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BIOPHYTIS, PARIS, FRANCE

COVA study: results from a double-blind, placebo-controlled phase 2/3 study to assess efficacy and safety of BIO101 in hospitalized COVID-19 patients

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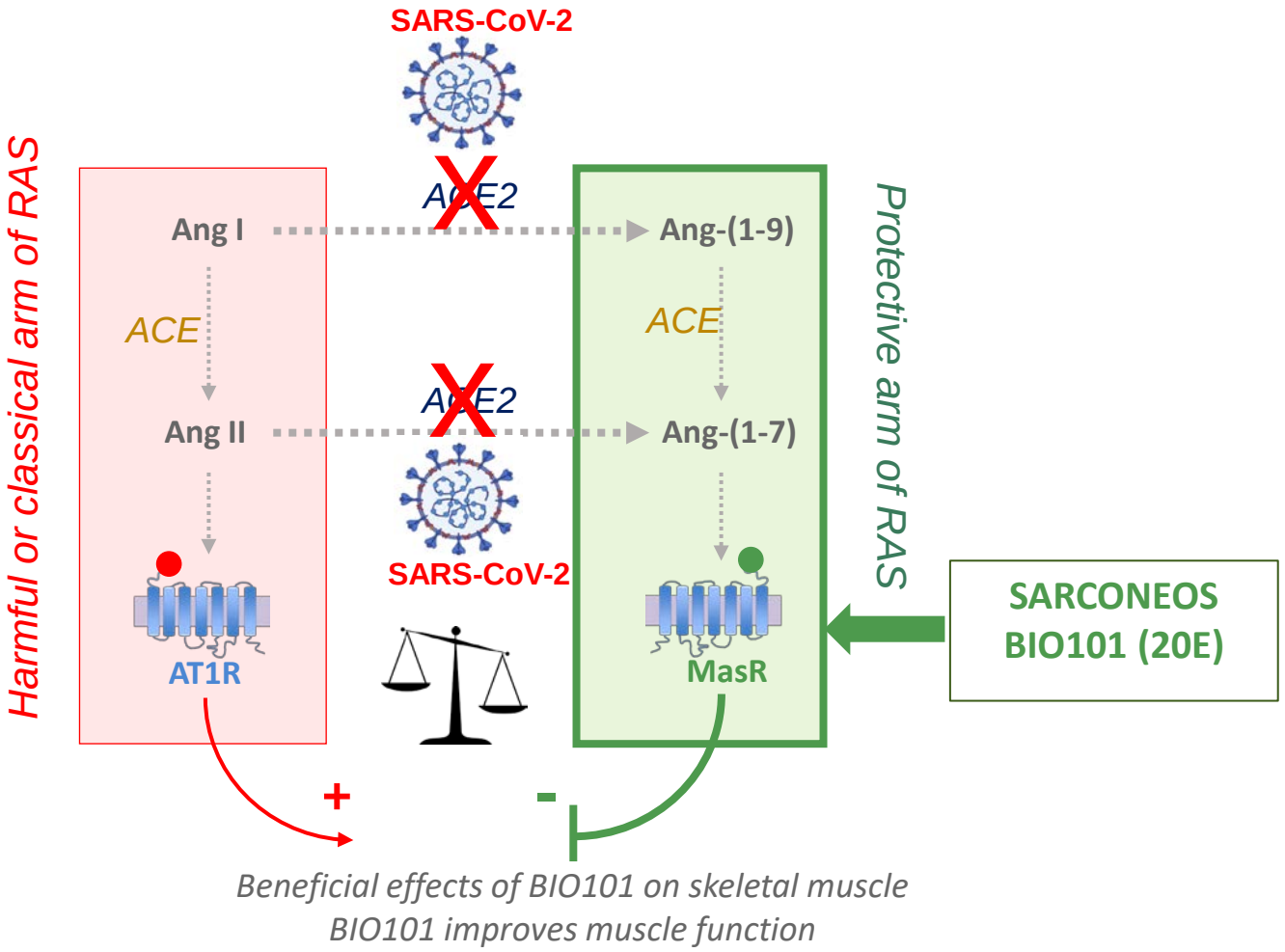
BIO101 Mechanism of action



- BIO101 activates Mas receptor on the protective arm of RAS
- Protection against respiratory function deterioration (lungs and respiratory muscles)
- Improved pulmonary function
- We believe that restoration of RAS balance is responsible for the significant improvement of respiratory function decline demonstrated in a preclinical COVID-19 animal model

Could improve the outcome of COVID-19 patients hospitalized with severe respiratory condition.

