Trial title: Evaluation of the efficacy and safety of a new dosage schedule of BIOMODULINA T® for the prevention of infections, including COVID-19, in older adults in Cuba.

FLOW OF PARTICIPANTS

162 elderly people were evaluated to finally include the number foreseen in the protocol of 160. Due to their deteriorated health conditions, two patients from the "Santa Susana" Home (HSS) were not included.

Being institutionalized older adults, there were no difficulties with inclusion. In the HGG, the 59 elderly were included and started treatment in unison (April 13). In the case of HSS, 101 elderly people were included and started treatment, in two blocks: on April 20, 72 elderly people, and on May 20, the remaining 29. This was fundamentally due to the availability of the small number of researchers in this home to carry out the activities foreseen in the protocol, in addition to their daily chores at home; and not for conditions related to patients or product availability.

As they were institutionalized individuals, the only thing that depended on the investigators was the proper compliance with the treatment, an action that was carried out without difficulty in both homes. Of the 160 patients included, 159, representing 99.4%, completed the 12 administrations. The interruption of treatment in this patient was due to the medical decision of the HGG investigators.

Of the 159 who were present at the end of the 6-month study, 55 from HGG (3 deceased and 1 was returned home by relatives) and 152 from HSS (7 deceased). In the event that the patients were deceased at the time of the evaluation of the month or the final evaluation at 6 months, the information related to the variable infections was completed until the time of death. In the case of the elderly woman who had returned home in the 6-month evaluation, the infection data was completed with what was presented until she remained at home. She was among the patients selected for an immunological study, so at 6 months we have the immunological evaluation of only 29 elderly people out of the initial 30.

In this way, the data of the infections variable were taken into account in 159 patients in the evaluation of the month (58 of HGG and 101 of HSS) and of 158 in the evaluation of 6 months (58 of HGG and 100 of HSS).

There were other variables that logically could not be evaluated at the corresponding times if the patients were not present. This is the case of the control variables that only had data from 148 patients in the final evaluation, of which 54 were HGG and 94 HSS.

BASELINE CHARACTERISTICS

The mean age of the patients evaluated was 78.4 ± 9.0 years, with similar results when the analysis is performed by households (Table 1). When analyzing all those included, male elderly slightly predominated, a relationship that is reversed in the HGG (Table 2). Regarding skin color, white skin was generally more frequent, followed by black. In the case of HSS this difference was more marked than in HGG (Table 3).

Table 1. Age

Age		HGG	HSS	Both Homes
N		59	101	160
Half		78.5	78.4	78.4
OF		7.3	9.8	9.0
95% CI		76.6-80.4	76.4-80.3	77.0-79.8
min		65	60	60
Max		95	99	99
Percentiles	25	73	72.5	70.5
	fifty	78	79	79
	75	83	85	86

Table 2. Distribution according to sex.

Sex	HGG		HSS		Both Homes	
	N	%	N	%	N	%
Male	26	44.1	63	62.4	89	55.6
Feminine	33	55.9	38	37.6	71	44.4
Total	59	100.0	101	100.0	160	100.0

Table 3. Distribution according to skin color.

Skin color	HGG		HSS		Both Homes	
	N	%	N	%	N	%
White	28	47.5	86	85.2	114	71.3
mestizo	eleven	18.6	6	5.9	17	10.6
black	19	32.2	9	8.9	28	17.5
Yellow	1	1.7	0	0.0	1	1.6
Total	59	100.0	101	100.0	160	100.0

When the PPAs of the patients included in the study are analyzed (Table 4), it is confirmed that the most frequent pathologies were cardiovascular diseases, arthritis and/or osteoarthritis , and dementia.
The percentage of elderly with immobility syndrome of the HSS (36.6%) was higher, which differs significantly ($z=2.883$; $p=0.002$), from the data registered in the HGG (15.3%). There was a significantly higher prevalence of COPD in the HGG cohabitants than in the HSS ($z=3.749$; $p<0.001$)

Table 4. Personal Pathological History

APP	HGG		HSS		Both Homes	
	N	%	N	%	N	%
heart disease	46	78.8	70	69.3	116	72.5
Mellitus diabetes	17	28.8	twenty	19.8	37	23.1
Neoplasm	7	11.9	16	15.8	23	14.4
Asthma	4	6.8	9	8.9	13	8.1
COPD	26	44.1	17	16.8	43	26.9
allergic diseases	3	5.1	10	9.9	13	8.1
Cerebro Vascular Disease	fifteen	25.4	17	16.8	32	20.0
Arthritis and/or Osteoarthritis	36	61.0	61	60.4	97	60.6
Rheumatic diseases	two	3.4	two	2.0	4	2.5
Neurological diseases	3	5.1	46	45.5	49	30.6
Alzheimer's disease and other dementias	38	64.4	47	46.5	85	53.1
immobility syndrome	9	15.3	37	36.6	46	28.8
Others	49	79.1	74	73.3	121	75.6

Table 5 shows the frequency of smoking in the elderly in the study, confirming a highly statistically significant difference ($z=4.660$; $p<0.001$) in the presence of this habit in the HGG in relation to the HSS.

