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Efficacy of Immunofree and Reginmune on Mild to Moderate Covid-19 Patients: A Multicenter, Randomized, Controlled Trial

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HUMAN

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ABSTRACT

Background: Covid-19 emerged in December 2019 in China and then got spread all over the world. By then, multiple studies have indicated the use of Herbs in Covid19 treatment. This research paper has highlighted the efficacy of products known as immune freee and reginmune, for the treatment of patients suffering from COVID-19. **Primary Study Objective**: The objective of this study is to evaluate the efficacy of a combination of the Herbal formulations Immunofree tablets and Regimmune capsules on mild and moderate covid19 patients in comparison with the standard treatment protocol. **Design:** An open-label, multicentre, randomized, comparative, parallel-group, controlled study. **Setting:** The study was done as per ICH GCP guidelines at 4 sites. **Participants:** 50 subjects received the test product and 50 subjects received Standard of care treatment as control. **Intervention:**2 tablets thrice a day at an interval of 4-5 hours for 10 days and 1 Reginmune capsule twice a day for 10 days. **Primary Outcome Measure:** The analysis was done on efficacy pathological tests like RT-PCR, ESR, C-reactive protein, SpO2, D-dimer, etc along with the Clinical and Subject's Global Assessment of Symptoms. The assessments were done on day 0, day 5, and day 10. **Results:**88% of the subjects in the Immunofree tablet + Reginmune capsule group were shown clinical improvement and were discharged from the hospitalon Day 5 when compared to 72% of the subjects in the standard of care group at Day 5. **Conclusion:** The time to 2-point clinical improvement as per 7 points ordinal WHO scale was seen in favor in Immunofree tablet + Reginmune capsule group.

INTRODUCTION

As of August 17, 2020, more than 20 million people worldwide have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and nearly 800 000 people have died of coronavirus disease 2019 (COVID-19). (1) Acute respiratory failure is a major cause of intensive care unit (ICU) admission for patients with COVID-19 (1,2). In the absence of specific intervention, the treatment of COVID-19 relies on relieving symptoms and organ support. However novel drug discovery and vaccine studies are time taking processes, repurposing old drugs against the COVID-2019 epidemic can help identify treatments, with known pre-clinical, pharmacokinetic, pharmacodynamic, and toxicity profiles, which can rapidly enter Phase 3 or 4 or can be used directly in clinical settings.

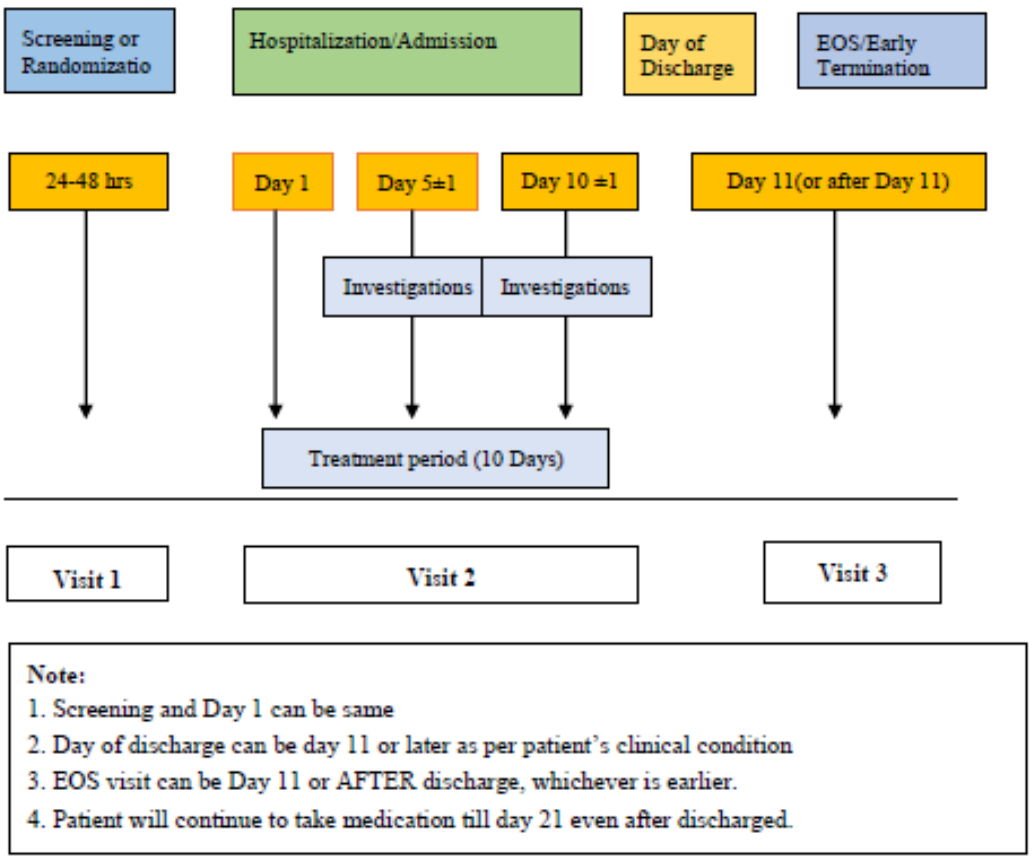
Immunofree is a herbal formulation specially made as antiviral, and composed of Andrographis paniculata, Phyllanthus Niruri, Glycyrrhiza glabra, Ocimum Sanctum, Tinospora cordifolia, Inula racemosa, Alpina galanga, Vitis vinifera, Curcuma longa, Terminalia Chebula, Aloe vera, Shilajit, Piper longum, Artemisia, and Jasad Bhasm; and Reginmune is a nutraceutical blend that acts as a supportive therapy for immune and composed of Echinacea, Cats Claw (Uncaria Tomentosa), Vitamin C, Zinc, Copper, L-lysine, L-glutamine, Aloe vera, L Arginine, L Isoleucine, and Magnesium Gluconate. Immunofree has many of the herbs which have been evaluated by other trials published for Covid-19 treatment. In the past, herbal medicine has played an important role in controlling infectious diseases. Clinical evidence from a range of studies of herbal medicine in the treatment of SARS coronavirus (SARS-CoV) has shown significant results and supported the idea that herbal medicine has a beneficial effect in the treatment and prevention of epidemic diseases [3]. Cochrane systematic review reported that herbal medicine combined with Western medicine may improve symptoms and quality of life in SARS-CoV patients [4]. A recently conducted meta-analysis also concluded that herbal medicine could reduce the infection rate of H1N1 influenza [4]. The test product “Reginmume Capsule is a combination of some phytochemicals, amino acids, vitamins and minerals and a biopolymer in the the cellular matrix and Immunofree tablet” is ann Ayurvedic proprietary medicine and is a combination of the the polyherbal mixture. Reginmume and Immunofree is a powerful anti-viral and anti-bacterial Immuno-booster for flu and cold/respiratory infections caused by Viruses/Bacteria. Numerous tests such as C reactive protein, Procalcitonin, D Dimer, and RT-PCR for novel

coronavirus have shown better improvement for the natural treatmentwhen compared to conventional treatment.

METHODS

This is an open-label, randomized, comparative, multi-centric, parallel-group, and controlled study. The study was conducted at 4 centers in India, having qualified Investigators. The study was initiated only after the receipt of ethics committee (EC) approval. After obtaining the informed consent, patients were screened by undergoing various assessments as mentioned in Schedule of Assessment and after confirming eligibility, eligible patients were randomized in the study and assigned either to the test group receiving a treatment regime of combination therapy of Reginmune and Immunofree or in a control group with Best standard of care as per institutional practice, for 10 days treatment period and were given randomization number based on computer-generated randomization. Patients were hospitalized during the treatment period. During the study, Specimen Collection, Packaging, and Transport of Nasopharyngeal swab & oropharyngeal swab were done as per regulations and keeping in mind GCP and GLP practices.

Figure 1: Study Flow Chart



During the study, assessments were performed as mentioned in Schedule of Assessment (Table A).

