

Trial title: Evaluation of the safety and efficacy of BIOMODULINA T® for the prevention of infections, including COVID-19, in older adults in Cuba. Phase IV Clinical Trial.

FLOW OF PARTICIPANTS

In relation to scenario 1, the intervention in the isolation centers was not carried out as planned. The treatment of travelers was included in the National Action Protocol for COVID-19, and was eliminated in version 1.5 of this. Therefore, in this scenario only safety was evaluated.

In scenario 2, older adults from the OSDE BioCubaFarma were not included, and since the possibility of other sites had been left open, the OC from Plaza de la Revolución was included. Individuals were followed for a period of six months after starting treatment and only the evaluation of safety and the effect of treatment on COVID-19 infection were taken into account.

In scenario 3, after the first cycle of treatment, the duration of the evaluation period was from April to September 2020, although in some sites until October, because they started treatment in May. Faced with the second pandemic peak, with the results obtained with the intervention, it was decided by the MINSAP authorities to apply a second cycle of treatment at least six months after the previous one, in long-term care institutions. This second cycle was not carried out in unison throughout the country. Although it began to be applied in some sites in November 2020, most of the sites carried it out in the month of January 2021. In this case, six months from the start of the treatment were taken into account for the evaluation, including the dates between November 2020 and June 30, 2021.

Scenario 1

For the safety analysis, the available data are taken, taking into account that at least 1 dose of the product was administered to 416 older adults.

scenario 2

This scenario included a total of 226 workers, distributed among 74 workers from BioCen, 110 from the central offices of MINSAP, and 42 from the Plaza de la Revolución.

In BioCen of a universe of 75 older adults, 74 were included, because one did not give consent.

Scenario 3

❖ Nursing Homes:

Cuba had 153 Homes for the Elderly, distributed in all the provinces of the country as shown in Table 1. The data for:

- Hogar Mario Muñoz in the Mayabeque province: they had completed treatment with BIOMODULINA T® in March as part of a drug utilization study promoted by BioCen
- Home No 3 of the province of Villa Clara: before starting the intervention in the country, a local transmission event had occurred in the home, in which a package of measures was applied, including the administration of BIOMODULINA T® and Nasalferon that helped control the situation
- Hogar Santa Susana from Mayabeque province and Hogar Alfredo Gómez Gendra from La Habana province: participants in another clinical trial with the product

Table 1 also shows, in relation to the total number of inmates on staff, the percentage of elderly people who received the product, according to provinces. A total of 92.0% of the employed staff of Nursing Homes were included. The second cycle of treatment was received by 91.0% of those who received the first, which represents 83.7% of the inmates on the staff. In the second cycle, a small group of elderly people who were not initially included in the study received the treatment for the first time. This is in line with the relaxation of the no entry home measure in some places.

Table 1. Elderly people in Nursing Homes who received treatment according to provinces

provinces	Nursing Homes	internal in template	Included	% in relation to Internal	received 2nd cycle	% in relation to Internal	% in relation to Included
Pinewood of the river	1	274	254	92.7	238	86.9	93.7
Sagebrush	5	204	176	86.3	184	90.2	104.5
Havana	32 of 33	2400	2216	92.3	1608	67.0	75.2
Mayabeque	5 of 7	370	315	85.1	316	85.4	100.3
killings	eleven	541	487	90.0	507	93.7	104.1
Hundred fires	5	347	347	100.0	340	98.0	98.0
Villa Clara	15 of 16	853	748	87.7	744	87.2	99.5
Sancti Spiritus	8	503	443	88.1	406	80.7	91.6
Ciego de Avila	8	515	450	87.4	407	79.0	90.4
Camaguey	fifteen	1083	988	91.2	930	85.9	94.1
prickly pears	9	526	476	90.5	460	87.5	96.6
Holguin	8	579	574	99.1	506	87.4	88.2
Granma	8	420	394	93.8	333	79.3	84.5
Santiago de Cuba	13	755	725	96.0	726	96.2	100.1
Guantanamo	5	3. 4. 5	3. 4. 5	100.0	317	91.9	91.9
Isle of Youth	two	80	77	96.3	78	97.5	101.3
TOTAL	149 of 153	9715	8938	92.0	8092	83.7	91.0

❖ Psychopedagogical Medical Centers:

There were 29 Psychopedagogical Medical Centers (CMPP) in the country, distributed in the provinces as shown in Table 2. 2,330 people resided in them, among them 133 were older adults. All of these were included, that is, 133 elderly who represent 100% of the elderly institutionalized in CMPP. It was recorded that only 69 of these elderly patients received the second cycle, which represents 51.9% of those included.

Table 2. Elderly people in CMPP included according to provinces

provinces	CMPP	internal in template	Included	% in relation to Internal	received 2nd cycle	% in relation to Internal	% in relation to Included
Pinewood of the river	0	-	-	-	-	-	-
Sagebrush	0	-	-	-	-	-	-
Havana	12	93	93	100	42	45.2	45.2
Mayabeque	two	10	10	100	3	30.0	30.0
killings	two	3	3	100	0	0	0

Hundred fires	1	0	-	-	-	-	-
Villa Clara	1	0	-	-	-	-	-
Sancti Spiritus	two	two	two	100	0	0	0
Ciego de Avila	1	1	1	100	0	0	0
Camaguey	1	two	two	100	3	150	150
prickly pears	two	9	9	100	9	100	100
Holguin	1	two	two	100	1	fifty	fifty
Granma	1	0	-	-	-	-	-
Santiago de Cuba	two	7	7	100	7	100	100
Guantanamo	1	4	4	100	4	100	100
Isle of Youth	0	-	-	-	-	-	-
TOTAL	29	133	133	100	69	51.9	51.9

❖ psychiatric hospitals:

Cuba has 19 psychiatric hospitals distributed in all provinces except Artemisa. As a whole, at the beginning of the study, 1,452 older adults were inmates, 1,256 being included and starting treatment, which represents 86.5%. Of them, 720, 57.3% in Havana), it was recorded that only 651 older adults began the second cycle, 51.8% of those who received the first.