→ ***Improved respiratory function / protection against deterioration***

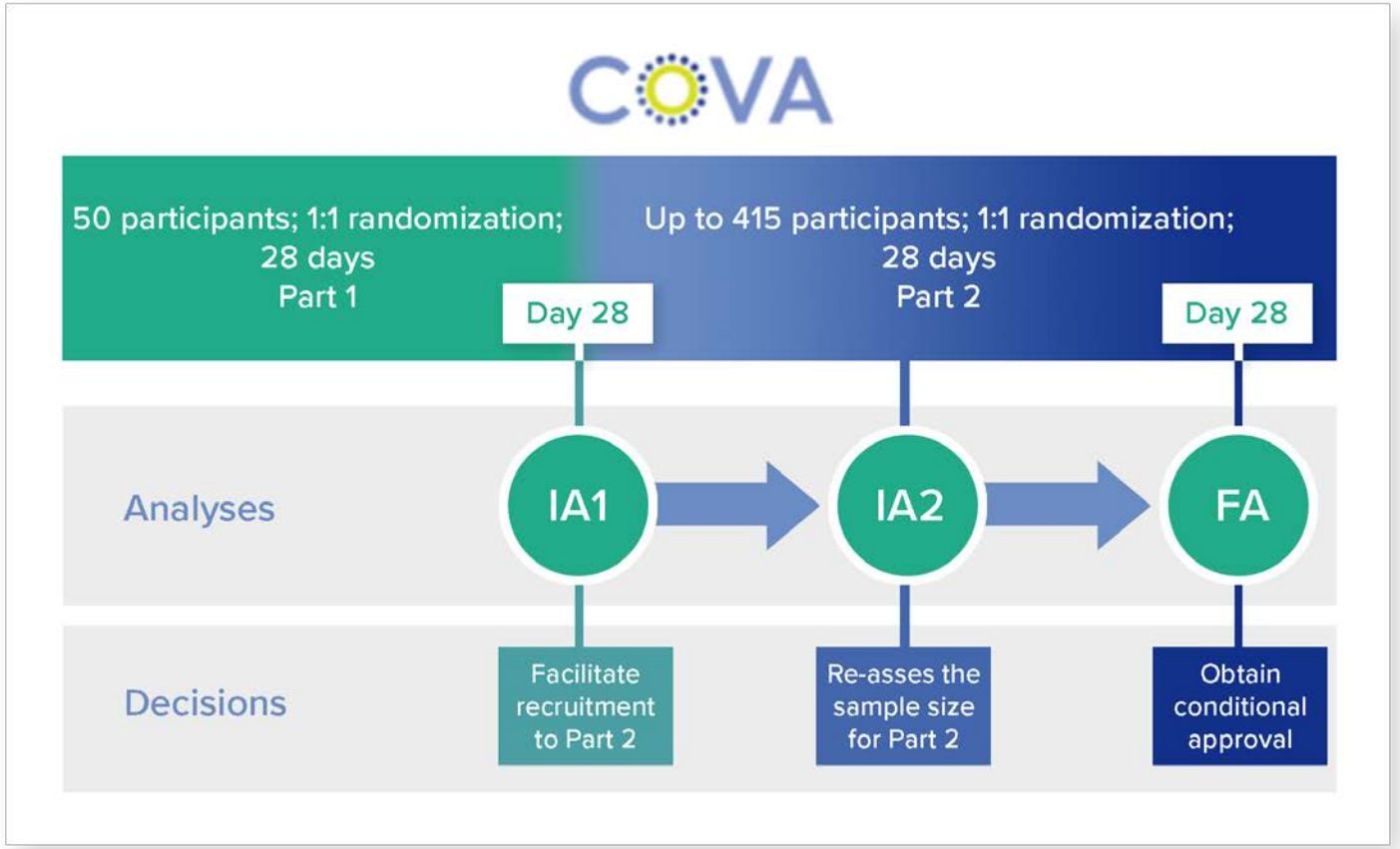
Adapted from Latil *et al*. 2021 *Drug Discov Today*

Study design: phase 2/3, double-blind, placebo-controlled, group-sequential and adaptive study

- BIO101 350 mg BID vs placebo, randomization 1:1

- Key inclusion criteria:
  - Age 45 and older
  - Proven Covid-19 infection
  - Hospitalized with or without supplemental oxygen (low-flow, CPAP/BiPAP, HFO*)
  - SpO_2 ≤92% and/or
  - ≥25 breaths per minute
  - AST/ALT/GGT/bili ≤5 × ULN
  - Any experimental or licensed drug accepted

