Study title: Safety and effectiveness of BIOMODULIN T in a long-lived population at high risk of COVID-19 infection. Intervention study.

FLOW OF PARTICIPANTS

In Ciego de Ávila, in the first stage, 2,892 adults aged 80 years and over were included, from a universe of 2,935 evaluated (98.5%). Later, within this same municipality, another 1,320 long-lived were included, which represented 99.2% of the new universe of 1,331 evaluated. In Sancti Spíritus only 100 selected elderly from a health area were included, while in Santiago de Cuba 3020 individuals were analyzed to finally include 2917 (96.6%). In Old Havana, of a universe of 2,473 elderly, 96.8% (2,394 individuals) were included.

In this way, in total, a universe of 9859 long-lived was analyzed, including 9623 in the study for 97.6%. The main cause of non-inclusion was non-voluntariness of the elderly (135 older adults), as shown in Table 1.

Table 1. Willingness of older adults to be included in the study.

Municipality	Universe	Included	Causes of non-inclusion			
			Denied	Outside the area	intercurrent disease	BMT less than 2m
Ciego de Avila 1st stage	2935	2892	23	12	7	1
Ciego de Avila 2nd stage	1331	1320	8	0	3	0
Sancti Spiritus	100	100	0	0	0	0
Santiago de Cuba	3020	2917	41	32	30	0
old Havana	2473	2394	63	10	5	1
Total	9859	9623	135	54	Four. Five	two

Of the 9,623 included, 9,233 elderly patients completed the treatment scheme, representing 95.9% (Table 2). A total of 56,595 doses were applied in the study, representing 98.0% of the 57,738 planned.

Likewise, in Table 4 it can be seen that Santiago de Cuba and Old Havana had the highest percentages of interruptions: 6.9 and 5.1% respectively. Within the reasons for interruption, the most frequent, both by municipalities and in general throughout the study, was voluntary abandonment (61.0%)

Table 2. Compliance with treatment by municipalities.

Municipality	Included	complete treatment	%	interruptions	%
Ciego de Avila 1st stage	2892	2850	98.5	42	1.5
Ciego de Avila 2nd stage	1320	1298	98.3	22	1.7
Sancti Spiritus	100	97	97.0	3	3.0
Santiago de Cuba	2917	2715	93.1	202	6.9
old Havana	2394	2273	94.9	121	5.1
Total	9623	9233	95.9	390	4.1

BASELINE CHARACTERISTICS

This is a sample of individuals all aged 80 and over (the so-called old men). It should be noted that, in Old Havana, 7 (0.3%) of the 2,394 long-lived included were 100 years old or older. In all the provinces, as well as in the total sample, there was a marked predominance of the female sex (Table 3), in line with the Cuban population statistics for this age group.

Table 3. Distribution by sex according to provinces.

Municipality	**Male**		**Feminine**		**Total**	
	.	**%**	**.**	**%**	**.**	**%**
Blind	1767	42.0	2445	58.0	4212	100.0
Sancti Spiritus	3. 4	34.0	66	66.0	100	100.0
old Havana	837	35.0	1557	65.0	2394	100.0
Santiago de Cuba	1135	38.9	1782	61.1	2917	100.0
Total	**3773**	39.2	**5850**	60.8	**9623**	100.0

Table 4 shows the APP of the individuals included in Old Havana and Sancti Spíritus. It was found that the most frequent pathologies were hypertension (65.0%, diabetes mellitus (24.1%) and ischemic heart disease (13.1%) in that order In general, 11% of the elderly were comorbid , that is, they presented three or more pathologies.

Table 4. Personal Pathological History according to sex

Municipality	**N**	**AHT**		**DM**		**IQ**		**COPD**		**CM**	
		.	**%**	**.**	**%**	**.**	**%**	**.**	**%**	**.**	**%**
Sancti Spiritus	100	68	68.0	30	30.0	9	9.0	5	5.0	18	18.0
old Havana	2394	1553	64.9	571	23.9	318	13.3	55	23	256	10.7
Total	2494	1621	65.0	601	24.1	327	13.1	60	2.4	274	11.0

PRIMARY AND SECONDARY OUTCOMES

COVID-19 infection

Table 5 shows the patients diagnosed with COVID-19 by municipality during the study. None of the 29 elderly positive for SARS-CoV-2 was seriously ill or died

Table 5. Patients diagnosed with COVID-19 by municipality.

Municipality	**N**	**cases COVID-19**	**%**
Ciego de Avila	4212	0	0.0
Sancti Spiritus	100	0	0.0
Santiago de Cuba	2394	7	0.3

old Havana	2917	22	0.8
Total	**9623**	29	0.3

When the study began in Ciego de Ávila, with a great dispersion of COVID-19 cases, the province with 27.68 was the one with the highest incidence rate per 100,000 inhabitants in the country, even above Havana. The situation had generated the opening of four transmission events, the most important of which was in the municipality of Ciego de Ávila, with 30 cases.

The first stage of the study begins here on September 26, 2020 with the first group of elderly. At the completion of the intervention in this group on November 6, none of the elderly had been diagnosed with COVID-19, in this context of high transmission, where the highest case fatality rates had also been shown to date. It began in other health areas of the same municipality on the 19th of the same month, completing the intervention at the end of December 2020. Until the month of completion of the treatment, none of the older adults in this area who had received the treatment had been diagnosed. with the disease, even though many of them were direct contacts of sick individuals, according to the attending physicians. The local newspapers gave coverage to the intervention, which due to its results had an excellent acceptance in the population.