❖ Social Protection Centers:

A total of 198 older adults belonging to the six Social Protection Centers in the country were included. Of them we have evidence that 77 (only 38.9% of these), received the second cycle.

BASELINE CHARACTERISTICS

The results of the variables age, sex, APP and frailty are shown below for all the individuals included in scenario 2 and in the case of scenario 3 for the elderly in the Homes, grouped by provinces.

scenario 2

The mean age of the patients evaluated was 77 ± 4.3 years, with similar results when the analysis by site is performed (Table 4). When analyzing all those included, older males predominated (Table 5). Hypertension was the most frequent of the APPs referred to, with very few individuals considered co-morbid, that is, with three or more pathologies (Table 6). Most of those included were elderly who were not frail or robust (Table 7).

Table 4. Age scenario 2

Age	BioCen	OC-MINSAP	OC-PR	Total
N	74	110	42	226
Half	64.2	65.6	65.0	65.0
OF	3.9	4.2	5.1	4.3
min	60	60	60	60
Max	74	77	77	77

Table 5. Distribution according to sex, scenario 2

Sex	BioCen		OC-MINSAP		OC-PR		Total	
	N	%	N	%	N	%	N	%
Male	63	85.1	63	57.3	twenty-one	50.0	147	65.0
Feminine	eleven	14.9	47	42.7	twenty-one	50.0	79	35.0
Total	74	100.0	110	100.0	42	100.0	226	100.0

Table 6. Personal Pathological Background scenario 2

APP	BioCen		OC-MINSAP		OC-PR		Total	
	N	%	N	%	N	%	N	%
AHT	3.4	45.9	16	14.5	33	78.6	83	36.7
IQ	5	6.8	0	0.0	4	9.5	9	4.0
DM	8	10.8	1	0.9	5	11.9	14	6.2
COPD	0	0.0	0	0.0	two	4.8	two	0.9
Others	28	37.8	5	4.5	twenty-one	50.0	54	23.9
CM	5	6.8	0	0.0	4	9.5	9	4.0

Table 7. Distribution according to frailty categories, scenario 2

A) Initial fragility	BioCen		MINSAP		PR		Total	
	N	%	N	%	N	%	N	%
Fragile	1	1.4	0	0.0	0	0.0	1	0.4
pre-frail	44	59.4	0	0.0	0	0.0	44	19.5
Not fragile – Robust	29	39.2	110	100.0	42	100.0	181	80.1
Total	74	100.0	110	100.0	42	100.0	226	100.0

Scenario 3

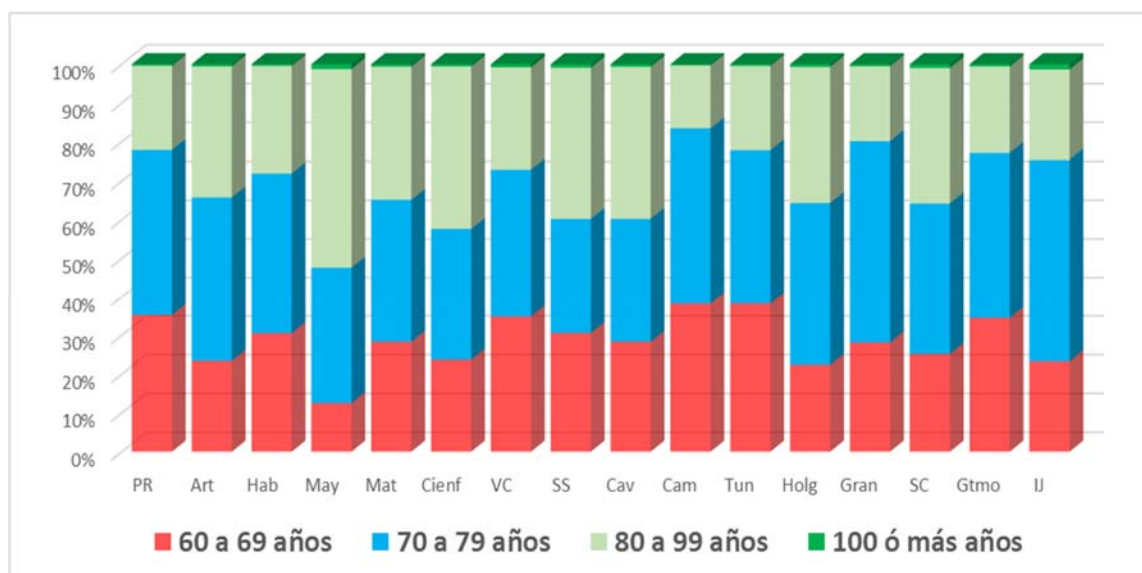
❖ Nursing Homes

The predominant age group was the group from 70 to 79 years old, with a non-negligible representation of centenarians (Table 8 and Graph 1). Male older adults predominated except in Havana where the percentages are similar (Table 9). Hypertension was also the most frequent of the PPAs registered, with just over a third of the individuals with 3 or more co-morbid bone pathologies (Table 10). When analyzing the categories of frailty, all individuals in this scenario were classified as frail (data not tabulated).