Table A: Schedule of Assessment

Parameters	**Screening**	**In-hospital Stay**										**Day of Discharge**
Visits	**1**	**2**										**3**
Day(+days)	**24-48 hrs**	**1**	**2**	**3**	**4**	**5**±1	**6**	**7**	**8**	**9**	**10**±1	**1**[1]
Written Informed Consent	**X**											
Hospitalization/admission to study facility		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Inclusion/Exclusion Criteria	**X**											
Medical & Surgical History	**X**											
Physical Examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital Signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
ECG	**X**					**X**					**X**	
Body Temperature	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Demographic Information	**X**											
PCR for COVID viral load	**X**					**X**[2]					**X**[2]	**X**
IP administration		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Hematology	**X**[3]					**X**					**X**	
Biochemistry (ALT/AST, S. creatinine, BUN, ALP)	**X**[3]					**X**					**X**	
Urinalysis (R/M)	**X**					**X**						
X-Ray Chest	**X**					**X**					**X**	
Urine Pregnancy Test (In case of a female subject)	**X**											
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medication		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

1. Day of discharge can be day 5/11 OR later as per the patients clinical condition.
2. During the hospital stay if PCR results come negative for COVID viral load, then another PCR after 24 hours needs to be performed
3. Absolute neutrophil count, Total bilirubin, and Random Blood Sugar was done only at screening

STUDY SITES

Lokmanya Hospital, Pune; Abhinav Multispeciality Hospital, Nagpur; Parul University, Vadodara and Government Medical College, Srikakulam; all in INDIA.

SUBJECT SELECTION AND IDENTIFICATION

For subjects at least 18 years of age, with a confirmed diagnosis of Covid-19 by RT-PCR were screened. After enrolment, the subjects were assigned to either to investigational product group or control group randomly.

TREATMENT ADMINISTERED

There were two groups of the subjects divided in 1:1 ratio, based upon the treatment administered.

The treatment administered to the study group was test product 2 tablets Immunofree 500 mg tablets thrice and 1 capsule Reginmmune 500 mg twice a day for a period of up to 11 days.

For the control group, the treatment and dose as per hospital protocol for Covid-19 was administered. As per the patient's clinical condition, the following medicines are getting prescribed on an SOS basis on and off as per the clinical improvement. Which included Tab. Paracetamol 650 Mg (SOS), Tab. B Complex (OD), Tab Vit C 500 Mg (TID), Tab Cetrizine 10 Mg (OD), Tab. Pantoprazole 40 Mg (OD), Tab Azithromycin 500 Mg (OD), and Tab Favipiravir 800 Mg (SOS).

EFFICACY AND SAFETY MEASUREMENTS ASSESSED

The focus of this study was to determine the Efficacy, Safety & Tolerability of Polyherbal blends- Reginmune and Immunofree in the treatment of mild to moderate COVID-19.

The primary efficacy variable was the number of Days to clinical improvement from study enrolment till the day of discharge.

Secondary efficacy variables were the normalization of fever, change in the mean values of SpO2, Respiratory rate, RT-PCR, Haematology, and Biochemistry from baseline to day of discharge. Change in quality of life from baseline to day 5. Global assessment for overall improvement by the investigator and by a patient at the end of the study treatment.

STATISTICAL ANALYSIS

Data will be analyzed using R software version 2.15.0 (R Development core team, R Foundation for Statistical Computing, Vienna, Austria) with appropriate statistical tests.

SAFETY MEASUREMENTS ASSESSED

- Change in clinical laboratory findings (e.g., BUN, SGOT, SGPT, and Creatinine)
- Incidence of adverse events. Adverse events will be classified according to their severity based on CTCAE v 5.0 criteria. Any clinically significant abnormal change from baseline in the concurrent medical condition(s), physical examination, and/or laboratory data shall be recorded as an AE.
- 12 lead ECG was conducted at screening, on Day 5 and if required on Day10, and as clinically indicated.

All adverse events (AEs) and SAE were recorded at each visit to assess the safety of the IP.

ASSESSMENT OF SYMPTOMS

The following symptoms were assessed by the Physician and Subject from day 1 till the day of discharge, and the scoring was done as Nil = 0, Mild = 1, Moderate = 2, and Severe = 3.

CLINICIAN'S GLOBAL ASSESSMENT OF SYMPTOMS

- Cough
- Fever with or without chil
- Shortness of breath
- Nasal congestion
- Gastrointestinal symptoms
- Anosmia
- Ageusia

- Fatigue
- Any alternative sign of Covid-19

SUBJECT'S GLOBAL ASSESSMENT OF SYMPTOMS

- Fever
- Nasal congestion
- Cough
- Difficulty in breathing
- Body pain
- Gastrointestinal
- Headache
- Fatigue

RESULTS AND OBSERVATIONS:

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 1: Demographic characteristics between Immunofree tablet + Reginmune capsule and Standard of care

S. No.	Demographics	Variable	Immunofree tablet + Reginmune capsule (N=50)	Standard of Care (N=50)	P-value
1.	Age	Mean	43.20	41.76	0.45
		SD	11.42	13.35	
		Min	20.00	19.00	
		Max	67.00	65.00	
2.	Height	Mean	164.93	163.95	0.67
		SD	8.01	7.52	
		Min	150.00	142.00	
		Max	190.00	176.00	
3.	Weight	Mean	62.46	61.78	0.83
		SD	7.38	6.74	
		Min	45.00	50.00	
		Max	80.00	75.00	
4.	BMI	Mean	23.02	23.05	0.54
		SD	2.89	2.66	
		Min	18.23	18.37	
		Max	30.30	29.30	

OTHER DEMOGRAPHIC VARIABLES:

Table 2: Other Demographic variables between Immunofree tablet and Reginmune capsule and Standard of Care

Variables	Immunofree tablet + Reginmune capsule Z (N=50)	Standard of Care (N=50)	P-value
Sex			
a. Male	35	35	0.8
b. Female	15	15	-
Race & Ethnicity			
a. Asian and Indian	50	50	-
b. Other	0	0	-
Marital Status			
a. Married	44	42	0.89
b. Not married	6	8	0.67
Living status			
a. Staying alone	31	32	0.9
b. Living with family	19	18	0.91
Income status			
a. Decline to answer	35	41	0.43
b. Less than 20,000	4	3	0.7
c. 20,000-40,000	4	1	0.1
d. 40,000-60,000	6	2	0.3
e. 60,0000-1,00,000	2	1	0.5
f. Above 1,00,000	0	1	0.1
Highest level of education			
a. Grades 1-8	3	1	0.8
b. High school (grade 9-11)	3	2	0.2
c. Highschool (grade 11-12)	4	3	0.7

d. College Graduate	2	12	0.08
e. Graduate school	8	6	0.8
f. Decline to answer	30	26	0.4
History of smoking			
a. Smoker	0	2	0.2
b. Non smoker	50	48	0.79
Occupation			
c. daily wage labour	8	6	0.78
d. Salesman	6	8	0.7
e. Businessman	3	4	0.4
f. Service/Job	22	17	0.54
g. Housewife	4	6	0.8
h. Student	5	6	0.7
i. Engineer	2	3	0.8
Medical history			
Asthma	1	1	-
Hypertension	2	1	0.5
Diabetes	2	1	0.5
Biochemistry at screening values*			
Random Blood Sugar	95±12.5	92±14.6	0.88
Absolute neutrophil counts	4300±350	4250±385	0.98
Total bilirubin	1.3±4.4	1.45±3.6	0.54

***Other test screening baseline values were mentioned in results tables.**

CONFIRMATORY ENROLLMENT VARIABLES:

Table 3: RT-PCR Cycle Threshold value (CT value) during enrolment of the study.

