SARA-PK: A single and multiple ascending oral doses to assess the safety and evaluate the pharmacokinetics of BIO101 in healthy young and older volunteers.

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Introduction

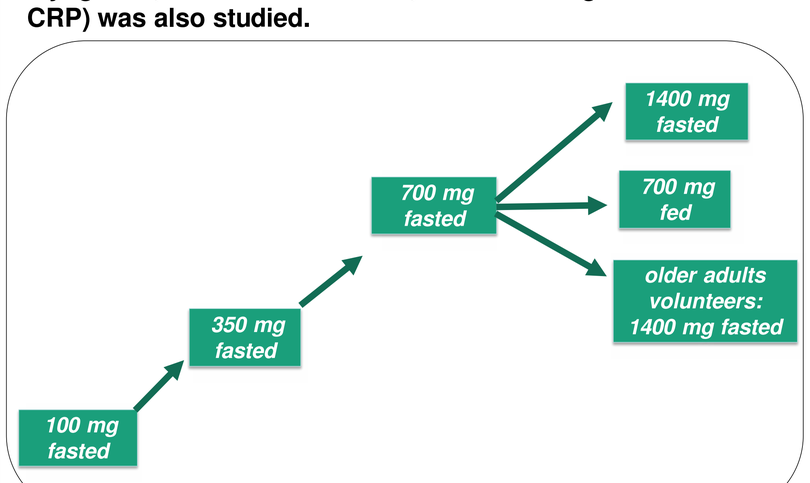
Age-related sarcopenia, characterized by the loss of muscle mass and function, represents a key underlying cause of physical frailty, a reversible condition in older patients that often leads to mobility disability and dependency.
Biophytis has developed the drug candidate Sarconeos (BIO101) and its derivative BIO103 (Dilda et al., Poster P217) that shows anabolic effects in rodent and human myocytes.
BIO101 also compensates the significant age induced loss of running velocity in rodents (Dilda et al., Poster P217).
Sarconeos (BIO101) effects for the treatment of sarcopenia, involves the Angiotensin 1-7/Mas receptor member of the Renin-Angiotensin Aldosterone System.
Sarconeos (BIO101) shows a very safe profile in rodents and non rodents toxicology and safety pharmacology assays.
The SARA clinical program, developed for BIO101 (DelSignore et al., Poster P186) is composed of three main studies dedicated to evaluate safety, pharmacokinetics and efficacy of Sarconeos (BIO101):

- **SARA-PK is the Phase 1 study that investigates safety and pharmacokinetics of Sarconeos in young and elderly subjects (completed).**
- **SARA-OBS (DelSignore et al., Poster P186) is the observational study that allows to characterize the population and main parameters of the next interventional study (Ongoing) .**
- **SARA-INT is the interventional study that will evaluate safety and efficacy of Sarconeos in older sarcopenic patients (Scheduled for second semester of 2017).**

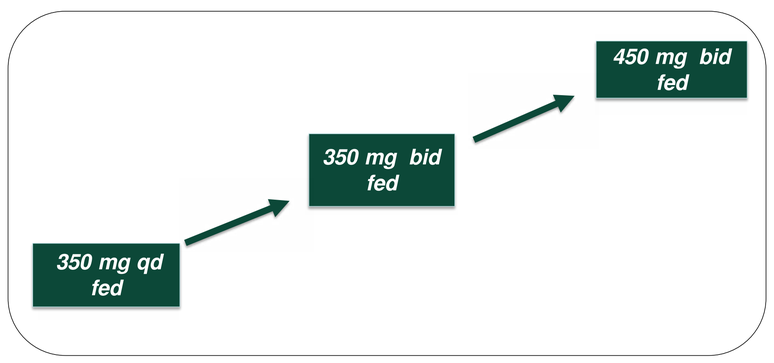
Our aim here is to present the main outcomes of SARA-PK, a randomised, double-blind clinical trial in healthy young and older volunteers evaluating single and multiple ascending oral doses of BIO101.

Clinical design & demographics

The Single Ascending Dose (SAD) consisted in a staggered design where the drug Sarconeos (BIO101) was administered to 24 subjects from two age groups: 2 cohorts of young adults (i.e., 18≤ age ≤55 years) at escalating doses of 100 to 1400 mg, and one cohort of older adults (65≤ age ≤85 years) at 1400 mg. In the Multiple Ascending Dose (MAD), 3 selected doses of BIO101 (350 mg qd; 350 mg bid and 450 mg bid) were administered by oral route to 3 panels of 10 older adults (65≤ age ≤85 years) over 14 days.
BIO101 safety and pharmacokinetics were evaluated in the SAD and MAD parts. The effect of BIO101 on exploratory pharmacodynamic biomarkers (Aldosterone, Renin, Myoglobin, Creatine kinase MB, PIIINP and high sensitive CRP) was also studied.



