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

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Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus and is still a serious and life-threatening disease. Any patient infected with COVID-19 can become seriously ill or die at any age, particularly elderly people and those with associated risk factors (e.g., cardiovascular disease, diabetes, chronic respiratory disease, cancer, obesity).

The drug candidate BIO101, a 97% 20 hydroxyecdysone (20E) purified from the plant *Cyanotis sp.* BIO 101 is a MAS receptor activator of the protective arm of the Renin-Angiotensin-System (RAS), which due to its mechanism of action may counteract the effects of ACE2 inactivation by the virus and have a potential beneficial effect in patients suffering from Covid-19 irrespective of the variant.

Objectives

To assess the efficacy and safety of BIO101 in hospitalized severe COVID-19 patients with signs of pneumonia who may or may not require oxygen supplementation, but who are not on invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation).

Methods

- Randomized, double-blind, placebo-controlled phase 2/3 trial with a planned sample of 310 patients.
- Hospitalized adults aged ≥45 years with respiratory decompensation due to Covid-19 randomized 1:1 to placebo (PLB) or BIO101.
- Oral administration of BIO101 350mg BID: 2 capsules in the morning and evening for up to maximally 28 days (until endpoint, either clinical improvement with hospital discharge or progression to mechanical ventilation, ECMO or death).
- Parameters assessed at Day 28
  - **Primary endpoint**: Proportion of patients with **respiratory failure** or **early death**
  - **Secondary endpoints**:
    - ✓ **Proportion of patients with hospital discharge** (key secondary)
    - ✓ **Time to respiratory failure or early death** and **time to death**

  In total, observation period of 90 days after randomization.
- **Safety endpoints**: SAEs, AESIs, AEs, vital signs, safety laboratory assessments, and ECGs.
- **Statistical Analysis Method:**
  Cochran-Mantel-Haenszel (CMH) and Kaplan-Meier (KM) tests - SAS software Version 9.4.

Results

233 patients were enrolled from 21 September 2020 to 8 March 2022, in 37 study centers in the United States (13 study centers), Belgium (3 study centers), Brazil (14 study centers), and France (7 study centers). The study has been early terminated (before reaching the 310 patients initially defined) because of the pandemic evolution which has led to stalled enrolment.
The statistical analysis was performed on 233 patients in the Intention To Treat (ITT) population and 180 patients in the Per Protocol (PP) population.

I/ BASELINE DEMOGRAPHICS

Table 1

	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		
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 groups (PLB/BIO101) except in use of immunosuppressants potentially favoring PLB and sex distribution with less males in the placebo group (risk factor for severe Covid-19) (Table 1).

II/ PRIMARY ENDPOINT

RESPIRATORY FAILURE OR EARLY DEATH – D28

Table 2

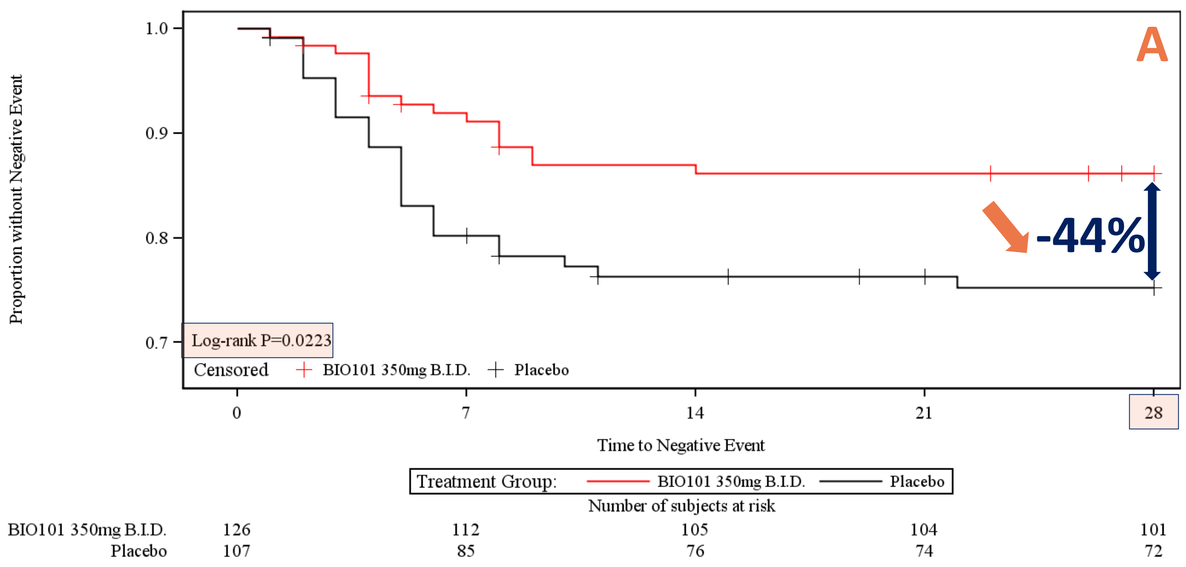
		Comparison of BIO101 350 mg BID vs PLB CMH test (ITT)		
BIO101 (N=126) n (%)	**PLB (N=107) n (%)**	**Unadjusted Difference (%)**	**Adjusted Difference (%) (95% CI)**	***P*-value**
19.85 (15.8)	27.86 (26.0)	-10.3	-11.4 (-22.4,-0.4)	**0.0426**

