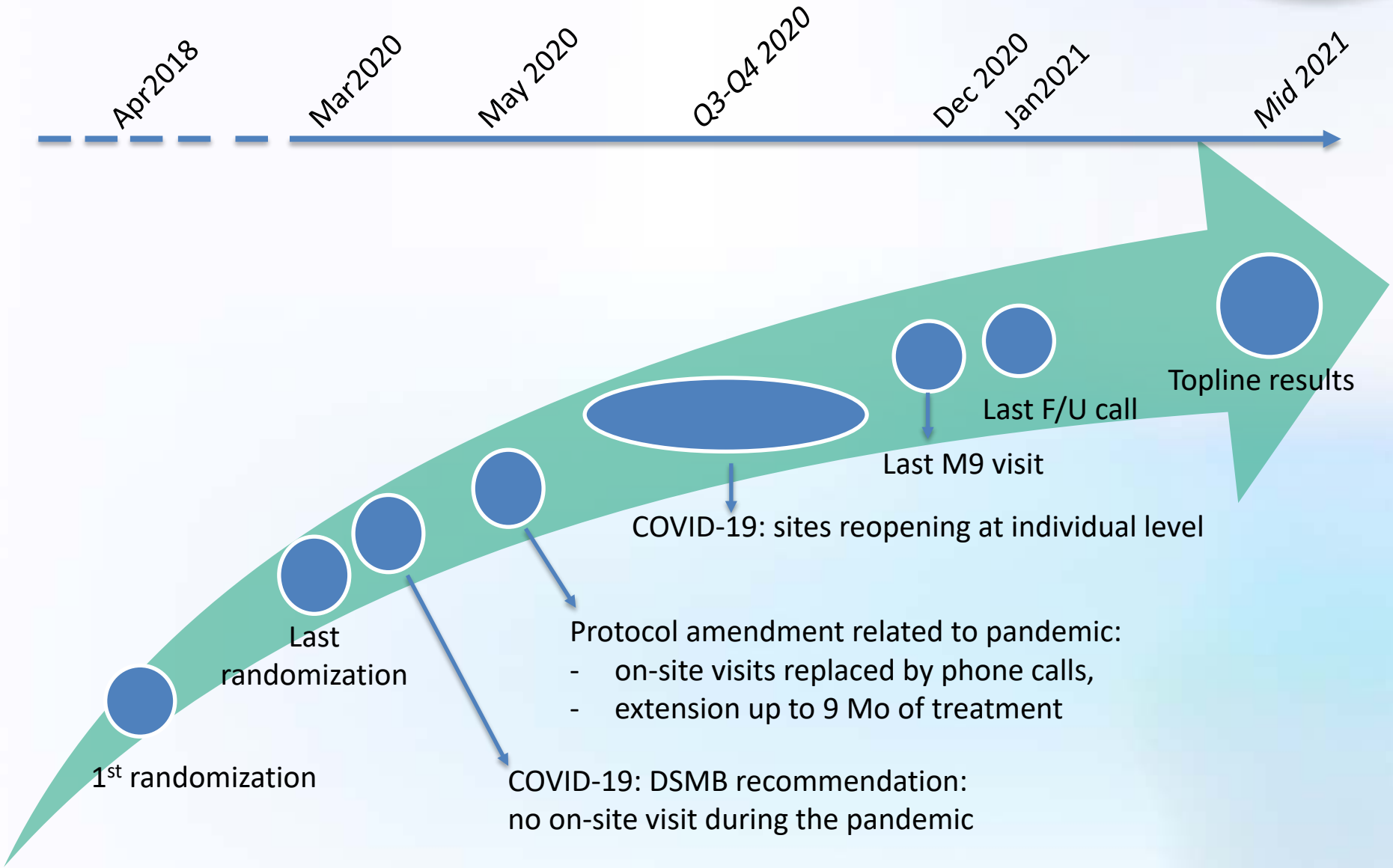
Std dev.	Expected diff from placebo	N / arm	N total	Expected change from BL (%)
0.20	0.05	253	759	5.5%
	0.08	111	334	8.9%
	0.10	64	192	11.0%

Population of the 2 studies have similar eligibility criteria and baseline characteristics

⇒ Sample size re-estimation to 192 participants, 231 including 20% premature termination.