- Key exclusion criteria:
  - Life expectancy <7 days
  - Invasive mechanical ventilation or ECMO



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* High-Flow Oxygen allowed at baseline after amendment 11 (n=112)

Endpoints

***Primary**, time frame – up to 28 days:*

Proportion of participants with '**negative' events**:

- All-cause mortality **or**
- Respiratory failure, defined as any of the following:
  - Requiring mechanical ventilation
  - Requiring ECMO
  - Requiring high-flow oxygen (for subjects who were enrolled under protocol version 1-11)

***Key secondary**, time frame – up to 28 days:*

Proportion of participants with **'positive' events** ie. official discharge from hospital care by the department due to improvement in participant condition

***Secondary**:*

- Proportion of participants with events of all-cause **mortality** (D28, 60, 90, overall)
- Time to death

Baseline Characteristics, Intention to Treat (ITT) analysis set

	BIO101 (N=126)	PLB (N=107)	Total (N=233)
Age (years), Mean (SD)	63.0 (9.82)	62.5 (8.46)	62.8 (9.21)
Age range (min-max)	40 - 90	40 - 90	40 - 90
Age categories, n (%)			
< 65 years	69 (54.8)	62 (57.9)	131 (56.2)
≥ 65 years	57 (45.2	45 (42.1)	102 (43.8)
Sex, n (%)			
Male	84 (66.7)	64 (59.8)	148 (63.5)
Female	42 (33.3)	43 (40.2)	85 (36.5)
BMI Mean (SD)	29.76 (6.06)	30.96 (7.25)	30.30 (6.64)
Any immunosuppressant during trial intervention, n (%)	4 (3.2)	9 (8.4)	13 (5.6)

Well balanced population between placebo and BIO101 regarding baseline characteristics and demographics except imbalance in use of immunosuppressants and less males in the placebo group (risk factor for severe Covid-19)

BIO101 reduced the proportion of patients with respiratory failure or early death