-44%

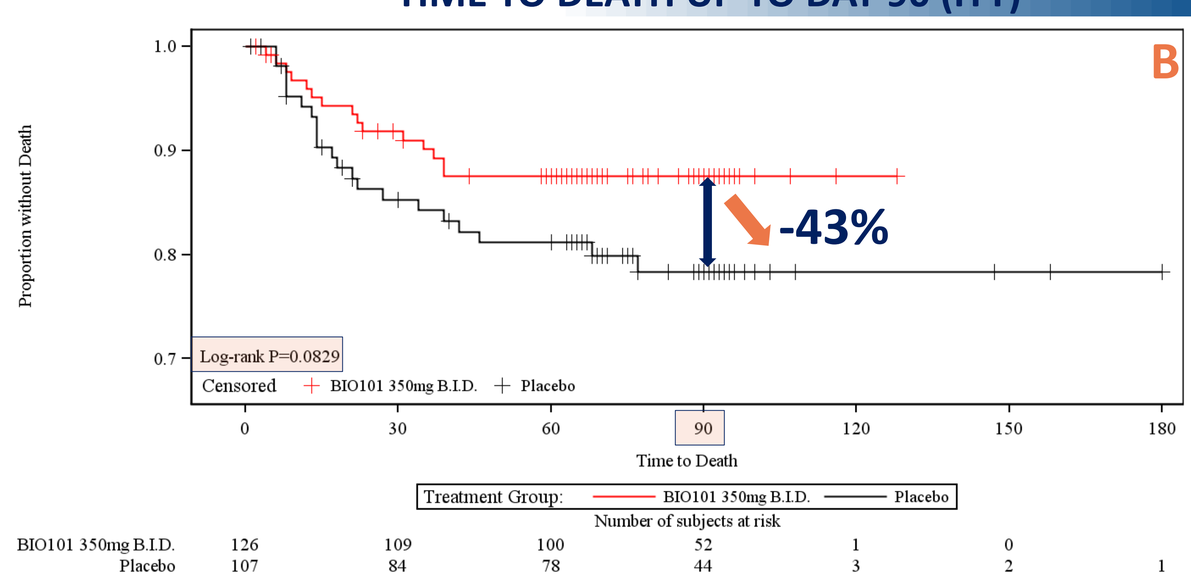
→ The CMH test showed a statistically significant lower proportion of respiratory failure or early death in BIO101 group compared to placebo at Day 28, p=0.0426, with a relative risk reduction of respiratory failure or early death of 44% (Table 2).

III/ SECONDARY ENDPOINTS

TIME TO RESPIRATORY FAILURE OR EARLY DEATH UP TO DAY 28 (ITT)



TIME TO DEATH UP TO DAY 90 (ITT)



→ **At Day 28**: ■ The adjusted difference in the proportion of patients with hospital discharge of 11% showed a trend towards a statistically significant difference in BIO101 group versus placebo in ITT population, p= 0.0586 – CMH test. ■ The KM analysis in the ITT population showed a statistically significant difference in proportion of patients with respiratory failure or early death between BIO101 and PLB, p=0.0223 with a reduction of 44% in the BIO101 arm (graph A).

→ **At Day 90**: The KM analysis showed a difference in proportion of deaths in the BIO101 group compared to the placebo group in the ITT population: 43% reduction, p=0.0829 (graph B).

IV/ SAFETY

The results showed a lower proportion of patients with TEAEs in the BIO101 group (57%) than in the placebo group (64.4%), in particular a lower frequency of serious TEAEs (25% vs 30.8%) and serious respiratory TEAEs (18.8% vs 26.0%). Frequency of orthostatic hypotension was similar between groups (7.0% vs 7.7%).

V/ LIMITATIONS

More frequent immunosuppressants use in the placebo group and higher proportion of males in the BIO101 group may have diminished differences.

Conclusion

The results of this phase 2-3 study assessing BIO101 in the treatment of hospitalized severe Covid-19 patients are very positive and show, in addition to a very good safety profile, a statistically significant reduction in the relative risk of early respiratory failure or death by 43.8% and in the mortality rate at day 90. BIO101 may offer a serious effective therapeutic option to hospitalized patients suffering from Covid-19, especially to the elderly with comorbidities and in the current context where the number of Covid-19 cases and number of deaths are still unacceptably high.

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