Table 5. Smoking habit.

smoking habit	HGG		HSS		Both Homes	
	N	%	N	%	N	%
Yes	28	47.6	14	13.9	42	26.3
Nope	31	52.4	87	86.1	118	73.7
Total	59	100.0	101	100.0	160	100.0

Next, the variables frailty, functional evaluation and nutritional evaluation are described. Likewise, the tables show the results in all the elderly and by households. In all cases similar results were obtained before vs after treatment.

When analyzing the frailty categories (Table 6), all the HGG individuals were classified as frail. The same did not happen in HSS where there is a small number of pre-frail or robust elderly. This is due to the existence in the HSS of a floor made up of independent rooms with furniture, electrical appliances and other structural conditions, where elderly people live who, by their own decision, have managed their income in the home.

Table 6. Distribution according to frailty categories.

initial fragility	HGG		HSS		Both Homes	
	N	%	N	%	N	%
Fragile	59	100.0	92	91.1	151	94.3

pre-frail	0	0.0	7	6.9	7	4.4
Not fragile – Robust	0	0.0	two	2.0	two	1.3
Total	59	100.0	101	100.0	160	100.0

When performing the functional evaluation of the study patients according to the Katz Index of independence for activities of daily living, which is shown in Table 7, it can be seen that a little more than 50% of the elderly in both households are evaluated within categories A and B, or either independent in feeding, continence, mobility, toileting, dressing, and bathing, or independent in all but one of the above functions. In the HSS there was a higher frequency of elderly classified within categories F and G, that is, dependent in 5 or 6 functions, this being consistent with the greater number of patients with immobility syndrome in this household.

Katz Index.

Initial functional evaluation	**HGG**		**HSS**		**Both Homes**	
	N	**%**	**N**	**%**	**N**	**%**
A	30	50.8	Four. Five	44.5	75	46.9
B.	4	6.8	7	6.9	eleven	6.9
C	6	10.2	3	3.0	9	5.6
D	3	5.1	two	2.0	5	3.1
AND	6	10.2	9	8.9	fifteen	9.4
F	1	1.6	4	4.0	5	3.1
G	6	10.2	28	27.7	3. 4	21.3
H	3	5.1	3	3.0	6	3.7
Total	59	100.0	101	100.0	160	100.0

The evaluation of the nutritional status of the study patients was carried out through the variables weight, height and BMI. Table 8 shows the summary and position measures of BMI at the initial evaluation, in the group of patients and by households.

Table 8. BMI of the patients at the beginning of the study.

BMI (kg/ m^2)		**HGG**	**HSS**	**Both Homes**
N		59	101	160
Half		22.7	25.3	24.4
OF		4.4	4.3	4.5
95% CI		21.6 – 23.9	24.5 – 26.2	23.7 – 25.1
min		13.9	14.5	13.9
Max		35.7	36.9	36.9
Percentiles	25	19.5	22.1	twenty-one
	fifty	22.2	25.6	24
	75	25.6	28.2	27.6

Based on the BMI values, the classification is established as underweight, normal weight , overweight or obese. Table 9 shows the results of the initial nutritional assessment by household. The results of the initial evaluation showed no significant changes at the end of the study with respect to baseline values.

In the set of patients, those classified as normal weight predominated (43.8%), but it is notable that there are significant differences in terms of nutritional status between both households. A higher proportion of individuals with low weight was obtained in the HGG (z=2.548; p=0.005) and a higher proportion of overweight in the HSS (z=2.855; p=0.002).

Table 9. Nutritional evaluation according to BMI.

Initial nutritional assessment	HGG		HSS		Both Homes	
	N	%	N	%	N	%
Under weight	24	40.7	22	21.8	46	28.8
normal weight	27	45.7	43	42.6	70	43.8
Overweight	6	10.2	30	29.7	36	22.5
Obese	two	3.4	6	5.9	8	5.0
Total	59	100.0	101	100.0	160	100.0

PRIMARY AND SECONDARY OUTCOMES

infections

Comparisons of respiratory and other system infections presented by the patients were made from the data collected in the medical records. In the initial evaluation consultation, data were collected and classified as "historical control". All infections presented in the period of 2019 were considered, in correspondence with the same period of 2020 for which these patients would be evaluated. All patients were followed up for a period of 6 months, from April-May (depending on their time of inclusion) to October-November 2020, therefore, the evaluation of these variables in the 6 months included in the study was taken as control. same period of 2019.