S. No.	Confirmatory Demography	Variable	Immunofree tablet + Reginmune capsule (N=50)	Standard of Care (N=50)
1.	CT Value in RT-PCR Test	Mean	26.12	26.20
		Min	15	16
		Max	33	34

EFFICACY EVALUATIONS

Table 4: Time to clinical improvement between Immunofree tablet + Reginmune capsule and Standard of care groups

Variable	Immunofree tablet + Reginmune capsule (N=50)		Standard of care (N=50)		Odd ratio#	P-value (Log rank)*
	Day 5 N (%)	Day 10 N (%)	Day 5 N (%)	Day 10 N (%)		
Clinical improvement	44 (88)	6 (12)	36 (72)	14 (28)	1.418 (0.9433-2.133)	0.0020

***The result is significant at p < .05**

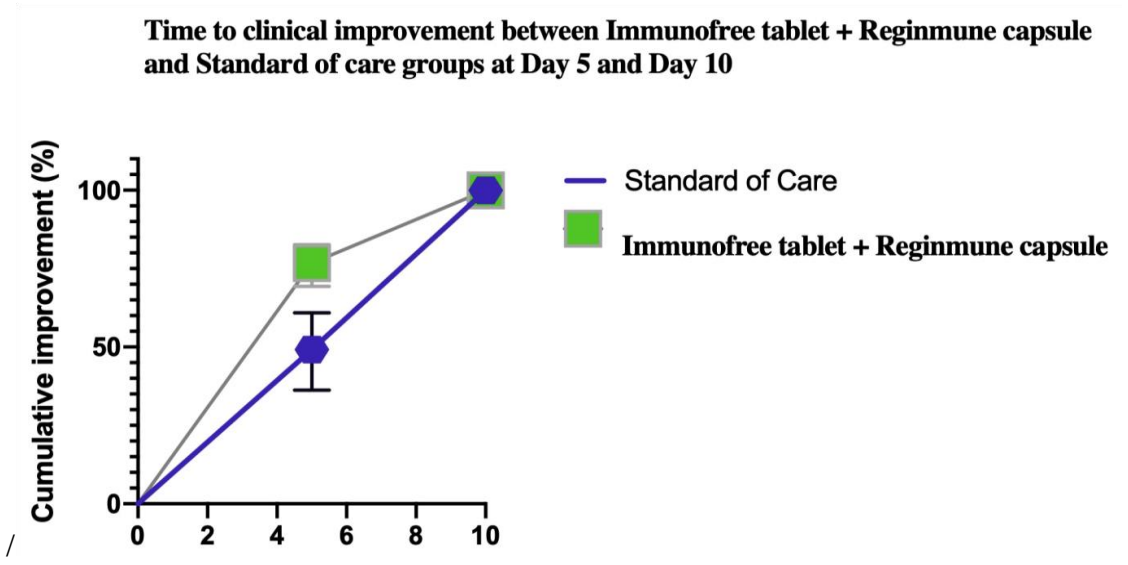


Figure 1: Time to clinical improvement between Immunofree tablet + Reginmune capsule and Standard of care groups

Table 5: Number of subjects in 7 points Covid-19 ordinal scale at Day 1, Day 5, and Day 10 between Immunofree tablet + Reginmune capsule and Standard of care groups.

Clinical status	Immunofree tablet + Reginmune capsule			Standard of care		
	Baseline (N=50)	Day 5 (N=50)	Day 10 (N=6)	Day 1 (N=50)	Day 5 (N=50)	Day 10 (N=14)
No clinical or virological evidence of infection	0	10	1	0	8	2
Not hospitalised, no limitations on activities	0	18	5	0	10	8
Not hospitalised, limitations on activities	0	16	0	0	18	4
Hospitalised, not requiring supplemental oxygen	40	6	0	43	14	0
Hospitalised, requiring supplemental oxygen	10	0	0	7	0	0
Hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	0	0	0	0	0	0
Death	0	0	0	0	0	0

NEGATIVE RT-PCR TEST RESULTS:

Table 6: Number of patients that had negative RT-PCR (virological cure) at Day 5 between Immunofree tablet + Reginmune capsule and Standard of Care groups.

RT-PCR	Immunofree tablet + Reginmune capsule (N=50)			Standard of care (N=50)			P-value *	P-value# (
	Baseline	Day 5	Day 10	Baseline	Day 5	Day 10		
The proportion of patients that had negative PCR	0/50	44/50	50/50	0/50	36/50	44/50	0.04	0.02

*p-value calculated between Day 5 values between Immunofree tablet + Reginmune capsule and Standard of care groups;# p value calculated between Day 10 values between Immunofree tablet + Reginmune capsule and Standard of care groups.

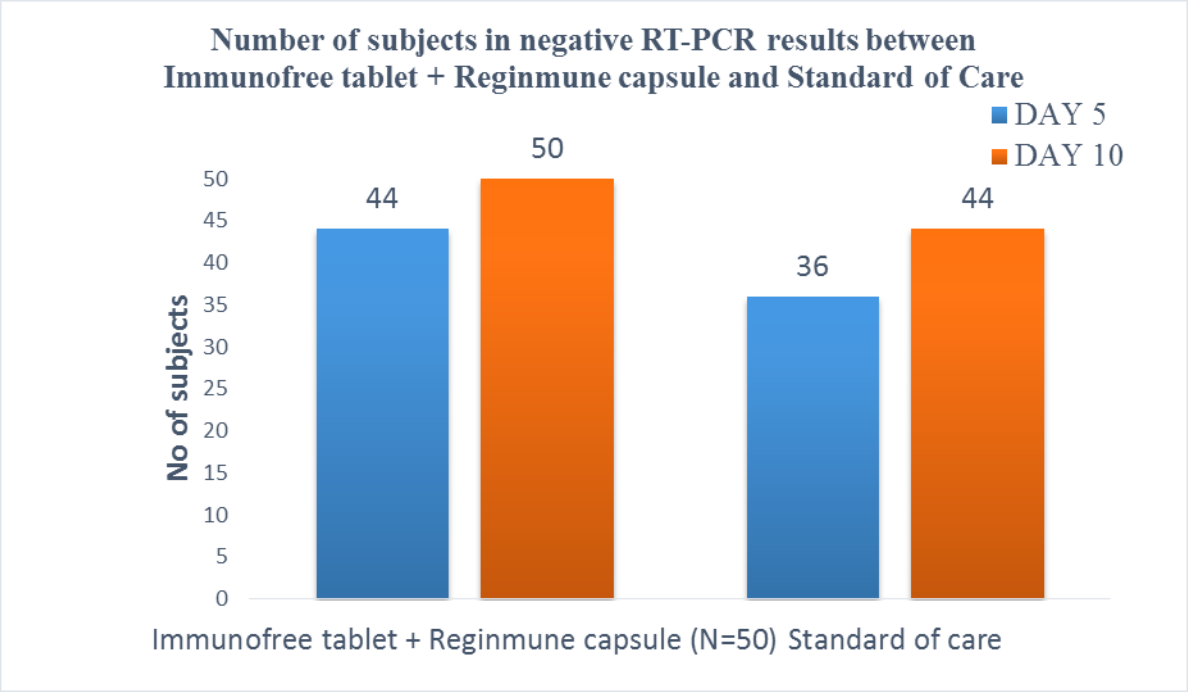


Figure 2: Number of patients negative RT-PCR (virological cure) results at day 5 and Day 10 between Immunofree tablet + Reginmune capsule and Standard of Care groups

Table 7: % Number of patients that had negative RT-PCR (virological cure) at Day 5 and Day 10 between Immunofree tablet and Reginmune capsule and Standard of Care groups.

RT-PCR	Immunofree tablet + Reginmune capsule (N=50)		Standard of care (N=50)	
	Day 5	Day 10	Day 5	Day 10
% of subejcts in Virological cure	88	100	72	88

GLOBAL ASSESSMENT OF COVID 19 SYMPTOMS (MEAN SCORES):

Table 8: Mean symptom scores 0-3 (Nil, Mild, Moderate, and severe) in Immunofree tablet + Reginmune capsule group from Day 1 to Day 10.