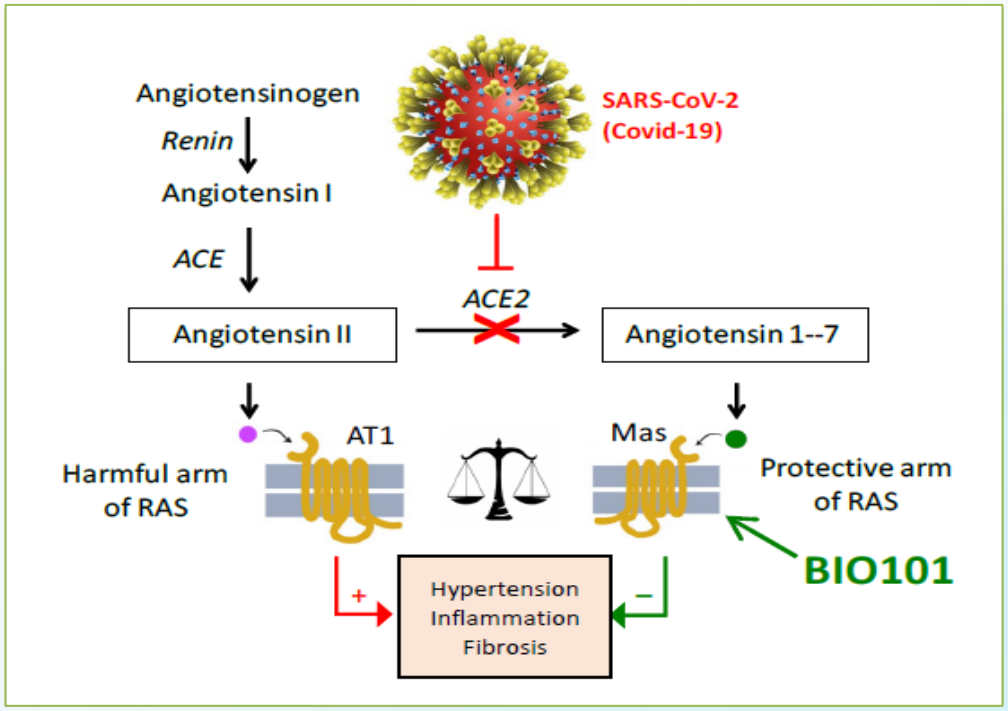
⇒ **233 participants were randomized in the SARA-INT study**

SARA-INT: STUDY STATUS



BIO101, AS A NEW DRUG CANDIDATE TARGETING COVID-19 PATIENTS

- COVID-19 pneumonia is targeting seniors and frail people, with the most severe outcomes
- Role of the Renin Angiotensin System



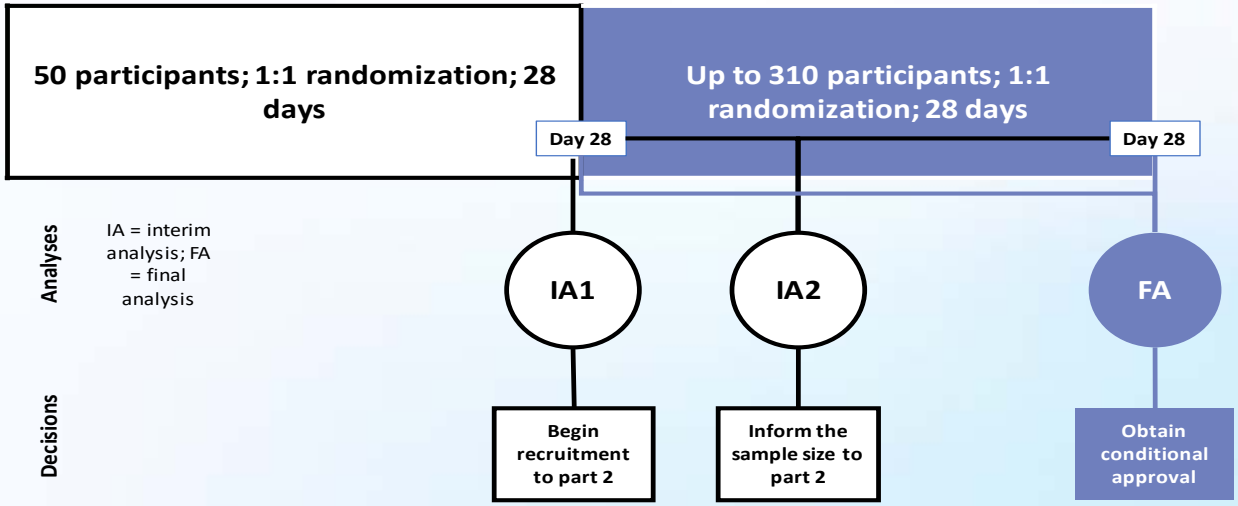
BIO101: Potential benefits based on previous data

- Protection of skeletal muscles against aging-related degradation (sarcopenia) and disuse atrophy
- Protection against respiratory function degradation (lungs and respiratory muscles) in an animal model of Duchenne myopathy (Biophytis data)
- Protection of lungs against LPS-induced acute lung injury in mice (Song et al. 2019)
- Protection of kidneys against fibrosis (Hung et al., 2012)

COVA TRIAL

The COVA study

Adaptive design phase 2 to 3, randomized, double-blind, multicenter, to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BIO101 in the prevention of the respiratory deterioration in hospitalized patients with COVID-19 pneumonia (severe stage)



Primary endpoints

Proportion of participants with 'negative' events:

- All-cause mortality
- Respiratory failure (requiring mechanical ventilation , ECMO or high-flow oxygen)

COVA has been approved and is ongoing in Belgium, France, UK, USA and Brazil
As of today, 19 participants are randomized

THANK YOU!

For more details on SARA-OBS study, please visit our poster

Abstract session 9 – Therapeutic development (clinical) + Therapeutic development (pre-clinical) I *Saturday 12 DECEMBER (7:55 pm – 8:45 pm)*

8-01 - SARA-OBS study: natural progression of sarcopenia and sarcopenic obesity in older adults

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