Bearing in mind that sometimes the same subject had more than one infection, so the number of infections at each time of evaluation does not coincide with the number of patients with infections, the data referring to subjects with infections are shown.

is shown in the number of upper and lower respiratory infections and in the number of subjects with said infections, for the HSS and for the group of patients (Tables 10 and 11).

No CNS, EMS, or generalized infections were recorded; neither before nor during the study. A significant decrease in the number of genitourinary infections is shown in the HSS $p < 0.001$ and in the group of patients $p = 0.007$. The same occurs in these two cases if the number of subjects with these infections is analyzed (Table 11).

The overall result in all patients was a significant reduction in the number of infections $p < 0.001$ (Table 18). The number of subjects with infections (Table 19), decreased in the HSS and in the group of patients, this decrease being significant ($p < 0.001$) only in the HSS. In the HGG there is a slight increase in this number, although it does not become significant. $p = 0.116$, and occurs at the expense of subjects with non-respiratory infections.

Tables 12 and 13 show the rates per subject of respiratory infections and infections in general. This simple indicator makes it possible to evaluate the effect of the intervention by means of the change experienced by said index and also allows evaluating compliance with the hypothesis set out in the protocol by calculating the percentage variation of the same during the study.

When analyzing it globally compared to the control data, a 70% decrease in respiratory infections (0.86 vs 0.16) is obtained in the group of patients, a figure that doubles the 35% estimated in the study hypothesis. As in the set of patients the data does allow calculating the odds ratio, in this case an OR = 31.69 was obtained; CI: 17.18 – 58.44.

The rate of infections per subject shows a similar behavior. Although here the precepts to be able to calculate OR (initially a higher number of infections than patients) are not fulfilled, in the group of patients a decrease of 79% of infections in general was observed compared to the control data (1.52 vs 0.73). In other words, infections decrease by half compared to those that occurred in the same period of 2019.

Table 10. Number of infections: control (6 months of 2019) vs 6 months of 2020

INFECTIONS	Home "Alfredo Gómez Gendra "					Home "Santa Susanna"					Both Homes				
	Before BMT		6 months after starting BMT		z-test; p	Before BMT		6 months after starting BMT		z-test; p	Before BMT		6 months after starting BMT		z-test; p
	N	%	N	%		N	%	N	%		N	%	N	%	
Total subjects	**59**	**100.0**	**58**	**100.0**		**101**	**100.0**	**101**	**100.0**		**160**	**100.0**	**159**	**100.0**	
TOTAL UPPER RESPIRATORY	two	3.4	1	1.7	*z = -0.0150; p = 0.988*	two	3.4	6	6.0	*z = 9.8446;* ***p < 0.001***	78	48.8	7	4.4	*z = 8.8024;* ***p < 0.001***
Common cold	0	0.0	0	0.0	--	55	54.5	3	3.0	*z = 7.8945;* ***p < 0.001***	55	34.4	3	1.9	*z=7.2604;* ***p < 0.001***
Sinusitis	0	0.0	0	0.0	--	3	3.0	1	1.0	*z = 0.4950; p = 0.621*	3	1.9	1	0.6	*z = 0.4905; p = 0.624*
Otitis	1	1.7	0	0.0	*z = -0.0086; p = 0.993*	12	11.9	0	0.0	*z = 3.2569;* ***p = 0.001***	13	8.1	0	0	*z = 3.3753;* ***p < 0.001***
Laryngitis	0	0.0	0	0.0	--	4	4.0	0	0.0	*z = 1.5051; p = 0.132*	4	2.5	0	0	*z = 1.4969; p = 0.134*
Pharyngotonsillitis	1	1.7	1	1.7	*z = -0.7011; p = 0.483*	two	2.0	two	2.0	*z = -0.4950; p = 0.621*	3	1.9	3	1.9	*z = -0.3966; p = 0.692*
TOTAL LOW RESPIRATORY	8	13.6	6	10.3	*z = 0.2508; p = 0.802*	51	50.5	12	12.0	*z = 5.7303;* ***p < 0.001***	59	36.9	18	11.4	*z = 5.1729;* ***p < 0.001***
Bronchitis	7	11.9	two	3.4	*z = 1.3611; p = 0.173*	14	13.9	1	***1.0***	*z = 3.2009;* ***p =0.001***	twenty-one	13.1	3	1.9	*z = 3.5770;* ***p < 0.001***
Bronchopneumonia	1	1.7	4	6.9	*z = -0.9337; p = 0.350*	37	36.7	eleven	11.0	*z = 4.0965;* ***p < 0.001***	38	23.8	fifteen	9.5	*z = 3.2603;* ***p = 0.001***
TOTAL UPPER AND LOW RESPIRATORY	10	1.7	7	12.1	*z = 0.4866; p = 0.065*	127	125.7	18	18.0	*z = 11.6840;* ***p < 0.001***	137	85.6	25	15.8	*z = 12.3373:* ***p < 0.001***
digestive	0	0.0	5	8.6	*z = 1.8479; p = 0.627*	4	4.0	0	0.0	*z = 1.5051; p = 0.132*	4	2.5	5	3.2	*z = 0.0191; p = 0.985*
skin and soft tissue	14	23.7	twent	36.2	*z = 1.2719;*	33	32.7	25	25.0	*z = 1.0448;*	47	29.4	46	29.1	*z = -0.0721;*