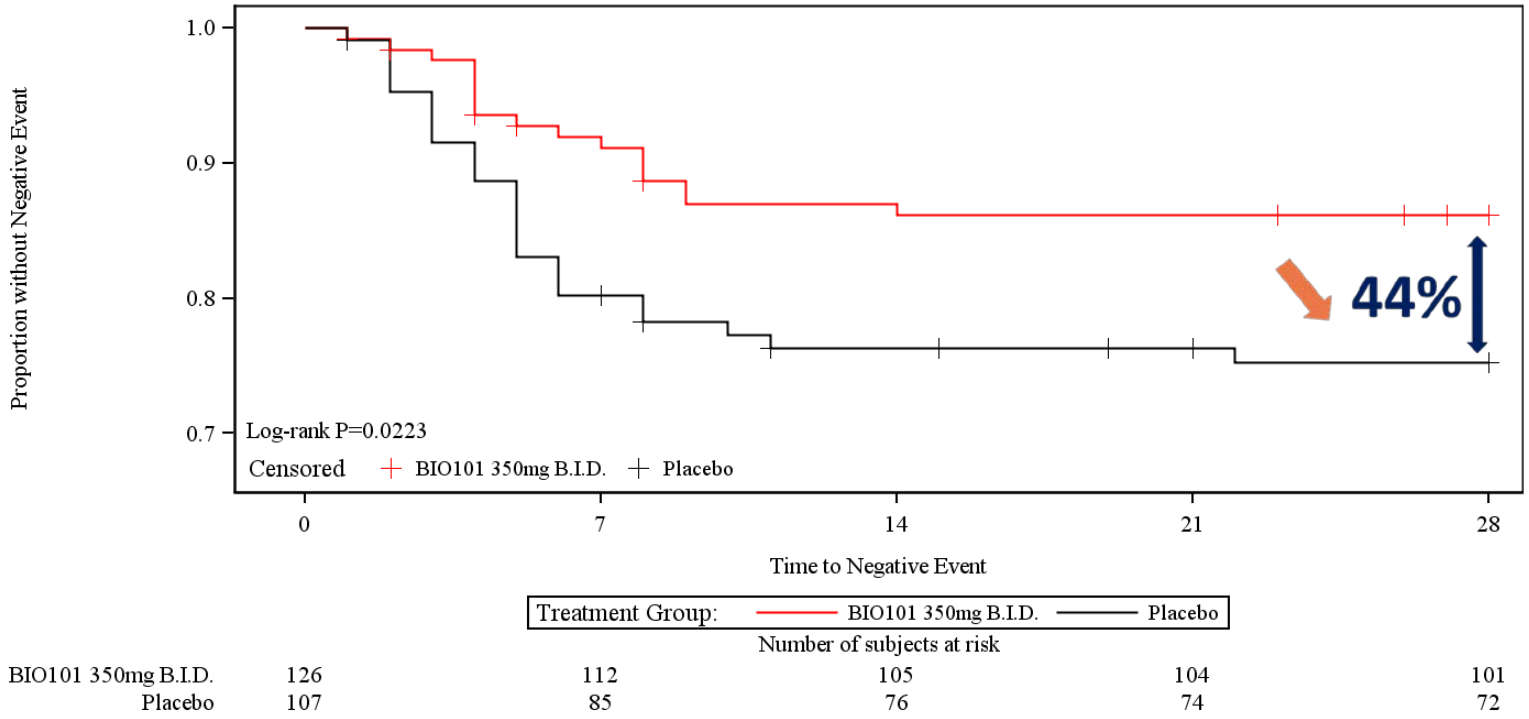
Primary endpoint

Comparison of BIO101 350 mg BID vs PLB CMH test (ITT)				
BIO101 (N=126) n (%)	**PLB (N=107) n (%)**	**Unadjusted Difference (%)**	**Adjusted Difference (%) (95% CI)**	**P-value**
19.85 (15.8)	27.86 (26.0)	-10.3	-11.4 (-22.4, -0.4)	**0.0426**

BIO101 reduced the **proportion of patients with respiratory failure or early death by 44%.**

Cochran-Mantel-Haenszel test, ITT analysis set

Reduction in the risk of early death and respiratory failure by 44% at 28 days in BIO101 group
Log-rank test, ITT Analysis set



- BIO101 group shows a **relative reduction of risk of early death and respiratory failure by 44%**
- Hazard Ratio (95% CI): 0.489 (0.265, 0.904)
- Log-rank test p = 0.0223

Stratification factors: RAS pathway modulator use, gender, co-morbidities and receiving CPAP/BiPAP/HFO2 at study entry

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Higher proportion of patients recovered and discharged

	BIO101 350mg B.I.D. (N=126) n (%)	Placebo (N=107) n (%)	Unadjusted Difference (%)	Adjusted Difference (%) (95% CI)	P-value
Combined Inference	100.94 (80.1)	75.91 (70.9)	9.2	11.0 (-0.4, 22.4)	**0.0586**

- BIO101 group had numerically **higher proportion of patients who recovered and were discharged** compared to placebo
- strong trend towards a nominally statistically significant difference (probably resulting from lower than planned sample size)

Stratification factors: RAS pathway modulator use, gender, co-morbidities and receiving CPAP/BiPAP/HFO2 at study entry

Primary analysis of key secondary endpoint
Cochran-Mantel-Haenszel test, ITT Analysis Set