BIO101 Safety and Pharmacokinetic evaluation in SAD



Safety, Pharmacokinetics and Pharmacodynamics of BIO101 were evaluated in a 14-day Multiple Ascending Dose

Safety evaluation: SAD and MAD

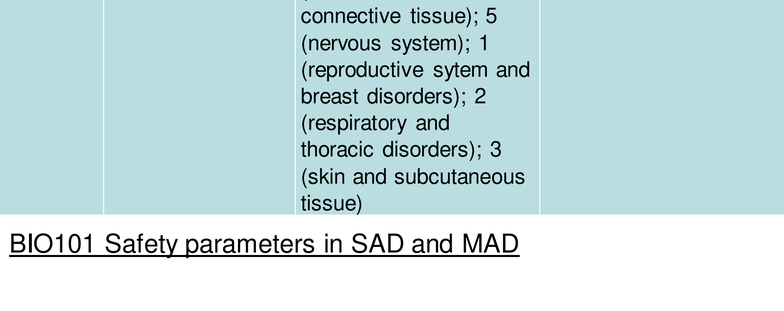
Phase	Dose	# of treated subjects with TEAE Type of TEAE	# of placebo subjects with TEAE Type of TEAE
SAD 6 active and 2 placebo per dose	100 mg Fasted	0	0
	350 mg Fasted	**2 subjects**: 1 (Nausea); 1 (Dizziness postural)	**1 Subject :** 1 (gastrointestinal disorders.)
	700 mg Fasted	0	0
	700 mg Fed	0	0
	1400 mg Fasted	**2 subjects**: 1 (food poisoning); 1 headache	0
	1400 mg Fasted older adults	**4 subjects:** 1 (back pain); 3 (headache)	0
MAD 8 active and 2 placebo per dose	350 mg qd	**2 subjects**. 1 (poisoning); 1 (wound); 1 (pain in extremity)	**3 subjects:** 1 (musculoskeletal and connective tissue; 1 nervous system disorders; 1 skin and subcutaneous tissue disorders
	350 mg bid	**7 subjects** . 7 (gastrointestinal disorders); 2 (infections and infestation); 4 (musculoskeletal and connective tissue); 1 (nervous system disorders); 1 (Respiratory, Thoracic and Mediastinal disorders)	
	450 mg bid	**8 subjects:** 4 (gastrointestinal disorders); 2 (administration site disorders) ; 3 (infections); 3 (musculoskeletal and connective tissue); 5 (nervous system); 1 (reproductive sytem and breast disorders); 2 (respiratory and thoracic disorders); 3 (skin and subcutaneous tissue)	

BIO101 Safety parameters in SAD and MAD

Oral administration of doses up to 1400 mg were safe and well tolerated in SAD. Oral administration of doses of 350 mg qd, 350 bid and 450 mg bid were safe and well tolerated in MAD. No abnormal clinical vital signs were reported as TEAE. No clinical laboratory parameters were reported as TEAE. All TEAEs were mild or moderate in severity (only 3 cases from the same subject in the 450 mg bid), no severe TEAEs were reported. All TEAEs were resolved by the end of the study.

Pharmacokinetics evaluation in SAD

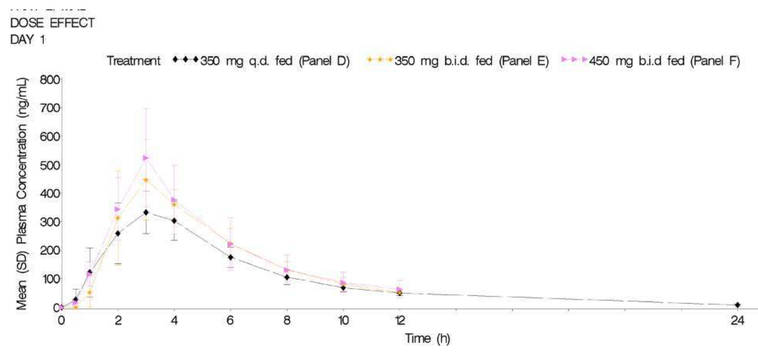
Dose and food effect were evaluated on BIO101 pharmacokinetic parameters. Pharmacokinetics were also compared between young and older adults.



Dose effect evaluation in SAD in fasted conditions for young and older adults.

After single oral administration, BIO101 C_{max} and AUCs showed an increased less than dose-proportional between 100 and 700 mg (2.8-fold increase [C_{max}] and 3.3-fold increase [AUCs] but roughly dose proportional between 700 mg and 1400 mg (1.8-fold increase [C_{max}] and 1.6-fold increase [AUCs].
BIO101 was rapidly absorbed with a median time to C_{max} of 2 h and 3.5 h for all doses (range 1.00-4.02 h).
BIO101 half-life is short (2.4 h- 4.9 h) .
Cmax and AUCs are slightly higher at 700 mg fed versus fasted (+24% for Cmax and + 20-22% for AUCs).
BIO101 concentration is slightly lower (- 22% for Cmax) as well as median time to Cmax (2.5 h and 3.5 h) in elderly subjects compared to younger adults at 1400 mg fasted.