	Mean scores of symptoms (Immunofree tablet + Reginmune capsule)										p-value*
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	
Cough	1.3	1	0.9	0.88	0.5	0.3	0.1	0.1	0.1	0.1	0.02
Fever with or without chill	1.4	1.1	0.9	0.88	0.7	0.5	0.3	0.1	0.1	0.2	0.0001
Shortness of breath	1.1	0.8	0.8	0.78	0.6	0.4	0.2	0	0.2	0.1	0.01
Nasal congestion	0.9	0.6	0.4	0.38	0.1	0.02	0.02	0.02	0.02	0	0.01
Neuro Disorders	0.9	0.6	0.3	0.28	0.1	0.07	0.07	0.07	0.07	0	0.45
Anosmia	0.7	0.4	0.3	0.28	0.1	0.07	0.07	0.07	0.07	0.01	0.34
Ageusia	0.8	0.5	0.4	0.38	0.2	0.04	0.04	0.04	0.04	0.03	0.43
Fatigue	1.4	1.1	1	0.98	0.6	0.4	0.4	0.3	0.2	0.1	0.01

**The p-value is significant at P<0.05 between Day 1 to Day 5/Day 10*

Table 9: Mean symptom scores 0-3 (Nil, Mild, Moderate and severe) in the standard of care group from Day 1 to Day 10.

	Mean scores of symptoms (Standard of care group)										
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**P-value**
Cough	1.4	1.3	1.1	1	0.98	0.9	0.8	0.6	0.4	0.3	0.01
Fever with or without chill	1.4	1.3	1.2	1	0.98	0.9	0.9	0.7	0.5	0.4	0.01
Shortness of breath	1.2	1.2	1.1	1	0.88	0.8	0.8	0.6	0.4	0.3	0.04
Nasal congestion	0.9	0.8	0.7	0.5	0.48	0.4	0.4	0.2	0	0.1	0.45
Neuro Disorders	1	0.7	0.7	0.4	0.38	0.3	0.3	0.1	0.1	0.1	0.35
Anosmia	0.8	0.7	0.5	0.4	0.38	0.3	0.3	0.1	0.1	0.3	0.02
Ageusi	0.9	0.8	0.6	0.5	0.48	0.4	0.4	0.3	0.1	0.3	0.01
Fatigue	1.5	1.4	1.2	1.1	1.08	1	0.9	0.7	0.5	0.4	0.45

**The p-value is significant at P<0.05 between Day 1 to Day 5/Day 10*

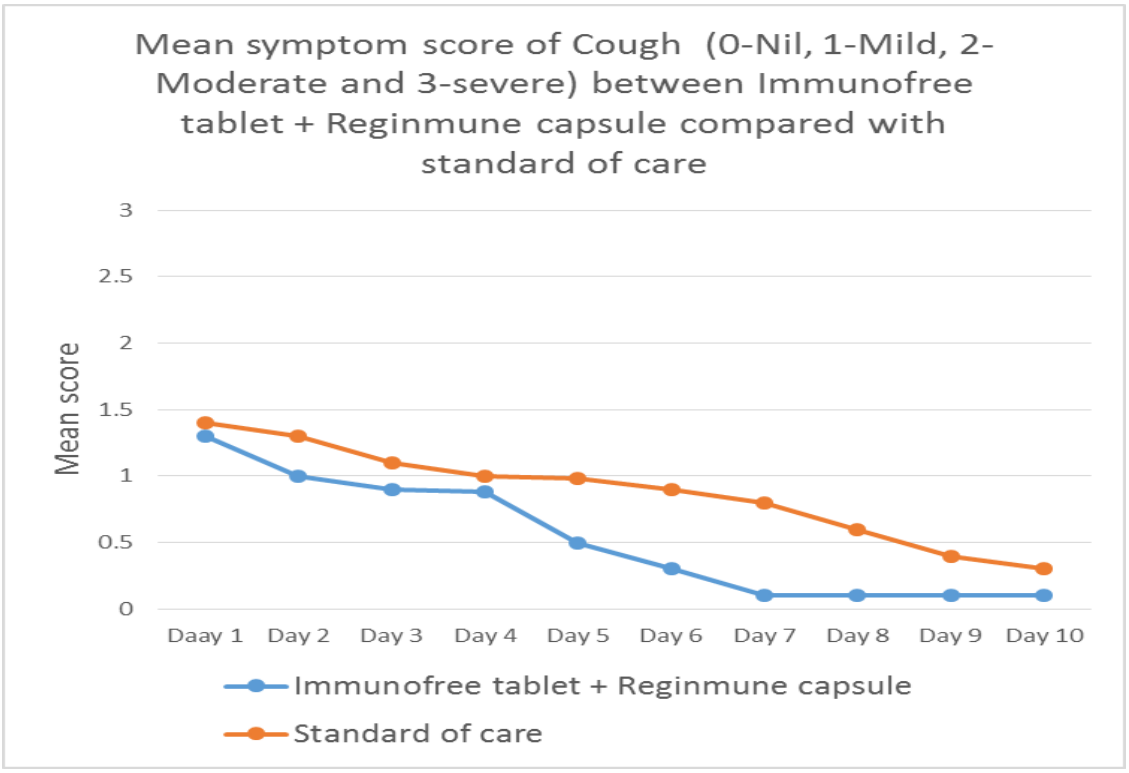


Figure 3: Mean symptom score (0-3) of Cough between Immunofree tablet and Reginmune capsule between Immunofree tablet + Reginmune capsule and Standard of Care groups

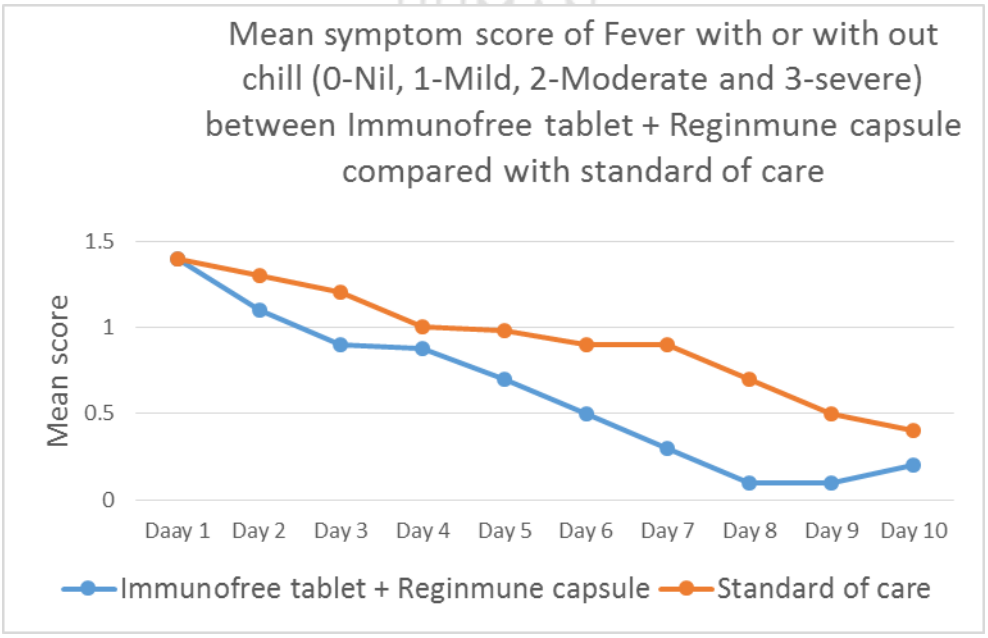


Figure 4: Mean symptom score (0-3) of Fever between Immunofree tablet + Reginmune capsule Standard of Care groups