Table 8. Distribution according to age group in Nursing Homes by provinces

provinces	N	60 to 69 years	%	70 to 79 years	%	80 to 99 years	%	100 or more years	%
Pinewood of the	254	86	33.9	114	44.9	53	20.9	1	0.4

river									
Sagebrush	176	41	23.3	75	42.6	59	33.5	1	0.6
Havana	2139	431	20.1	859	40.2	837	39.1	12	0.6
Mayabeque	315	53	16.8	112	35.6	146	46.3	4	1.3
killings	487	134	27.5	174	35.7	176	36.1	3	0.6
Hundred fires	347	81	23.3	116	33.4	148	42.7	two	0.6
Villa Clara	748	253	33.8	287	38.4	202	27.0	6	0.8
Sancti Spiritus	443	132	29.8	139	31.4	168	37.9	4	0.9
Ciego de Avila	450	126	28.0	147	32.7	174	38.7	3	0.7
Camaguey	988	364	36.8	431	43.6	190	19.2	3	0.3
prickly pears	476	177	37.2	196	41.2	101	21.2	two	0.4
Holguin	574	126	22.0	247	43.0	197	34.3	4	0.7
Granma	394	106	26.9	209	53.0	77	19.5	two	0.5
Santiago de Cuba	725	175	24.1	291	40.1	252	34.8	7	1.0
Guantanamo	3. 4. 5	119	34.5	147	42.6	77	22.3	two	0.6
Isle of Youth	77	17	22.1	42	54.5	17	22.1	1	1.3
Total	8938	2421	27.1	3586	40.1	2874	32.2	57	0.6



Graph 1. Distribution according to age group in Nursing Homes by provinces

Table 9. Distribution according to sex in Nursing Homes by provinces

provinces	M	%	F	%	Total	%
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Pinewood of the river	164	64.6	90	35.4	254	100.0
Sagebrush	117	66.5	59	33.5	176	100.0
Havana	991	46.3	1148	53.7	2139	100.0
Mayabeque	215	68.3	100	31.7	315	100.0
killings	338	69.4	149	30.6	487	100.0
Hundred fires	244	70.3	103	29.7	347	100.0
Villa Clara	521	69.7	227	30.3	748	100.0
Sancti Spiritus	348	78.6	95	21.4	443	100.0
Ciego de Avila	350	77.8	100	22.2	450	100.0
Camaguey	750	75.9	238	24.1	988	100.0
prickly pears	368	77.3	108	22.7	476	100.0
Holguin	499	86.9	75	13.1	574	100.0
Granma	299	75.9	95	24.1	394	100.0
Santiago de Cuba	523	72.1	202	27.9	725	100.0
Guantanamo	283	82.0	62	18.0	3. 4. 5	100.0
Isle of Youth	14	18.2	63	81.8	77	100.0
Total	2865	32.1	6073	67.9	8938	100.0

Table 10. Personal Pathological History in Nursing Homes by provinces

provinces	N	AHT	%	IQ	%	DM	%	COPD	%	Others	%	CM	%
Pinewood of the river	254	159	62.6	60	23.6	3.4	13.4	twenty	7.9	227	89.4	147	57.9
Sagebrush	176	85	48.3	25	14.2	25	14.2	10	5.7	137	77.8	75	42.6
Havana	2139	1531	71.6	420	19.6	471	22.0	403	18.8	540	25.2	1004	46.9
Mayabeque	315	150	47.6	33	10.5	43	13.7	29	9.2	117	37.1	18	5.7
killings	487	179	36.8	72	14.8	39	8.0	66	13.6	110	22.6	136	27.9
Hundred fires	347	181	52.2	93	26.8	83	23.9	85	24.5	93	26.8	117	33.7
Villa Clara	748	626	83.7	179	23.9	90	12.0	127	17.0	223	29.8	243	32.5
Sancti Spiritus	443	2. 3. 4	52.8	79	17.8	48	10.8	59	13.3	fifteen	3.4	92	20.8
Ciego de Avila	450	129	28.7	65	14.4	85	18.9	56	12.4	0	0.0	307	68.2
Camaguey	988	444	44.9	108	10.9	102	10.3	76	7.7	172	17.4	393	39.8
prickly pears	476	249	52.3	95	20.0	fifty	10.5	fifty	10.5	168	35.3	198	41.6
Holguin	574	93	16.2	26	4.5	19	3.3	49	8.5	19	3.3	231	40.2
Granma	394	230	58.4	76	19.3	Four. Five	11.4	38	9.6	44	11.2	69	17.5
Santiago de Cuba	725	423	58.3	111	15.3	86	11.9	60	8.3	419	57.8	42	5.8
Guantanamo	3. 4. 5	231	67.0	51	14.8	35	10.1	22	6.4	112	32.5	200	58.0
Isle of Youth	77	47	61.0	8	10.4	13	16.9	22	28.6	5	6.5	33	42.9
Total	8938	4991	55.8	1501	16.8	1268	14.2	1172	13.1	2401	26.9	3305	37.0

The population for safety analysis was made up of all patients who received a dose of treatment at least once, which is summarized in Table 11. Following this, the details in each scenario .

Table 11. Population for security analysis by scenarios

Scenery		No of exposed individuals
Scenario 1		416
scenario 2	BioCen	74
	OC-MINSAP	110
	OC-PR	42
	Subtotal	226
Scenario 3	HE HAS	8,938
	CMPP	133
	hp	1,256
	CPS	198
	Subtotal	10,525
Total		11 167

Scenario 1

They were already referred to the irregularities of the intervention in this scenario. The reports to the MINSAP did not have adequate regularity, so a coherent analysis of treatment compliance could not be made. In addition, it was not possible to have proof of compliance with the treatment after the elderly person was discharged. Finally, this indication was withdrawn from the action protocol. For these reasons, only the compilation of the reports obtained until August 4, 2020, in relation to the applied doses, is presented (Table 12). Due to the discontinuity of the reports obtained from MINSAP, the possibility of a sub-registration should be considered, that is, the doses applied should have been higher. However, the available data is taken only for security analysis.