Pharmacokinetics evaluation: MAD

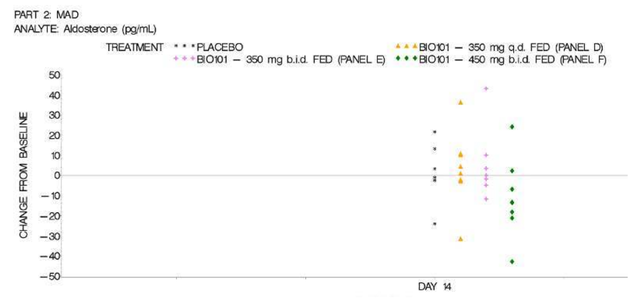


PK Parameter (Unit)	350 mg qd Fed N=8		350 mg bid Fed N=8		450 mg bid Fed N=8	
	Day 1	Day 14	Day 1	Day 14 (N=7)[a]	Day 1	Day 14
C_{max} (ng/mL)	346 (16.6)	388 (23.5)	453 (29.9)	506 (15.7)	524 (32.9)	560 (34.5)
t_{max} (h)	3.00 (2.00-4.00)	3.00 (3.00-4.00)	3.00 (2.02-4.37)	3.00 (2.00-4.00)	3.00 (3.00-3.00)	3.00 (2.00-4.00)
AUC_{0-t} (ng.h/mL)	2140 (18.4)	2389 (18.0)	2230 (17.6)	2766 (14.5)	2424 (28.5)	3203 (37.9)
$AUC_{0-\tau}$ (ng.h/mL)	2141 (18.4)	2389 (18.0)	2234 (17.6)	2768 (14.5)	2429 (28.5)	3203 (37.8)
$AUC_{0-\infty}$ (ng.h/mL)	2193 (18.0)	2414 (18.0)	2451 (16.0)	3028 (15.0)	2566 (28.1) [n=7]	3486 (38.6)
$t_{1/2}$ (h)	4.39 (20.7)	3.39 (10.9)	3.00 (12.1)	3.06 (21.3)	3.72 (28.1)	2.81 (8.62)
R_{ac}	NA	1.14 (23.6)	NA	1.31 (16.7)	NA	1.31 (20.2)

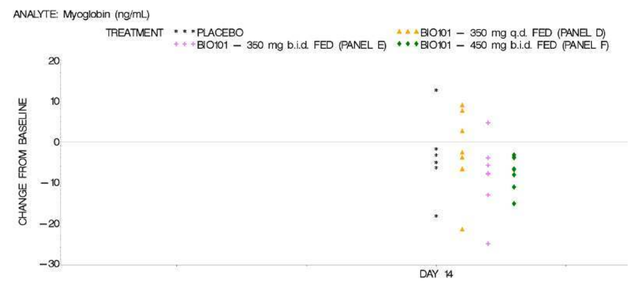
Main BIO101 Pharmacokinetic parameters -MAD

No accumulation of BIO101 was observed after qd administration of 350 mg BIO101 for 14 days (mean R_{ac}: 1.14).
A slight accumulation was observed after bid administrations at 350 mg and 450 mg for 14 days (mean R_{ac}: 1.31 in both cohorts).
Given the short half-life of BIO101 (3-4 h) and based on trough concentrations profiles, steady-state was reached on Day 2 in all cohorts.

Pharmacodynamic evaluation in MAD Changes at day 14 from baseline



Aldosterone plasma concentrations: changes at D14 from baseline



Myoglobin plasma concentrations: changes at D14 from baseline

BIO101 administration tended to decrease Renin, Aldosterone, CRP and Myoglobin plasma concentrations and to increase PIIINP concentrations compared to baseline Reductions of Renin and Aldosterone concentrations confirmed the involvement of the Renin Angiotensin Aldosterone System in BIO101 effects.
The adaptative biomarkers will be assayed in a larger sample in the SARA-INT phase 2 interventional study with BIO101.

Conclusion

- **Sarconeos (BIO101) was safe and well tolerated after a 14-day per os administration in healthy older volunteers.**
- **Pharmacokinetic profile revealed a short half-life and no plasma accumulation, compatible with a bid administration in phase 2 studies.**
- **Observed changes in the Renin Angiotensin Aldosterone System biomarkers are consistent with the mechanism of action of BIO101.**
- **SARA-PK safety, pharmacokinetics and pharmacodynamics results allowed us to define the doses of SARA-INT, the Sarconeos (BIO101) Phase 2 interventional study.**