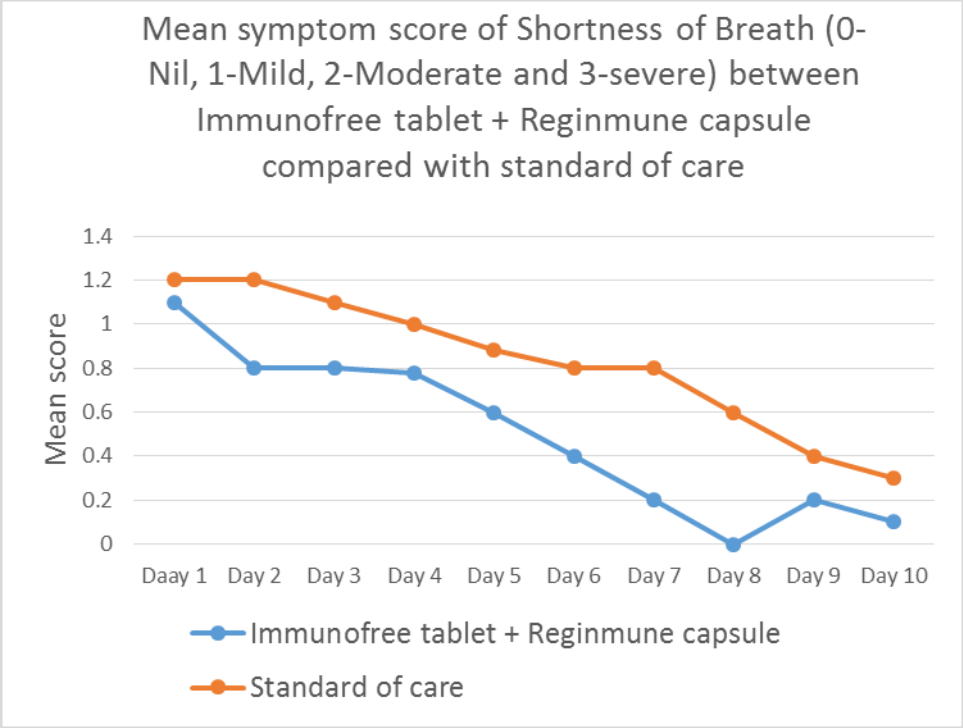


Figure 5: Mean symptom score (0-3) of breath between Immunofree tablet + Reginmune capsule and Standard of Care groups

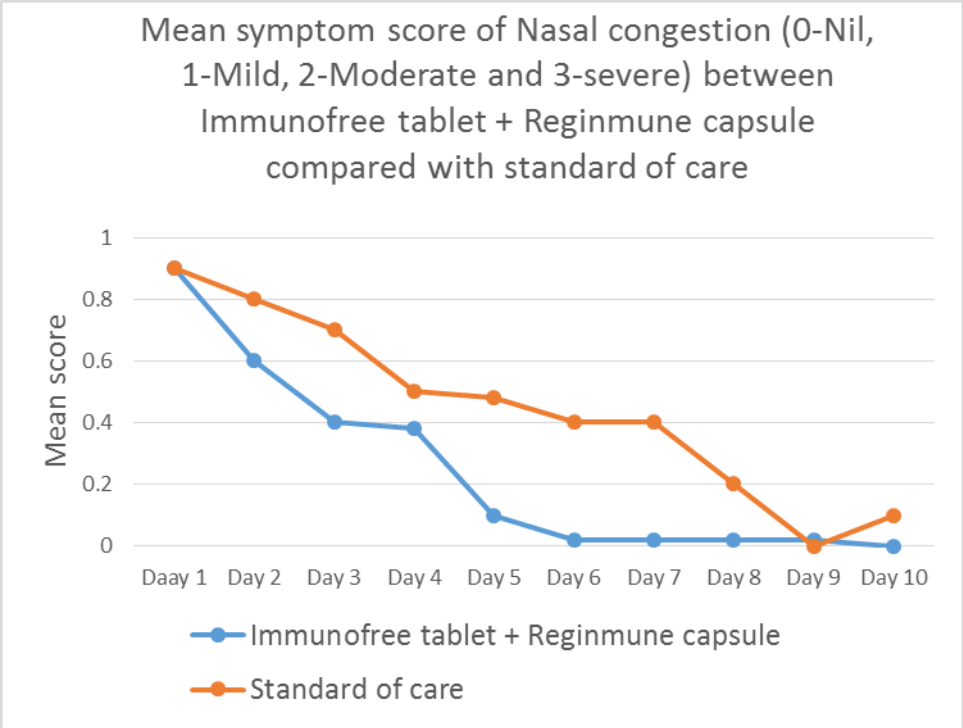


Figure 6: Mean symptom score (0-3) of Nasal Congestion between Immunofree tablet + Reginmune capsule and Standard of Care groups

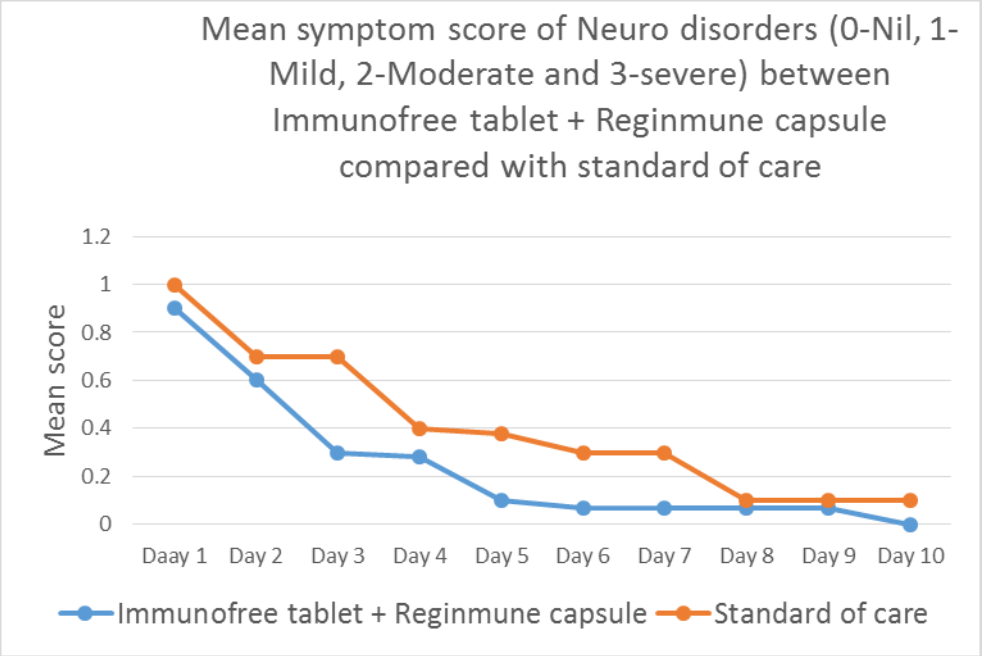


Figure 7: Mean symptom score (0-3)of Neuro disorders between Immunofree tablet +Reginmune capsuleand Standard of Care groups

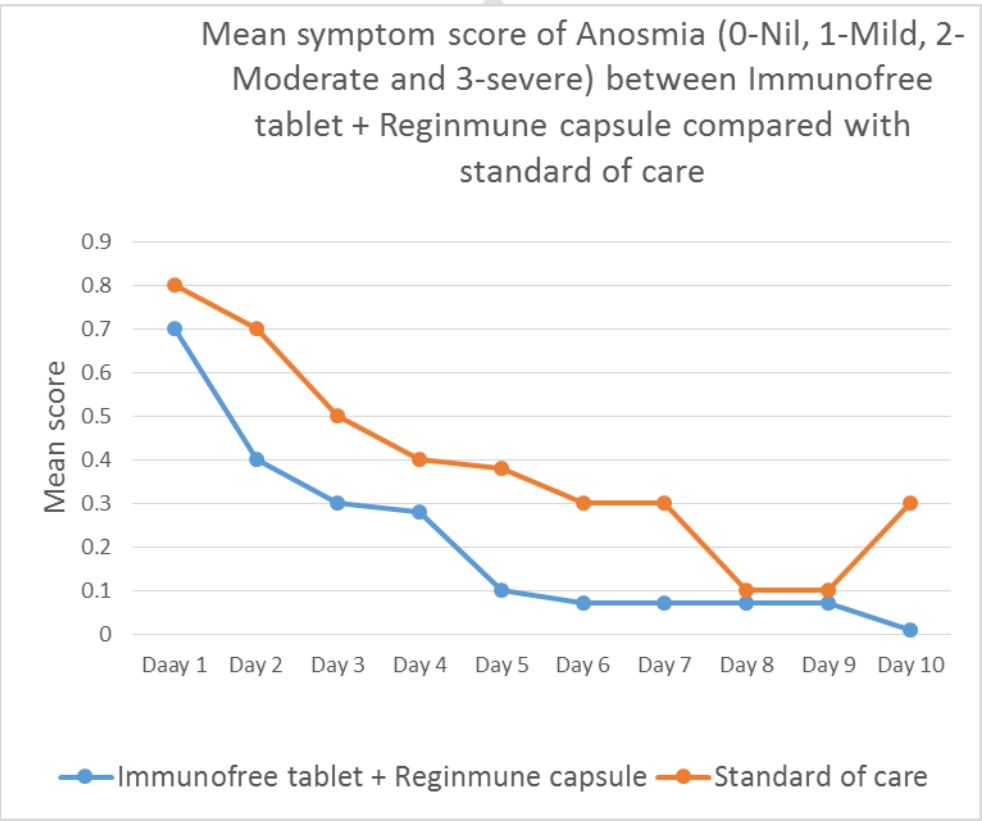


Figure 8: Mean symptom score (0-3) of Anosmia between Immunofree tablet + Reginmune capsule and Standard of Care groups