Table 12. Doses applied in Scenario 1 according to provinces

PROVINCES	1st dose	2nd dose	3rd dose	4th dose	Total
Pinewood of the river	31	18	1	two	52
Sagebrush	86	84	twenty-one	23	214
Havana	17	17	3	5	42
Mayabeque	twenty	twenty	0	0	40
killings	7	0	0	0	7
Hundred fires	29	32	10	19	90
Villa Clara	122	105	89	0	316
Sancti Spiritus	27	12	7	1	47
Ciego de Avila	27	3	0	0	30
Camaguey	6	6	0	0	12
prickly pears	4	0	0	0	4
Holguin	17	4	1	1	23
Granma	two	0	two	0	4

Santiago de Cuba	5	0	0	0	5
Guantanamo	16	16	16	0	48
Total	416	317	150	51	934

scenario 2

This scenario included workers from BioCen, from the central offices of MINSAP and from the Plaza de la Revolución, distributed in the two treatment groups according to Table 13. In all cases there was 100% treatment compliance, according to the assigned scheme. . Therefore, in this scenario, 2286 administrations [(155x12) + (71x6)] were applied.

Table 13. Distribution according to treatment group in Scenario 2

treatment group	BioCen		OC-MINSAP		OC-PR		Total	
	N	%	N	%	N	%	N	%
Group I	Four. Five	60.8	110	100.0	0	0.0	155	68.6
Group II	29	39.2	0	0.0	42	100.0	71	31.4
Total	74	100.0	110	100.0	42	100.0	226	100.0

Scenario 3

❖ Nursing Homes:

Of the 8,938 elderly included, 8,686, which represents 97.2%, completed the treatment schedule of 12 administrations. In total, 105,533 doses were administered, which represents 98.4% of what was planned.

A total of 252 elderly patients did not complete the treatment, with a mean number of dropouts per week of 42 patients. A large part of them for being returned by their relatives to their residences, being contemplated in the package of measures established for the Homes for the Elderly, the indication that once the elderly person left the institution they could not return to it.

Within treatment interruptions, even when the elderly remained at home, there were 21 voluntary dropouts, distributed according to Table 14. These 21 elderly had to receive a total of 252 administrations and together they received only 56, which represents 22.2 % of what was planned.

A total of 27 elderly patients discontinued treatment due to related AEs (20 during the first cycle and 7 during the second). None of these AEs were serious AEs. Treatment was interrupted by 133 elderly patients due to death (73 in the first cycle and 60 in the second).

The other interruptions were to a lesser extent due to intercurrent illness or changes in the patient's conditions that, in the opinion of the attending physician, prevented the continuation of the administrations. In the second cycle, a total of 95,826 doses were administered to these patients.

Table 14. Treatment interruptions due to voluntary abandonment of the elderly according to provinces.

Province	Voluntary dropouts	No dose received
Pinewood of the river	1	1 patient:1 dose
Villa Clara	5	3 patients: 1 dose 2 patients: 5 doses
Camaguey	5	4 patients: 3 doses 1 patient: 8 doses

prickly pears	10	1 patient:3 doses 2 patients: 6 doses 1 patient: 7 doses
Total	twenty-one	56

❖ **Psychopedagogical Medical Centers:**

Of the 133 older adults included in CMPP, 130 residents completed the treatment scheme for 97.7%. In total, 1,565 doses were administered, which represents 98.1% of what was planned. The causes of interruption were in the three cases due to return home (two from Havana who received two doses and one from Las Tunas who received only one dose). In the second cycle, a total of 802 doses were administered to these individuals.

❖ **psychiatric hospitals**

Of the 1256 individuals included from these institutions, 1134 completed the treatment scheme for 90.3%. In total, 14,028 doses were administered, which represents 93.1% of what was planned. The known causes of discontinuation were two patients due to non-severe AD and one patient who died due to terminal cancer. We do not know the causes of the other interruptions. In the second cycle, a total of 7,596 doses were administered to these patients.

❖ **Social Protection Centers**

Of the 198 individuals included from these institutions, 192 completed the treatment scheme for 97.0%. Discontinuations were due to patient refusals to continue. In total, 2,337 doses were administered, which represents 98.4% of what was planned. In the second cycle, only a total of 869 doses were administered in these centers.

PRIMARY AND SECONDARY OUTCOMES

The main variable of this study was the safety variable. In this regard, all the reports obtained by all possible means were analyzed. As for the rest of the variables, the results are only presented according to the availability of data obtained that are considered reliable.

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 15 summarizes the distribution of these registered AE by scenarios, with the specifications for each component.

In scenario 1, out of a total of 934 known doses or administrations, two patients reported local adverse events at the administration site. One of them for having been injected the product in the deltoid region (region that does not allow more than 1ml and each bulb of BIOMODULINA T® brings 3ml).

In scenario 2, 2,286 administrations were applied and five individuals presented six AEs.

In scenario 3, with a total of 228,556 administrations, 39 older adults who presented 59 AE were registered. Of these, 42 AEs were registered in 30 individuals from Nursing Homes (Table 16).

Table 15. Adverse events recorded in the study by scenarios.