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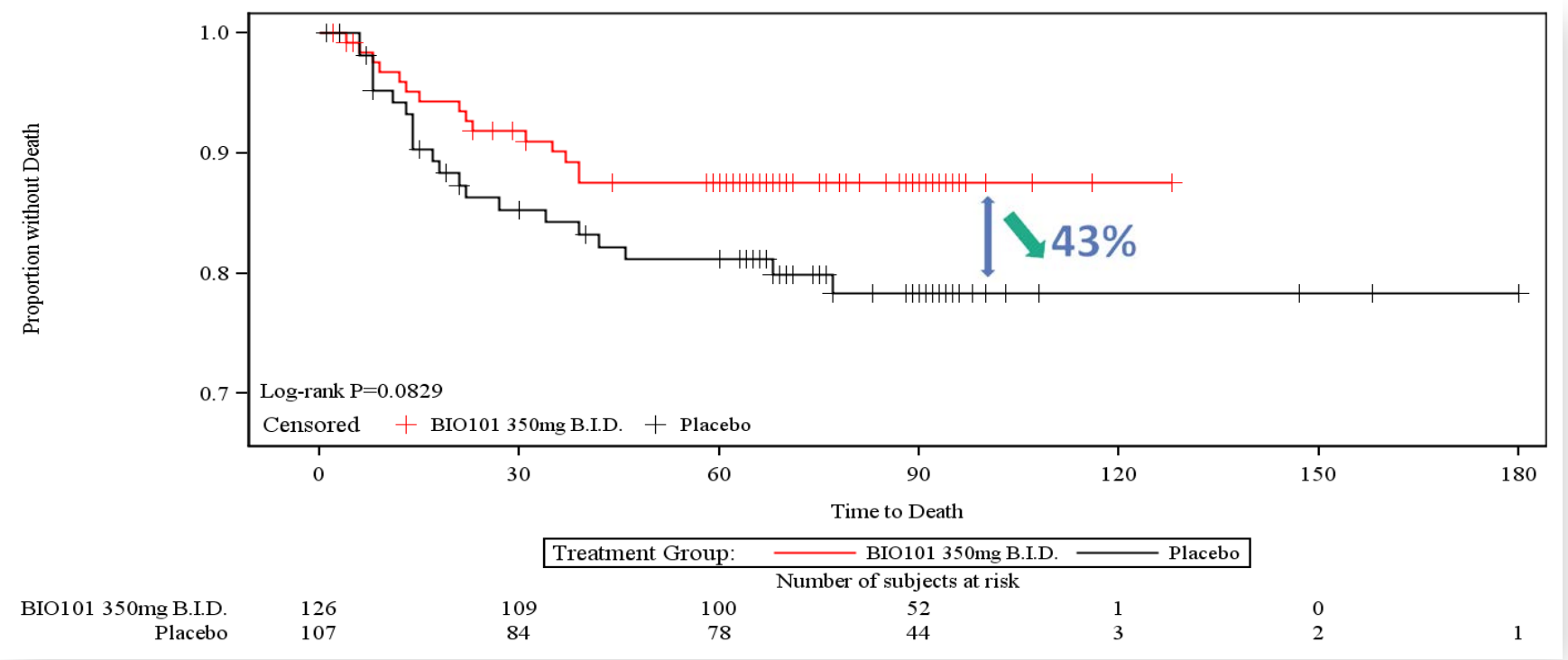
Relative reduction in risk of death observed of 43% in BIO101 group at 90 days



- BIO101 group shows a **relative reduction of risk of death by 43%**
- Hazard Ratio (95% CI) 0.554 (0.285, 1.077), p = 0.0829

Stratification factors: RAS pathway modulator use, gender, co-morbidities and receiving CPAP/BiPAP/HFO2 at study entry

Other efficacy endpoint: all-cause mortality at 90 days
Log-rank test, ITT Analysis set

Adverse Events Overview: BIO101 demonstrates a very good safety profile

Safety Analysis Set

Treatment emergent adverse events (TEAE)	BIO101 (N=128) n (%)	Placebo (N=104) n (%)
TEAEs	73 (57)	67 (**64.4**)
Serious TEAEs	32 (25.0)	32 (**30.8**)
Fatal TEAEs	14 (10.9)	15 (**14.4**)
TEAE related to treatment	12 (9.4)	14 (**13.5**)
Serious TEAEs related to treatment	0	3 (**2.9**)

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- **A lower proportion of patients experienced TEAEs in the BIO101 than in the placebo group (57% vs 64.4%)**
- **The most frequent serious TEAEs were respiratory failure, acute respiratory distress syndrome, acute respiratory failure, and hypoxia.**
- **A lower proportion and number of serious TEAEs were reported in the BIO101 group than in the placebo group: (32 subjects (25.0%), vs. 32 subjects (30.8%).**
- **Proportion of subjects with GGT ≥2x baseline or ≥5x ULN was higher in BIO101 group (20.3%) than placebo (12.5%) -> GGT increase cannot be ruled out completely at this time**
- **These results support efficacy data and confirm BIO101 good safety profile already demonstrated in phase I and in Sarcopenia phase II trials.**

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Conclusions

- **Primary endpoint: BIO101 reduced proportion of patients with respiratory failure or early death** at day 28 (p=0.043).
  Relative reduction in risk of 44%

- **Key secondary endpoint:** strong trend towards **higher proportion of recovered and discharged patients** at day 28 in BIO101 group (p= 0.059)
- **Mortality: relative reduction in risk of death of 43%** at day 90 in BIO101 group (p=0.083)

- Higher proportion of patients with immunosuppressants and lower proportion of males in placebo group may have biased the trial in favor of placebo, reducing negative event rate

- **Excellent safety profile:**
  Frequency of TEAEs, SAEs and serious respiratory events higher in placebo group, in line with the efficacy data
  No ADRs* identified to date, although the association of BIO101 with increase in GGT cannot be excluded

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* ADR: Adverse Drug Reaction

Acknowledgements

COVA Steering Committee

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