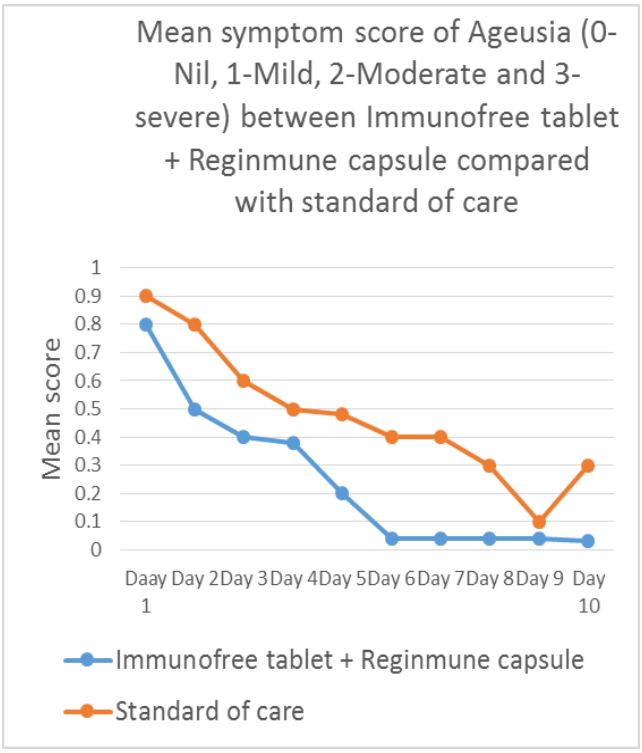


Figure 9: Mean symptom score (0-3of Ageusia between Immunofree tablet + Reginmune capsule and Standard of Care groups

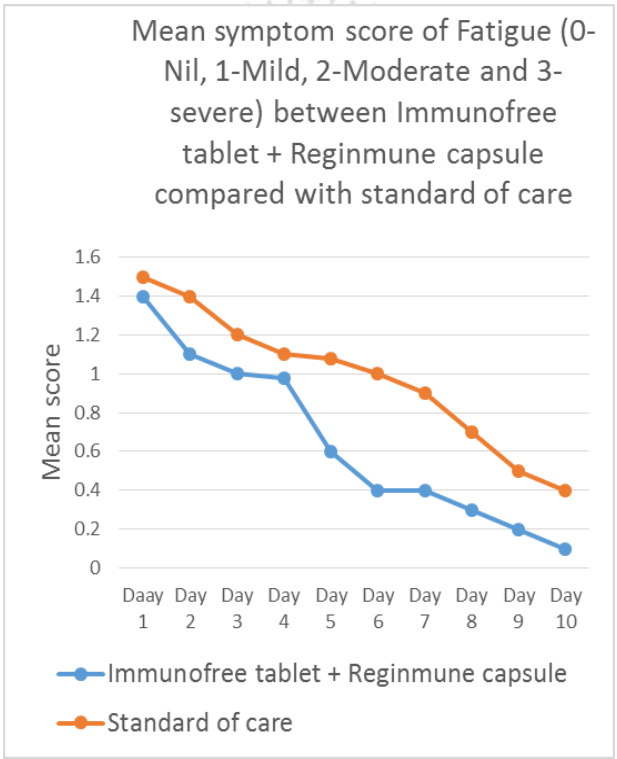


Figure 10: Mean symptom score (0-3)of Fatigue between Immunofree tablet + Reginmune capsule and Standard of Care groups

SUBJECT'S GLOBAL ASSESSMENT OF SYMPTOMS:

Table 10: Subject's global assessment of symptoms in a number of patients between Immunofree tablet + Reginmune capsule group and Standard of Care groups.

	Severity	Immunofree tablet + Reginmune capsule					Standard of Care				
		Day1	Day 2	Day3	Day 4	Day5	Day 1	Day2	Day 3	Day4	Day 5
Cough	Nil	3	7	10	10	22	11	10	12	17	19
	Mild	33	29	36	40	28	31	33	34	32	30
	Moderate	14	14	3	0	0	8	7	4	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Fever	Nil	9	11	22	33	39	11	11	24	25	36
	Mild	29	32	22	16	11	31	31	24	23	12
	Moderate	11	7	4	0	0	4	8	2	0	0
	Severe	0	0	0	0	0	3	0	0	0	0
Difficulty in breathing	Nil	35	42	38	46	48	36	37	44	44	45
	Mild	5	3	11	4	2	8	10	4	5	4
	Moderate	10	5	0	0	0	6	3	1	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Body pain	Nil	29	30	31	32	37	34	35	32	36	36
	Mild	15	15	17	18	13	11	10	15	13	13
	Moderate	6	5	1	0	0	5	5	3	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Nasal congestion	Nil	41	38	42	43	46	37	38	44	45	43
	Mild	8	9	7	7	4	11	10	5	3	6
	Moderate	1	1	0	0	0	2	2	1	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Gastrointestinal symptoms	Nil	48	47	47	49	49	47	50	49	48	47
	Mild	2	3	2	1	1	1	0	1	1	2
	Moderate	0	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Fatigue	Nil	22	22	22	31	27	23	22	29	28	29
	Mild	22	22	25	19	22	22	24	19	21	20
	Moderate	6	5	1	0	0	5	4	2	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Headache	Nil	32	35	32	39	42	34	32	37	31	37
	Mild	17	15	16	11	8	15	18	13	18	12
	Moderate	1	0	1	0	0	1	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0

Table 11: Subject's global assessment of symptoms Day 6 to Day 10 in proportion of patients in Immunofree tablet and Reginmune capsule and Standard of care

	Severity	Immunofree tablet + Reginmune capsule (N=6)					Standard of Care (N=14)				
		Day 6	Day 7	Day 8	Day 9	Day 10	Day 6	Day 7	Day 8	Day 9	Day 10
Cough	Nil	1	3	3	5	6	9	10	11	10	12
	Mild	5	3	2	1	0	4	3	2	3	2
	Moderate	0	0	0	0	0	1	1	1	1	0
	Severe	0	0	0	0	0	0	0	0	0	0
Fever	Nil	4	5	5	6	6	10	12	12	13	13
	Mild	2	1	1	0	0	4	2	2	1	1
	Moderate	0	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Difficulty in breathing	Nil	4	5	5	6	6	9	10	12	13	14
	Mild	1	1	1	0	0	3	3	2	1	0
	Moderate	1	0	0	0	0	2	1	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Body pain	Nil	4	4	5	5	5	11	11	11	11	12
	Mild	2	2	1	1	1	3	3	3	3	2
	Moderate	0	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Gastrointestinal symptoms	Nil	6	6	6	6	6	11	12	13	13	13
	Mild	0	0	0	0	0	3	2	1	1	1
	Moderate	0	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Neuro	Nil	6	6	6	6	6	14	14	14	14	14
	Mild	0	0	0	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Fatigue	Nil	1	3	3	5	5	10	10	10	11	12
	Mild	5	3	3	1	1	4	3	4	3	2
	Moderate	0	0	0	0	0	0	1	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0
Headache	Nil	5	6	6	6	6	10	13	14	14	14
	Mild	1	0	0	0	0	2	1	0	0	0
	Moderate	0	0	0	0	0	2	0	0	0	0
	Severe	0	0	0	0	0	0	0	0	0	0