Scenery		Number of administrations	Number of elderly with AD	Number of AE	
Scenario 1		934	two	two	
scenario 2	BioCen	714	3	4	
	OC-MINSAP	1 320	0	0	
	OC-PR	252	two	two	
	Subtotal	2 286	5	6	
Scenario 3	HE	1st cycle	105 533	23	30
		2nd cycle	95 826	7	12
	HAS	1st cycle	1,565	0	0
		2nd cycle	802	0	0
	CMPP	1st cycle	14,028	7	7
		2nd cycle	7,596	two	two
	hp	1st cycle	2 337	0	0
		2nd cycle	869	0	0
	CPS	1st cycle	2 337	0	0
	2nd cycle	869	0	0	
	Subtotal	228 556	39	51	
Total		231 776	46	59	

Table 16. Adverse events recorded in Nursing Homes

Province	Number of patients with AD	Number of AE
Pinewood of the river	0	0
Sagebrush	0	0
Havana	13	19
Mayabeque	1	two
killings	0	0
Hundred fires	0	0
Villa Clara	1	two
Sancti Spiritus	two	3
Ciego de Avila	0	0
Camaguey	4	6
prickly pears	0	0
Holguin	4	4
Granma	3	4
Santiago de Cuba	two	two
Guantanamo	0	0
Isle of Youth	0	0
Total	30	42

Table 17 summarizes the types of related AE registered by OrganoSystem and Table 18 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 17. AE according to Organ/ System

Organ/System	Type of AE
Cutaneous	
- Local reaction at the injection site (pain and/or erythema)	4
- Systemic allergic reaction / Rash / Eruption	eleven
Gastrointestinal	
-Nausea and Vomiting	two
CNS	
- Headache	7
- Syncope	two
Others	
- Fever	25
- Asthenia	1
- face blush	6
- Dizziness	1
Total	59

Table 18. Classification of registered AE

ADVERSE EVENTS	No. (%)
Location:	
• <i>local ae</i>	4/59 (6.8%)
• <i>systemic AE</i>	55/59 (93.2%)
Appearance Time:	
• <i>Immediate EA</i>	59 (100.0%)
Duration	
<i>Less than one day</i>	55/59 (93.2%)
<i>older than one day</i>	4/59 (6.8%)
Prior knowledge	
• <i>expected AE</i>	48/59 (81.4%)
• <i>unexpected AE</i>	11/59 (18.6%)
Intensity	
<i>Mild</i>	47/59 (79.7%)
<i>moderate</i>	12/59 (20.3%)
Impact	
<i>not serious</i>	59 (100.0%)
Causality	
<i>Very likely/certain</i>	7/59 (11.9%)
<i>Probable</i>	43/59 (72.9%)
<i>Possible</i>	9/59 (15.2%)
Outcome	
<i>Recovered</i>	59 (100.0%)
Attitude towards treatment	
<i>Continuation</i>	32/59 (54.2%)
<i>Interruption</i>	27/59 (45.8%)

In this way, the related AEs recorded in the study have been described earlier in this document. All of them classified as immediate and with a recovered outcome. Most of them were systemic and lasted less than one day (93.2% in both cases). Likewise, the majority classified as expected (81.4%), of mild intensity (79.7%) and 72.9% of probable causality. No serious AEs related to BIOMODULIN T® were reported .

The eleven unexpected related AEs were of the following types: nausea and vomiting, dizziness, syncope, and facial flushing. In relation to the two patients who had nausea and vomiting and the one who had dizziness, in all three cases they were classified as possible causality, due to their reasonable temporal relationship with the medication, but they could also be explained by concomitant disease. The two syncopes occurred in the same elderly person with the third and fourth dose, the event being classified as possible on the first occasion because it could be explained by conditions inherent to the elderly person, and on the second occasion, when it occurred again, it was classified as very probable/certain . On both occasions, the patient recovered immediately without requiring medical treatment for the event, but refused to continue treatment with BIOMODULINA T® .

The six reports of facial flushing were classified as unexpected as they were not described in the product's package insert, but had previously been reported with the use of BIOMODULINA T® in a published

study. Five of the cases were classified as probable and one as very possible/certain when repeated in the same individual.

Incidence of COVID-19

scenario 2

Up to 6 months after starting treatment with BIOMODULIN T®, none of the 226 older adults included in this scenario was diagnosed with COVID-19.

Scenario 3

The evaluation of effectiveness for COVID-19 covered the variables of incidence, mortality and lethality, each one evaluated in the first and second cycles of treatment in a period that covered 6 months from the start of each cycle.

-First treatment cycle

❖ Nursing Homes

The duration of the evaluation period was from April to September. Until the beginning of September 2020, no older adult institutionalized in Nursing Homes, who had received prophylactic treatment with BIOMODULINA T®, had been diagnosed with COVID -19. Subsequently, a single elderly woman was diagnosed in a home in Ciego de Ávila, detected in an investigation of the entire institution with PCR, being the only case between elderly people and workers, remaining asymptomatic and with a very favorable evolution. In October, another isolated case was detected in a similar way in a home in the province of Holguín. Even though this case was reported in October, it was taken into account for the evaluation.

❖ Psychopedagogical Medical Centers:

At the “La Castellana” Psychopedagogical Medical Center, in Havana province, a local transmission event occurred at the end of August, with 18 sick residents, five of them elderly, who had been treated with BIOMODULINA T®. These had a much more favorable evolution than untreated patients under 60 years of age. Only one of the five presented symptoms, none presented complications, was serious or died.