INFECTIONS	Home "Alfredo Gómez Gendra "					Home "Santa Susanna"					Both Homes				
	Before BMT		6 months after starting BMT		z-test; p	Before BMT		6 months after starting BMT		z-test; p	Before BMT		6 months after starting BMT		z-test; p
	N	%	N	%		N	%	N	%		N	%	N	%	
			y-one		*p = 0.203*					*p = 0.296*					*p = 0.942*
Genitourinary	7	11.9	fiftee n	25.9	*z = 1.7008; p = 0.089*	43	42.6	13	13.0	*z = 4.5189;* ***p < 0.001***	fifty	31.3	28	17.7	*z = 2.6731;* ***p = 0.007***
CNS	0	0.0	0	0.0	--	0	0.0	0	0.0	--	0	0.0			--
SOMA	0	0.0	0	0.0	--	0	0.0	0	0.0	--	0	0.0	0	0.0	--
widespread	0	0.0	0	0.0	--	0	0.0	0	0.0	--	0	0.0	0	0.0	--
Others	1	1.7	1	1.7	*z = -0.7011; p = 0.483*	4	4.0	eleve n	11.0	*z = 1.6305; p = 0.103*	5	3.1	12	7.6	*z = 1.5224; p = 0.128*
TOTAL INFECTIONS	32	54.2	49	84.5	*z = 3.3437;* ***p < 0.001***	211	208.9	67	67.0	*z = 6.1244;* ***p < 0.001***	243	151.9	116	73.4	*z = 6.8346;* ***p < 0.001***

Table 11. Subjects with infections: control (6 months of 2019) vs 6 months of 2020.

PATIENTS	Home "Alfredo Gómez Gendra "					Home "Santa Susanna"					Both Homes				
	Before BMT		6 months after starting BMT		z-test; p	Before BMT		6 months after starting BMT		z-test; p	Before BMT		6 months after starting BMT		z-test; p
	N	%	N	%		N	%	N	%		N	%	N	%	
Total subjects	**59**	**100.0**	**58**	**100.0**		**101**	**100.0**	**101**	**100.0**		**160**	**100.0**	**159**	**100.0**	
no infections	38	64.4	28	48.3	*z = 1.5728; p = 0.116*	26	25.7	52	52.0	*z = 3.6748;* ***p < 0.001***	64	40.0	80	50.6	*z = 1.7919; p = 0.073*
with any infection	twenty-one	35.6	30	51.7	*z = 1.5728; p = 0.116*	75	74.3	48	48.0	*z = 3.6748;* ***p < 0.001***	96	60.0	78	49.4	*z = 1.7919; p = 0.073*
No respiratory infections (upper and/or lower)	fifty	84.7	51	87.9	*z = 0.2323; p = 0.816*	35	34.6	86	86.0	*z = 7.2918;* ***p < 0.001***	85	53.1	137	86.7	*z = 6.4004;* ***p < 0.001***
With respiratory infections (upper and/or lower)	9	15.3	7	12.1	*z = 0.2323; p = 0.816*	66	55.4	14	14.0	*z = 7.2918;* ***p < 0.001***	75	46.9	twenty-one	13.3	*z = 6.4004;* ***p < 0.001***
With upper respiratory infections	two	3.4	1	1.7	*z = -0.0150; p = 0.988*	56	55.4	4	4.0	*z = 7.8152;* ***p < 0.001***	58	36.3	5	3.2	*z = 7.2604;* ***p < 0.001***
With lower respiratory infections	7	11.9	6	10.3	*z = -0.0327; p = 0.974*	39	38.6	7	7.0	*z = 5.0385;* ***p < 0.001***	46	28.8	13	8.2	*z = 4.5628;* ***p < 0.001***
with digestive infections	0	0	5	8.6	*z = 1.8479; p = 0.627*	4	4.0	0	0.0	*z = 1.5051; p = 0.132*	4	2.5	5	3.2	*z = 0.0191; p = 0.985*
With skin and soft tissue infections	10	16.9	14	24.1	*z = 0.7338; p = 0.463*	25	24.7	19	19.0	*z = 0.8156; p = 0.415*	35	21.9	33	20.9	*z = 0.0783; p = 0.938*
With genitourinary infections	5	8.5	10	17.2	*z = 1.1416; p = 0.254*	39	38.6	12	12.0	*z = 4.1734;* ***p < 0.001***	44	27.5	22	13.9	*z = 2.6731;* ***p = 0.007***
with other infections	1	1.7	1	1.7	*z = -0.7011; p = 0.483*	4	4.0	eleven	11.0	*z = 1.6305; p = 0.103*	5	3.1	12	7.6	*z = 1.5224; p = 0.128*