CHEST CT/X-RAY FINDINGS:

Table 12: Cumulative proportion of patients in normal chest finding between Immunofree tablet + Reginmune capsule and Standard of Care groups

Parameter	Immunofree tablet and Reginmune capsule (N=50)			Standard of Care (N=50)			P-value*
Chest X-ray	Baseline	Day 5	Day 10	Baseline	Day 5	Day 10	
Cumulative proportion of patients showing normal chest finding	22/50	40/50	48/50	25/50	35/50	44/50	0.306
% Cumulative proportion of patients showing normal chest finding	44	80	96	50	70	88	

***The result is not significant at p < .05.**

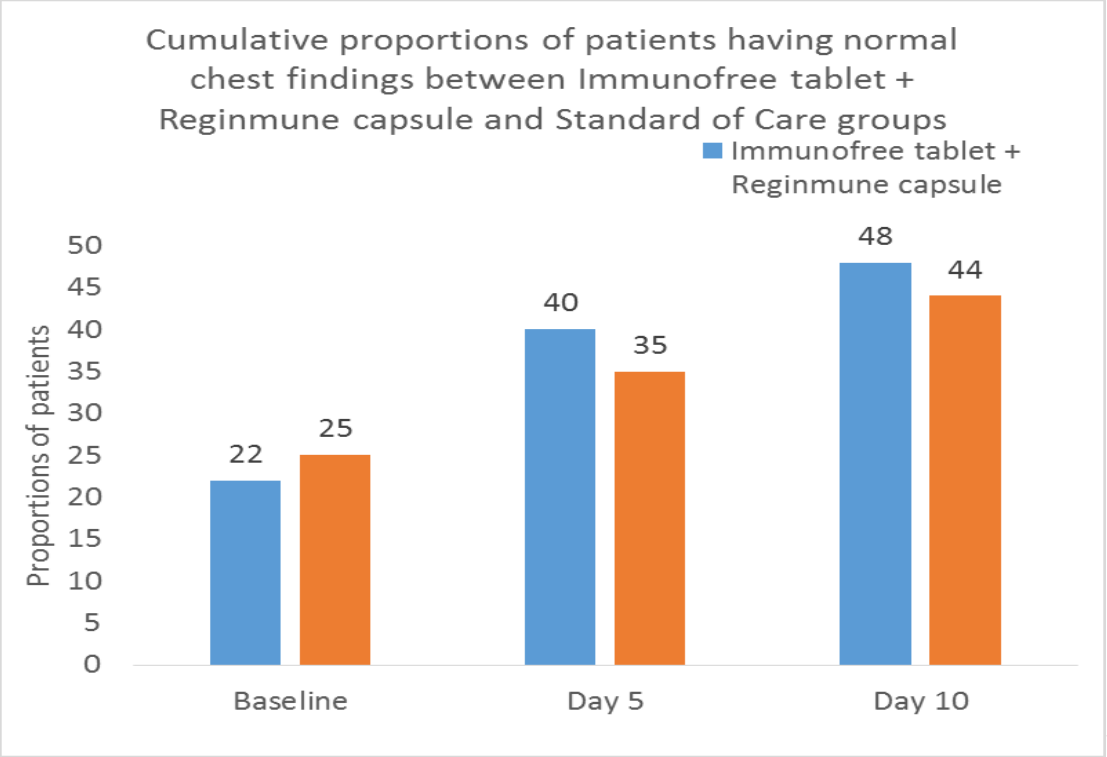


Figure 11: Number of patients showing abnormal chest finding between Immunofree tablet and Reginmune capsule group and Standard of Care groups

C-REACTIVE PROTEIN (CRP):

Table 13: CRP mean values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups.

Lab Tests	Variable	Immunofree tablet + Reginmune capsule (N=50)			Standard of Care (N=50)			
CRP (mg/dL)		Baseline (N=50)	Day 5 (N=50)	Day 10 (N=6)	Baseline (N=50)	Day 5 (N=50)	Day 10 (N=14)	p-value *
	Mean	4.16	1.45	1.35	4.02	1.38	1.20	0.78
	SD	2.61	0.37	0.1	2.79	0.14	0.40	
	P-value#	0.01			0.02			

***The result is not significant at p < .05.**

 # The result is significant at p < .05.

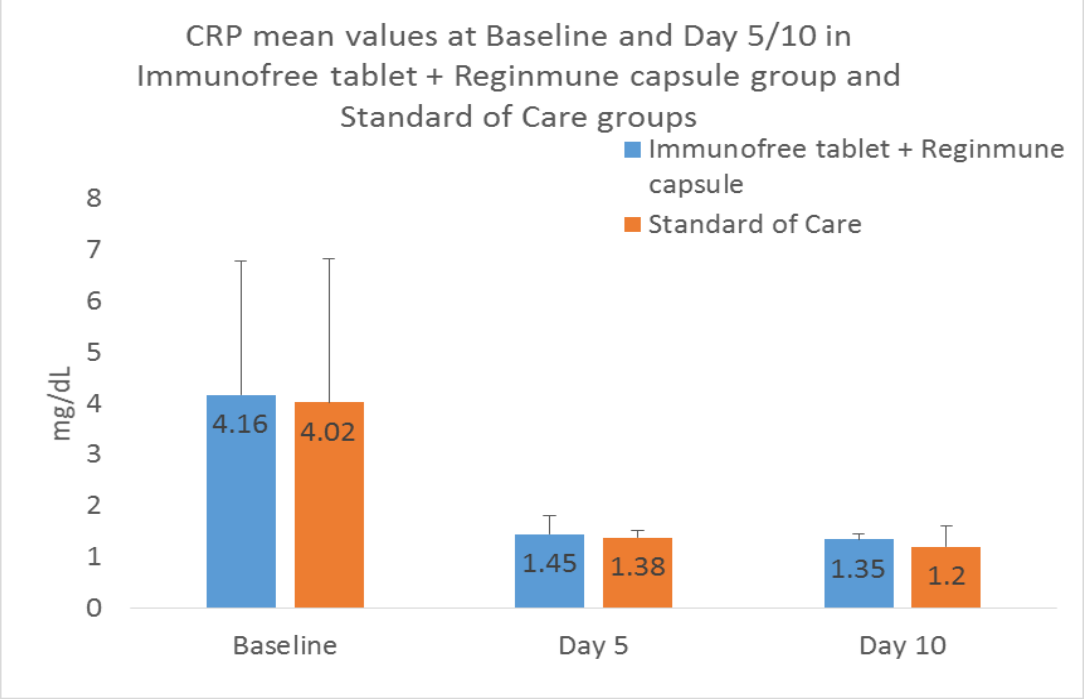


Figure 12: CRP mean values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

PROCALCITONIN:

Table 14: Mean Procalcitonin values at Baseline, Day 5 and Day 10 between Immunofree tablet + Reginmune capsule and Standard of care group.

Lab Tests	Variable	Immunofree tablet + Reginmune capsule treatment			Standard of care			p-value
Procacitonin (ng/mL)		Baseline (N=50)	Day 5 (N=50)	Day 10 (N=6)	Baseline (N=50)	Day 5 (N=50)	Day 10 (N=14)	
	Mean	0.20	0.08	0.01	0.19	0.10	0.03	
	SD	0.23	0.16	0.13	0.23	0.07	0.04	0.76
	P-value	0.01			0.04			

***The result is not significant at p < .05.**

 # The result is significant at p < .05.

Table 15: % reduction of Procalcitonin values at Day 5/Day 10 compared to baseline in Immunofree tablet + Reginmune capsule group and Standard of Care groups in Covid-19 patients

Lab Tests	Variable	Immunofree tablet + Reginmune capsule		Standard of Care	
		Day 5 (N=50)	Day 10 (N=6)	Day 5 (N=36)	Day 10 (N=14)
Procalcitonin (ng/mL)	Percent reduction	-83.38	-95	-47.3	-84.2