-Second treatment cycle

❖ Nursing Homes

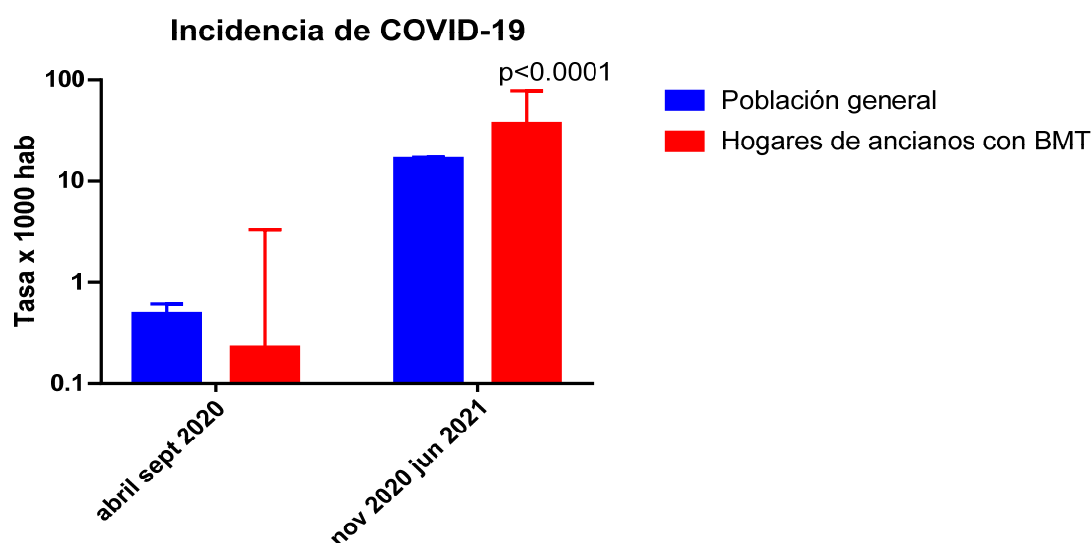
Due to the results of the first cycle and with the beginning of the increase in cases, it was decided by the MINSAP authorities to apply a second cycle of treatment at least 6 months after the previous one, in long-term care institutions. It has already been explained that the above was not done in unison throughout the country. Although it began to be applied in some sites in November 2020, most sites had this second cycle in January 2021. Six months from the start of treatment were taken into account for the evaluation, including dates between November 2020 and June 30, 2021.

The positive cases for COVID-19 in Nursing Homes, as well as those who died from this disease until the end of June 2021, are shown in Table 20.

Table 20 . COVID-19 cases in Nursing Homes with the second cycle (November 2020 – June 2021)

Province	Number of patients with COVID-19	Deceased by COVID-19	Deaths with complete cycle
Pinewood of the river	eleven	0	0
Sagebrush	4	0	0
Havana	92	6	0
Mayabeque	14	4	3
killings	3	1	0
Hundred fires	Four. Five	1	1
Villa Clara	17	0	0
Sancti Spiritus	5	0	0
Ciego de Avila	27	0	0
Camaguey	two	1	1
prickly pears	9	0	0
Holguin	13	1	1
Granma	0	0	0
Santiago de Cuba	0	0	0
Guantanamo	52	two	two
Isle of Youth	0	0	0
Total	294	16	8

When performing the intention-to-treat analysis in Nursing Homes, during the first cycle, in the group of 8,938 older adults, with an incidence of COVID-19 of 2 cases, an incidence rate of 0.02% and a rate of 0.22 per 1,000 inhabitants. During the second cycle, in the group of 8,092 older adults, with an incidence of COVID-19 of 294 cases, an incidence rate of 3.6% and a rate of 36.33 per 1,000 inhabitants is obtained. Graph 10 compares the incidence rates of COVID-19 in Nursing Homes for both periods evaluated, compared to the general population. Unfortunately, despite all the measures implemented, during the second cycle (which coincided with the most intense outbreak of the pandemic in Cuba), an incidence almost twice higher than the population average in the country was observed.



Graph 10 Incidence of COVID-19 in Nursing Homes, both periods evaluated, compared to the general population

Mortality and Lethality due to COVID-19

During the observation period of the second cycle of the 294 elderly in whom the diagnosis of COVID-19 was confirmed, 16 died. Of those who died, only half had completed the treatment cycle with BIOMODULIN T® (Table 20).

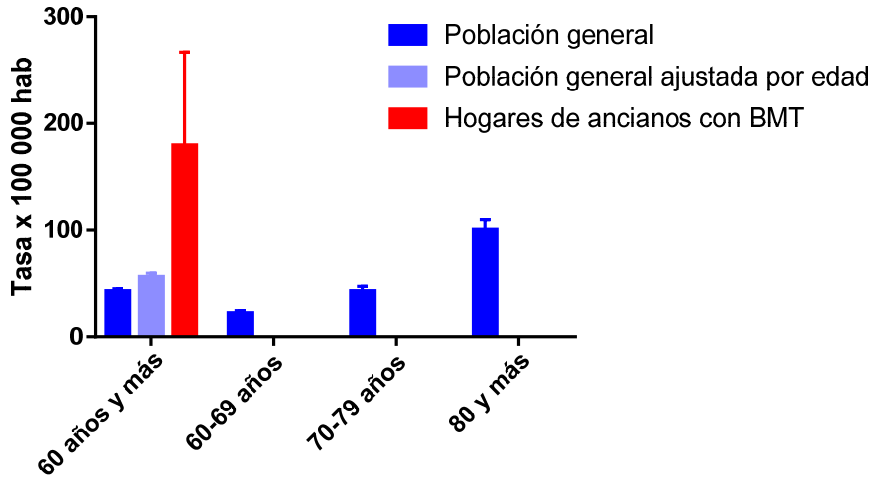
The comparison is made with respect to the general population with an age-adjusted rate for those over 60 years of age, according to the age distribution of the population in Nursing Homes, which is far from that of the general population. The adjustment matrix shown in Table 21 was used.

Table 21. Adjustment matrix used

Age range	Subjects in the HA	Weighting factor for adjustment (P_{age})
60-69	2 421	0.2709
70-79	3,586	0.4012
80 and over	2,931	0.3279
Total	8,938	1

The observed mortality rate exceeds the average value of the general population in Cuba aged 60 or over, adjusted according to the age distribution of Nursing Homes, in the evaluated period (Graph 11).