Table 12. Index of respiratory infections by subjects

Both Homes	**BEFORE BMT**	**6 MONTHS AFTER STARTING BMT**
Total subjects	160	158
Total respiratory infections	137	25
Infections / subjects	***0.86***	***0.16***
OR = 31.69; CI 17.18 – 58.44		

Table 13. Rate of infections by subjects

Both Homes	**BEFORE BMT**	**6 MONTHS AFTER STARTING BMT**
Total subjects	160	158
Total infections	243	116
Infections / subjects	***1.52***	***0.73***

Etiology of infections

In relation to the suspected etiology of the infections presented by the patients in the 3 evaluation moments, it was not asked in the case of colds, since by definition they are viral diseases. All the sinusitis and pneumonia that occurred, as well as the urinary infections, were classified by the doctors as having a bacterial cause.

(Table 14) and non-respiratory infections (Table 15) are grouped according to their etiology , and a comparison is made between the control (6 months of 2019) and the full 6-month period of 2020, the significant decrease in the number can be seen. of bacterial infections before vs. after, both respiratory ($p = 0.013$) and non-respiratory ($p < 0.001$).

Table 14. Etiology of respiratory infections.

Respiratory infections	**Prior to BMT**		**6 months after starting BMT**	
Etiology	N	%	N	%
bacterial	66	48.2	twenty	80.0
Viral	69	50.4	5	20.0
mycotic	two	1.4	0	0.0
Total	137	100.0	25	100.0

χ^{2} test	**gl .**	**p**
$\chi 2^{-} = 8,666$	*two*	***0.013***

Table 15. Etiology of non-respiratory infections.

non-respiratory infections	**Prior to BMT**		**6 months after starting BMT**	
Etiology	N	%	N	%
bacterial	96	90.6	62	68.1
Viral	3	2.8	6	6.6
mycotic	5	4.7	5	5.5
parasitic	two	1.9	18	19.8
Total	106	100.0	91	100.0

χ^{2} **test**	**gl .**	**p**
$\chi 2^{-} = 20{,}091$	*3*	< ***0.001***

Antibiotic treatment for infections

Tables 15 and 16 show the use of antibiotics as treatment for respiratory and non-respiratory infections, respectively, in the group of patients. Each table shows the number of patients who required antibiotics orally, parenterally, and both.

When analyzing the set of patients who used antibiotics before the BMT intervention and after it, both for respiratory and non-respiratory infections; it can be affirmed that a significant decrease in this number occurred, which is shown in Table 17.

In all cases, the use of oral antibiotics was more frequent in relation to parenteral use.

Table 15. Use of antibiotics for respiratory infections.

Both Homes	**Before BMT N=160 (100.0%)**			**Ev.1 N=159 (100.0%)**			**Ev.2 N=158 (100.0%)**		
Use of Antibiotics	both ways	Oral	Parenteral	both ways	Oral	Parenteral	both ways	Oral	Parenteral
Patients who do not	113 (70.6%)	118 (73.8%)	146 (91.3%)	153 (96.2%)	154 (96.9%)	156 (98.1%)	141 (89.2%)	146 (92.4%)	152 (96.2%)
Patients who Yes	47 (29.4%)	42 (26.2%)	14 (8.7%)	6 (3.8%)	5 (3.1%)	3 (1.9%)	17 (10.8%)	12 (7.6%)	6 (3.8%)

Table 16. Use of antibiotics for non-respiratory infections.