In the province of Sancti Spíritus, treatment begins on October 24 in a sample of only 100 long-lived patients from a medical office with a critical situation in that community. In that time, 17 cases of COVID-19 were diagnosed in that small area, none of them from study participants.

At the end of January 2021, specifically on the 25th, the intervention begins in the capital of Santiago de Cuba. In the report from the PAHO/WHO office in Cuba, this province showed the third highest incidence rate in the last 14 days with 180.4 x 105 inhabitants. During the last week, 1,055 positive cases had been reported, 213 more than in the previous week and an increase of 20.2%. Autochthonous cases were reported during the week in eight of the nine municipalities. The most affected was the provincial capital, Santiago de Cuba, with 85.3% of the cases in the province; 878 are native and 22 imported. The cumulative incidence rate in the last 14 days in this municipality was 323.8 per 100,000 inhabitants, ranking seventh among the country's municipalities with the highest rate. COVID-19. In this complex context, only seven long-lived, 0.3% of those who received treatment with BIOMODULIN T ® were positive for COVID-19. None of them were serious or died.

In Old Havana, the intervention began on February 24, 2021 and lasted until April 20, 2021. Havana had remained the province with the highest number of diagnosed cases since the beginning of the pandemic. In the week prior to the intervention, more than 350 cases per day were diagnosed in the province, and of these, an average of 26 cases per day in the Habana Vieja municipality. During the study period Old Havana had an equal or more complex situation. Accumulated incidence rates x 10^{5} inhabitants were reported in the last 14 days, very high and in constant increase, reaching in several weeks to have this municipality the highest rate in the country.

In the total accumulated until April 24, the capital contributed 48.7% of the country's cases and 52.6% of the deceased, as well as the highest accumulated incidence rate . In this context, so complex that only 22 elderly, 0.8% of the long-lived included in the study, became infected, it is undoubtedly a very favorable result, in addition to the fact that all these elderly survived the disease without complications.

BIOMODULIN T® is not a vaccine, it does not prevent the individual from becoming infected. But due to its effects on the immune system, the treated individual will be in a better position to deal with this infection. We cannot rule out that, in these contexts of high transmission, many of these elderly have passed the disease asymptomatically. Remember the health status of the population in question, being individuals at very high risk of complications and death from this disease.

With the data shown in this report, it is evidenced once again that BIOMODULIN T® is a drug with a very favorable risk-benefit balance.

osteoarticular pain and sleep disorders.
As we do not have complete information on these variables in all or most of the sample, results referring to them are not shown in this report, with no output for objective 3.

ADVERSE EVENTS
The AEs classified with Very probable/certain causality are analyzed below; Probable and Possible recorded during the study, that is, those related AEs that can be considered as ADRs by BIOMODULINA T® . These include expected and unexpected EAs
Table 6 summarizes the types of related AE registered by Organ/System and Table 7 describes the same according to their classification according to location, time of appearance, duration, prior knowledge, intensity, consequence, causality, outcome of the AE; and attitude towards the study treatment.

Table 6. AE according to Organ/System

Organ/System	Type of AE
Cutaneous - Local reaction at the injection site (pain and/or erythema) - Systemic allergic reaction / Rash / Eruption	 10 7
CNS - Headache	 14
Others - Fever - Asthenia - Chills	 two 4 4
Total	**41**

Table 7. Classification of registered AE

ADVERSE EVENTS	**No. (%)**
Location:	
• *local ae*	10/41 (24.4%)
• *systemic AE*	31/41 (75.6%)
Appearance Time:	
• *Immediate EA*	41 (100.0%)
Duration	
Less than one day	39/41 (95.1%)
older than one day	2/41 (4.9%)
Prior knowledge	
• *expected AE*	37/41 (90.2%)
• *unexpected AE*	4/41 (9.8%)
Intensity	
Mild	33/41 (80.5%)
moderate	8/41 (19.5%)
Impact	
not serious	41 (100.0%)
Causality	

Very likely/certain	10/41 (24.4%)
Probable	26/41 (63.4%)
Possible	5/41 (12.2%)
Outcome	
Recovered	41 (100.0%)
Attitude towards treatment	
Continuation	34/41 (82.9%)
Interruption	7/41 (17.1%)

The deaths that occurred during the administration of the product, which constituted unrelated serious AEs, as well as other intercurrent diseases, which by concept also constitute AEs, are not detailed in this report. Understand that it is an intervention in a long-lived population with deteriorated health conditions and where logically deaths and other medical conditions are expected and frequent.
A total of 9,623 older adults were included in the study, to whom a total of 56,595 administrations were applied. A total of 41 ADRs were reported, for a frequency of 0.43% ADR per patient and 0.07% per administration.

GENERAL CONCLUSIONS

❖ As a preventive measure to confront COVID-19 in long-lived adults in Cuba, BIOMODULINA T® had a large extension in primary care, with no serious related reactions reported, nor any new safety problem, with the adverse reactions that occurred classified as occasional or infrequent, mostly mild and most often headache-like.

❖ Treatment with BIOMODULINA T® contributed to the lower number of cases and complications from COVID-19 in the elderly population in areas of high epidemiological risk.