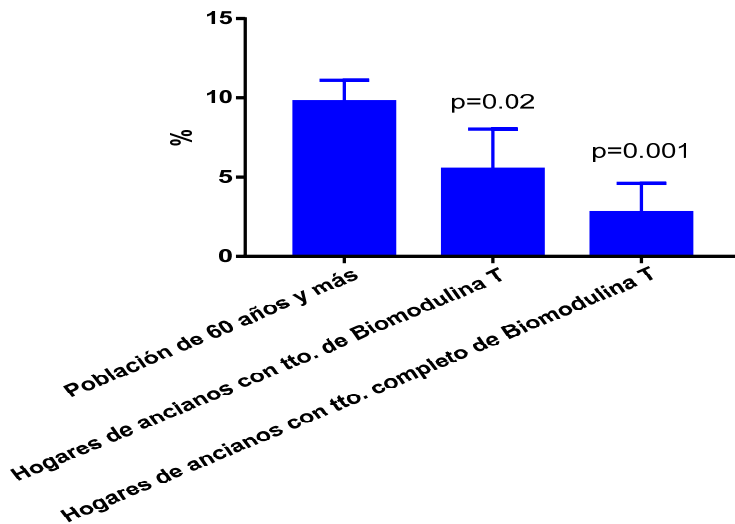
Mortalidad por COVID-19 en adultos mayores



Graph 11 Mortality rate due to COVID-19 in Nursing Homes undergoing intervention with BIOMODULINA T® during the second administration cycle corresponding to the period November 2020 to June 2021 and comparison with population values in the same period.

However, the lethality analysis, that is, the ratio of deaths among patients corresponding to the second cycle, that is, the pandemic peak, did show a very significant effect of BIOMODULIN T® . The analysis also including the subjects who did not complete the second cycle of treatment also showed a significant reduction, although lower than that achieved with the full treatment (Graph 12).

Letalidad de la COVID-19 en adultos mayores



Graph 12. Lethality of COVID-19 in Nursing Homes with BIOMODULINA T® treatment (complete or incomplete) compared to the lethality in the Cuban population aged 60 and over during the period corresponding to the second cycle (Nov 2020- June 2021).

Thus, the Relative Risk of mortality from COVID-19 in Nursing Homes (Table 22), with respect to the general population of the same age, after administering the second cycle was only 0.2882 (CI 0.1419 to 0.5852).

The NNT obtained (14,475), indicates that it is necessary to treat 15 elderly people with BIOMODULIN T® to prevent an elderly patient with COVID-19 from dying, compared to the untreated elderly.

Table 22. Relative risk of fatality from COVID-19 in Nursing Homes

	Subjects with complete treatment	Total
Relative risk	0.2882	0.5607
CI 95%	0.1419 to 0.5852	0.3361 to 0.9355
z	3,442	2,215
Significance	P = 0.0006	P = 0.0268
Number Needed to Treat		
	14,475	23,454
CI 95%	9,537 to 30,016	12,622 to 165,417

Acute Respiratory Infections (ARI)

- Incidence of ARI

The incidence of ARI was analyzed from data collected in the medical records of a subset of 21 Homes, all located in Havana, in which a total of 1,327 elderly people resided, these being similar to those of all the elderly in Homes. of the country and with an equal high presence of chronic pathologies and comorbid individuals . Table 26 shows the incidence of AKI corresponding to the follow-up period of the first cycle of treatment (April - September 2020) , as well as the historical statistics during the same period of the previous year (April - September 2019), to avoid data bias. taking into account possible changes in incidence due to seasonal factors.

The results show a very significant reduction ($p < 0.0001$) in the ARI index by subjects, both globally and in terms of behavior by Households compared to the period preceding the intervention with BIOMODULINA T® (Table 27 and Graph 13)

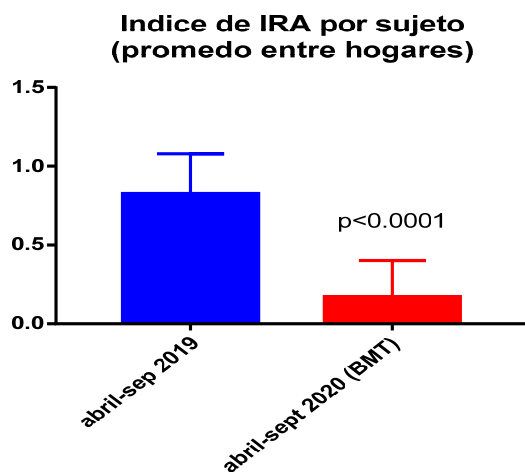
Table 26. Incidence of ARI in the periods April-September 2019 and April-September 2020, by Households in Havana .

Nursing Homes	IRA Cases April-Sep 2019	IRA Cases April-Sep 2020
January 28	92	0
General Peraza	42	0
Saint Francis of Paola	fifty	26
March 13	114	18
Saint Joseph	48	8
Celia Sanchez	37	two

Lazo de la Vega	eleven	7
to start living	36	7
Servants of Saint Joseph	fifteen	10
chun wha	58	6
Bernarda Bull	78	10
Cattle Dogs	48	27
Saint John of God	22	0
Belen	100	4
Servants of Mary	3	0
William Booth	10	7
Giralt Sisters	twenty-one	0
Methodist	14	0
San Rafael	239	105
Cotorro Baptist	13	3
Masonic	13	0
Total	1064	240

Table 27. ARI index/subject

	Base period (April-Sept 2019)	First cycle with BMT (April-Sept 2020)
N	1,327	1,327
ARI cases	1064	240
IRA index	0.8018	0.1809
	p<0.0001	z-test