C) Both Households	**Before BMT** N=160 (100.0%)			**Ev.1** N=159 (100.0%)			**Ev.2** N=158 (100.0%)		
Use of Antibiotics	both ways	Oral	Parenteral	both ways	Oral	Parenteral	both ways	Oral	Parenteral
Patients who do not	98 (61.3%)	103 (64.4%)	150 (93.8%)	142 (89.3%)	145 (91.2%)	156 (98.1%)	124 (78.5%)	127 (80.4%)	154 (97.5%)
Patients who Yes	62 (38.7%)	57 (35.6%)	10 (6.2%)	17 (10.7%)	14 (8.8%)	3 (1.9%)	3. 4 (21.5%)	31 (19.6%)	4 (2.5%)

Table 17. Use of antibiotics before vs. after in the group of patients.

USE OF ANTIBIOTICS	Before BMT		6 months after starting BMT		z-test; p
	N	%	N	%	
Total subjects	**160**	**100.0**	**158**	**100.0**	
For respiratory infections	47	29.4	17	10.8	*z = 3.999* ***p < 0.001***
For non-respiratory infections	62	38.7	3. 4	21.5	*z = 3.347* ***p < 0.001***

Hospital admission for infections

No variations were found in this variable.

Mortality due to infections

Due to the design of the study, it was not possible to assess the variable mortality from infections as control data, since it is a study where the patient is his own control (historical control).

During the 6 months of follow-up of the elderly, 3 deaths occurred due to respiratory infection, specifically due to hypostatic bronchopneumonia, in bedridden patients and the three in the "Santa Susana" Home. One of these deaths was considered an adverse event because it occurred during the month after the end of the treatment, a period of time established in the protocol for the follow-up of the AE.

COVID-19 infection

During the study period, no patient was diagnosed with COVID-19. All patients who presented respiratory infections underwent PCR, which was negative in all cases.

Immunological evaluation

- CBC

The results of each parameter of the hemogram were classified by the physicians as normal, non-clinically significant abnormal (NCS) and clinically significant abnormal (CS). Table 18 shows the beginning vs. end contrasts of the classifications of these laboratory parameters according to their values at each moment, which did not show significant differences before vs. after.

Table 18. Initial vs. final contrasts of the classifications of the components of the complete blood count. (∗: Yacht Correction)

Variables (N)	Normal N(%)	NCS N(%)	CS N(%)	Contrast
Initial hemoglobin (135)	68 (50.4)	57 (42.2)	10 (7.4)	$\chi^2 = 4.9265$; df = 2; p = 0.0825
Final hemoglobin (94)	52 (55.3)	41 (43.6)	1 (1.1)	
Hematocrit (133)	93 (69.9)	30 (22.6)	10 (7.5)	$\chi^2 = 7.7524$; df = 2; p = 0.021
Hematocrit (97)	70 (72.2)	26 (26.8)	1 (1.0)	
Total leukocytes (136)	128 (94.1)	8 (5.9%)	-	$\chi^2 = 0.0285$; df = 1; p = 0.866∗
Total leukocytes (90)	86 (95.6)	4 (4.4)	-	
Neutrophils (135)	123 (91.1)	10 (7.4)	2 (1.5)	$\chi^2 = 3.0632$; df = 2; p = 0.216
Neutrophils (90)	87 (96.7)	3 (3.3)	-	
Lymphocytes (135)	126 (93.3)	9 (6.74)	-	$\chi^2 = 0.1001$; df = 1; p = 0.752∗
Lymphocytes (90)	83 (92.2)	7 (7.8)	-	
Monocytes (127)	39 (30.7)	87 (68.5)	1 (0.8)	$\chi^2 = 0.7344$; df = 2; p = 0.693
Monocytes (90)	27 (30.0)	63 (70.0)	-	
Eosinophils (130)	58 (44.6)	68 (52.3)	4 (3.1)	$\chi^2 = 3.4537$; df = 2; p = 0.178
Eosinophils (89)	36 (40.4)	53 (59.6)	-	

-Lymphocyte subpopulations

Thirty HGG patients had blood drawn for an immunological study before starting treatment (T0), one week after it ended (T1) and 6 months after starting treatment (T2). On this last occasion, there were only 29 patients, since one of those selected left home. In one of these 29 samples, the anti-CD19 antibody did not label well.

Table 19 shows the analysis of these data, taking into account the classification as normal, decreased or increased, based on the reference values of the IHI laboratory where they were performed.

It can be seen in the specific case of B lymphocytes, that 43.3% had decreased values at T0, a situation that was corrected throughout the evaluated period. At T1, 22 elderly reached normal values, but in 83.3%, that is, in 25 individuals, these values increased in relation to baseline. In T2 and only 3 individuals, 10.3%, maintain decreased B lymphocyte values.

CD3-/CD56+ NK cells is observed , but not in the subpopulations of CD3+CD4+ T lymphocytes. and TCD3+CD8+. In addition, a significant increase in the CD4/CD8 ratio in T1 ($p = 0.021$) was confirmed. At T2, although the mean of the ratio continues to be greater than that obtained at T0, the statistical significance of this increase is lost (Table 20).

When analyzing the values of the CD4/CD8 ratio in the three times evaluated, initially 60% of the elderly showed a ratio less than or equal to 2 (18 out of 30) and at T1 this percentage decreased to 50 (15 out of 30). . At T2, only 37.9% (11 of 29) had a decreased CD4/CD8 ratio.

In the study protocol, only the quantification of these subpopulations was included, because the necessary laboratory reagents for their study were guaranteed, but it was possible, from the same blood samples, to analyze what is known in the field of immunology as "extended phenotype", which is nothing more than the determination within these subpopulations of other markers that characterize the different lymphocyte subsets . These results are published in international journals.

Table 19. Classification of the values of the lymphocyte subpopulations in the three evaluated times.

Evaluation Lymphocyte Subpopulations	T0; N = 30			T1; N = 30			T2; N = 29		
	Normal N(%)	diminished N(%)	augmented N(%)	Normal N(%)	diminished N(%)	augmented N(%)	Normal N(%)	diminished N(%)	augmented N(%)
CD3+/CD4+	29 (96.7)	1 (3.3)	---	22 (73.3)	6 (20.0)	2 (6.7)	19 (65.5)	4 (13.8)	6 (20.7)
CD3+/CD8+	26 (86.7)	4 (13.3)	---	21 (70.0)	9 (30.0)	---	20 (69.0)	6 (20.7)	3 (10.3)
CD19	17 (56.7)	13 (43.3)	---	22 (73.3)	8 (26.7)	---	26 (89.6)	3 (10.3)	---
CD3-/CD56+	26 (86.7)	3 (10.0)	1 (3.3)	22 (73.3)	3 (10.0)	5 (16.7)	7 (24.1)	1 (3.5)	21 (72.4)

Table 20. Contrasts between the values of the lymphocyte subpopulations in the three evaluated times.

moments	diff . stockings	95% CI diff . stockings	you	gl	p
CD3+CD4+					
T0-T1	1.77	-1,874 – 5,414	*0.9933*	*29*	*0.328*
T0-T2	-2.88	-7,542 – 1,782	*-1.2635*	*29*	*0.216*
T1-T2	-4.65	-0.647 – 9.947	*-1.7955*	*29*	*0.083*
CD3+CD8+					
T0-T1	3.46	-0.039 – 6.959	*2.0225*	*29*	*0.052*
T0-T2	1.40	-2,360 – 5,160	*0.7615*	*29*	*0.452*
T1-T2	-2.06	-1,805 – 5,925	*-1.0902*	*29*	*0.285*
CD19+					
T0-T1	-4.61	-7,227 – -1,990	*-3,599*	*29*	***0.001***
T0-T2	-7.77	-10,889 – -4,653	*-5,114*	*27*	***<0.001***
T1-T2	-3.07	-7,513 – 1,371	*-1,419*	*27*	*0.167*
CD3-CD56+					
T0-T1	-3.42	-0.534 – 7.374	*1.7688*	*29*	*0.087*
T0-T2	-24.96	-30,819 – -19,101	*8.7133*	*29*	***<0.001***
T1-T2	-21.54	-28,534 – -14,546	*6.2990*	*29*	***<0.001***
CD3+CD4+/ CD3+CD8+					
T0-T1	-0.615	-1.133 - -0.099	*-2,438*	*29*	***0.021***
T0-T2	-0.399	-1.033 – 0.234	*-1,292*	*28*	*0.207*
T1-T2	0.218	-0.705 – 1.141	*0.484*	*28*	*0.632*

- Quantification of Immunoglobulins

No significant changes occurred when the baseline immunoglobulin values were contrasted with the two subsequent evaluation moments.

ADVERSE EVENTS

Table 21 shows the AEs by household and in the group of patients. A total of 38 AEs occurred in the 160 patients in the study; There are no differences between households, in relation to the number of AE occurred ($p = 0.844$). These AEs occurred in 36 individuals. Two infections occurred in two elderly: in one case viral conjunctivitis and sinusitis; and in the other pyodermitis and urinary tract infection.