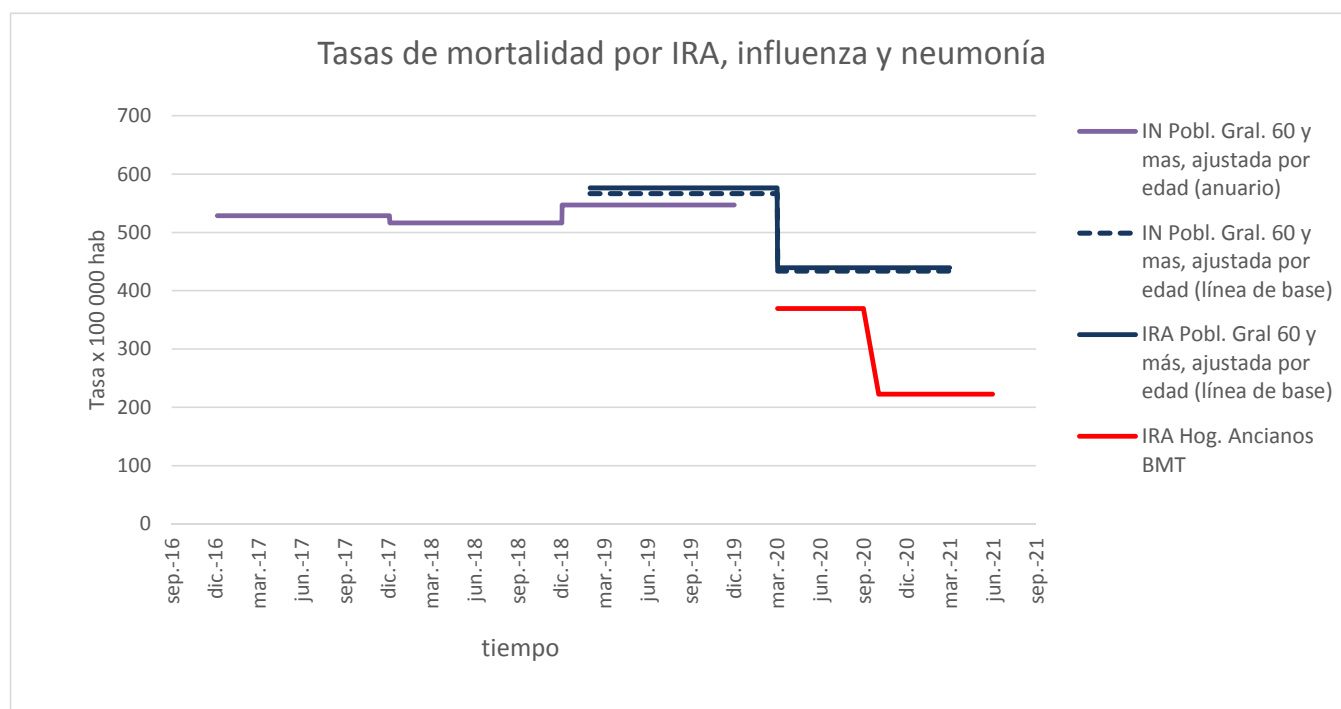


Graph 13. ARI index by subjects. Average values among the 21 Nursing Homes. The bars show the 95% Confidence Interval.

- ARI mortality

For the analysis of mortality due to ARI, the historical data of the previous three years of the general population reported by the Statistical Yearbook of Health of mortality due to Influenza and pneumonia for the age ranges 60-69 were taken into account; 70-79 and 80 and over, as well as ARI mortality rates in the general population in the year preceding the intervention with BIOMODULINA T® (April 2019 to March 2020) and concurrent with it (April 2020 to March 2021). , provided by the Department of Statistics of the MINSAP. There are no reliable statistics on mortality due to ARI in Nursing Homes, so the comparison was made with respect to the general population with an age-adjusted rate for those over 60 years of age, according to the age distribution of the population. population in Nursing Homes using the same adjustment matrix shown in Table 21.

Graph 14 illustrates the reduction observed between the ARI mortality rate in Nursing Homes during both cycles of BIOMODULINA T® with respect to both the previous historical values of ARI or influenza and pneumonia (IN), and with respect to the value concurrent in the general population aged 60 and over, according to the adjusted rate. The difference is significant ($p < 0.01$) only in the second cycle. Thus, the Relative Risk of dying from ARI in Nursing Homes (Table 28), with respect to the general population of the same age, after administering the second cycle was only 0.598 (CI 0.3200 to 0.8059).



Graph 14. Behavior over time of the ARI mortality rate in Nursing Homes during the first and second cycles, compared to historical values for the general population (adjusted for age), as well as to the concurrent value during that period

Table 28. Relative Risk of dying from ARI in Nursing Homes

Relative risk	0.5078
CI 95%	0.3200 to 0.8059
z	2,876
Significance level	P = 0.0040

GENERAL CONCLUSIONS

❖ As a preventive measure to confront COVID-19 in older adults in Cuba, BIOMODULINA T® had an unprecedented extension of use, with no serious related reactions reported, nor any new safety problem, being the adverse reactions that occurred classified as occasional or infrequent, mostly mild and more usually of the fever type.

❖ BIOMODULINA T® contributed to the fact that during the first pandemic peak, Cuba showed morbidity and mortality results from COVID-19 in older adults from social institutions that were very different from what happened in the world. With the most intense outbreak of the pandemic in the country, during which a second cycle of treatment with this drug was established, the incidence and mortality rates in Nursing Homes were higher than the population average, but with a reduction of more than three times the fatality rate from COVID-19 compared to that of the Cuban population aged 60 and over in the same period.

❖ Although it was not possible to evaluate the clinical response to treatment in relation to all the infections or in all the patients in the study, in the sample of more than a thousand residents of Nursing Homes in Havana, a great reduction in acute respiratory infections was evidenced in comparison with the period preceding the intervention with BIOMODULIN T®

❖ Contrary to the usual behavior described, the lower risk of mortality due to respiratory infections was evidenced in older adults in Nursing Homes compared to the general population of the same age, after administering the second cycle of BIOMODULINA T® treatment .

❖ BIOMODULINA T® is a very safe drug for use in older adults for the prevention of respiratory infections, including COVID-19, with a very favorable benefit-risk balance.