Table 21. Adverse events.

Adverse events	HGG		HSS		Both Homes		*z-test; p*
	N	%	N	%	N	%	
Number of patients	59	36.9	101	63.1	160	100	
Number of AE	13	22.0	25	24.8	38	23.8	*z=0.1973; p = 0.844*
AD patients	12	20.3	24	23.8	36	22.5	

Table 22 describes the AE that occurred according to their classification according to location, time of appearance, prior knowledge, intensity, consequence, causality, outcome of the AE; and attitude towards

the study treatment. As we mentioned before, they were all unexpected AE, as they were not described among the possible ones to occur with the use of BMT. As they did not occur at the site of product administration, all AEs were considered systemic. When starting after the first half hour of administering the product, all were considered late, and also considering their start and end date, all lasted more than one day. In the causality analysis, all were classified as unlikely or unrelated, taking into account their temporal relationship with the administration of BMT and the explanation for another concomitant disease.
Only 1 AE, specifically pneumonia in a 94-year-old bedridden patient, was considered serious, when the elderly man died. The rest had a recovered outcome. 71% were of mild intensity as they were well tolerated by the subjects, causing minimal discomfort and not interfering with their daily activities. In relation to the attitude towards the treatment, in 12 of them (31.6%) the treatment with BMT was continued, the rest, which was the majority, occurred when the patients had already finished the administration of the investigational product (included in this case the severe AE).
In relation to the treatments used for these AE, they were mostly antimicrobial and more frequently orally.

Table 22. Classification of registered AE

ADVERSE EVENTS	**No. (%)**
Location:	
• *systemic AE*	38 (100.0%)
Appearance Time:	
• *late AD*	38 (100.0%)
Prior knowledge	
• *unexpected AE*	38 (100.0%)
Causality	
• *Unlikely*	20/38 (52.6)
• *Not related*	18/38 (47.4)
Duration	
• *older than one day*	38/38 (100.0)
Outcome	
• *Recovered*	37/38 (97.4)
• *Death*	1 (2.6)
Intensity	
• *Mild*	27 (71.0)
• *moderate*	9 (23.7)
• *Severe*	2 (5.3)
Impact	
• *not serious*	37/38 (97.4)
• *Serious (causes death of the patient)*	1 (2.6)
Attitude towards treatment	
• *Continuation*	12/38 (31.6)
• *Treatment already completed*	26 (68.4)
Lots with which the EA is produced	
• *906B01-0*	*13 (34.2)*
• *908B01/0*	*7 (18.4)*
• *004B01/0*	*18/38 (47.4)*
treatments used	

• *oral antibiotics*	*24/48 (50.0)*
• *Parenteral antibiotics*	*10 (20.8)*
• *Antipyretic (Dipyrone IM)*	*3 (6.3)*
• *Topical antifungals or antiparasitics*	*11(22.9)*

No product-related AEs were recorded in the study. The infections collected as EAs are actually part of the frequent clinical manifestations in institutionalized older adults, which in fact gave rise to this clinical trial.

GENERAL CONCLUSIONS

The results achieved in this study allow us to formulate the following conclusions:

❖ The new dosage schedule of BIOMODULINA T®, showed a high efficacy for the prevention of upper and lower respiratory infections, in the elderly in nursing homes, by achieving a large decrease in the incidence of these, compared to the same period of the year above, far exceeding the hypothesis of the study.

❖ Treatment with BIOMODULINA T® also had an impact on the reduction of genitourinary and skin and soft tissue infections, as well as all infections in general, especially of bacterial aetiology; which resulted in a decrease in the use of antibiotics in the study patients.

❖ During the six months of follow-up, no patient was diagnosed with COVID-19, in which the protocol established in homes for the prevention of this disease also played a role.

❖ The patients in the study showed significant signs of immunosenescence , fundamentally a decrease in B lymphocytes, naïve T and B lymphocytes, and an increase in terminally differentiated effector cells; BIOMODULIN T® being capable of stimulating an increase in the CD4+/CD8+ ratio, the number of B lymphocytes, TCD4+ and virgin CD8+ lymphocytes, as well as the ability to activate the immune response, although it did not show effects on terminally differentiated effector cells nor on the antibody response.

❖ The effects on the immune system of treatment with BIOMODULIN T® are evidenced for the first time, up to 6 months after starting it, constituting the basis of the clinical results obtained.

❖ The excellent safety profile of BIOMODULINA T® was once again demonstrated, as no adverse events related to the product were recorded.