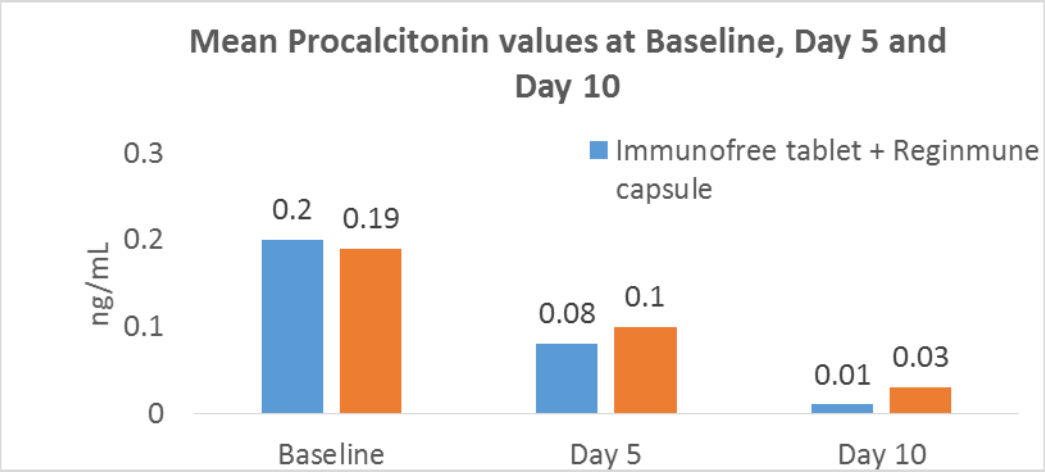


Figure 13: Mean Procalcitonin values at Baseline, Day 5 and Day 10 between Immunofree tablet + Reginmune capsule and Standard of care group.

BLOOD OXYGEN SATURATION LEVELS (SP02):

Table 16: Blood oxygen saturation (SpO_2) values at Baseline, Day 5 and Day 10 in Immunofree tablet and Reginmune capsule compared to Standard of care group

Test	Variable	Immunofree tablet + Reginmune capsule			Standard of Care			p-value*
		Day 0 (N=50)	Day 5 (N=50)	Day 10 (N=6)	Day 0 (N=50)	Day 5 (N=50)	Day 10 (N=14)	
SpO_2 (%)	Mean	94.57	97.33	98.36	94.53	96.57	97.33	0.43
	SD	2.54	1.19	1.50	2.45	1.78	2.42	
	P-value	0.03#			0.07			

***The result is not significant at p < .05.**

 # The result is significant at p < .05.

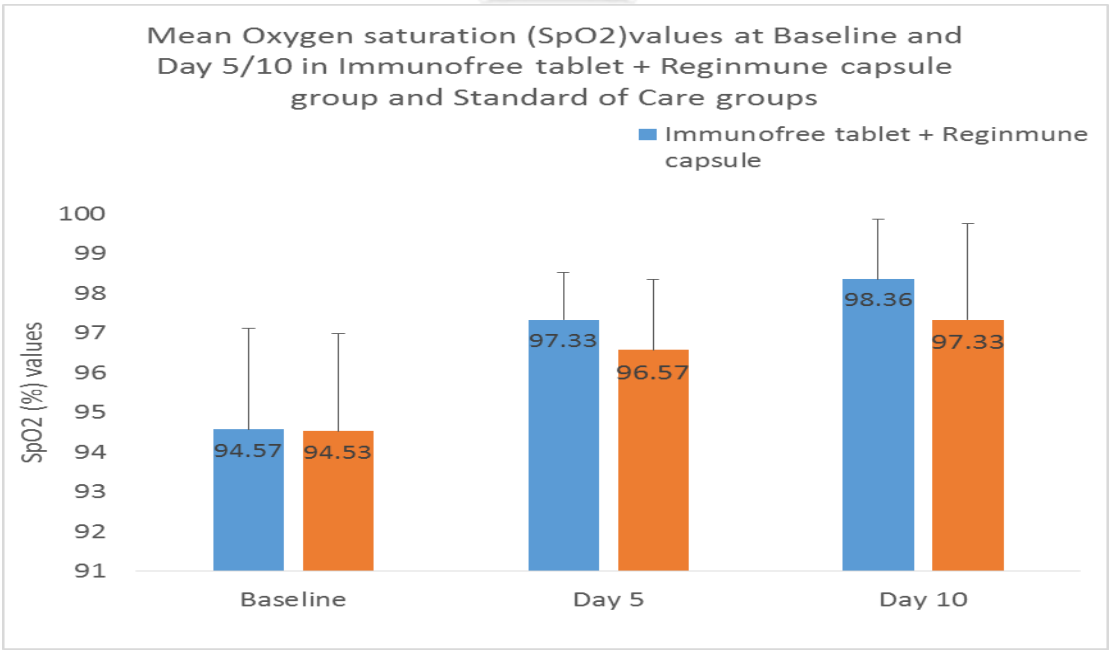


Figure 14: Mean blood oxygen saturation (SpO2) values at Baseline, Day 5 and Day 10 in Immunofree tablet + Reginmune capsule compared to Standard of care group

CLINICAL LABORATORY EVALUATIONS

Table 17: Haematology evaluation between Immunofree tablet + Reginmune capsule and Standard of Care group

Lab Tests	Variable	Immunofree tablet + Reginmune capsule			Standard of Care			P-value
		Baseline	Day 5	Day 10	Baseline	Day 5	Day 10	
Haemoglobin	**Mean**	13.05	12.74	14.00	12.52	15.33	13.63	**0.56**
	SD	1.47	1.35	1.74	1.36	16.97	1.66	
	Min.	9.6	8.9	11.00	8.9	9.6	11.80	
	Max.	15.9	15.7	16.50	15.2	130	16.10	
RBC	**Mean**	4.63	4.55	5.12	4.47	4.43	4.54	**0.43**
	SD	0.62	0.54	0.69	0.70	0.61	0.86	
	Min.	3.3	3.5	3.70	2.8	3.1	3.60	
	Max.	6.27	5.6	6.07	6.35	5.5	5.66	
Total	**Mean**	5885.00	7774.08	6513.62	5423.90	7066.67	5565.33	**0.87**
Leucocyte	**SD**	1821.66	1685.50	4423.13	1765.66	2026.95	2568.97	
Count	**Min.**	2300	4310	1086.00	1321	3000	1282.00	
	Max.	9500	10630	11940.00	9300	12300	7600.00	
Platelets	**Mean**	2.21	2.52	4.26	2.12	2.54	2.68	**0.45**
	SD	0.70	0.70	1.04	0.78	0.88	1.29	
	Min.	1.14	1.4	2.10	1.1	1.2	1.80	
	Max.	4.1	5.2	6.00	5.3	5.3	5.20	
MCV	**Mean**	79.77	81.91	83.39	82.30	84.62	86.22	**0.32**
	SD	13.86	8.59	19.78	8.06	8.92	7.84	
	Min.	3	60	27.10	66	65	76.00	
	Max.	108	105.1	116.90	100	109	86.22	
ESR	**Mean**	17.34	15.04	14.69	20.47	17.73	10.17	**0.65**
	SD	13.52	12.60	8.14	13.51	13.13	5.38	
	Min.	0.5	2	3.00	4	4	5.00	
	Max.	55	51	30.00	55	60	19.00	
Neutrophils	**Mean**	65.27	67.92	65.65	66.22	66.36	66.46	**0.98**

	SD	8.42	5.14	7.97	6.46	6.33	4.46	
	Min.	49	57	55.90	45	54	60.00	
	Max.	84	76	76.00	78	77	71.70	
Lymphocytes	**Mean**	30.02	24.98	25.29	27.96	25.70	26.60	
	SD	6.20	5.68	6.77	5.59	6.41	5.76	**0.54**
	Min.	15	2	12.00	18	13	18.20	
	Max.	47	35	34.90	49	41	34.00	
Eosinophils	**Mean**	3.35	2.89	2.25	3.53	2.81	3.03	
	SD	2.39	1.37	1.99	2.23	1.39	2.32	**0.56**
	Min.	1	0.1	0.10	0.2	0.1	0.10	
	Max.	10	7	7.70	10	6	6.00	
Basophils	**Mean**	0.07	0.35	0.71	0.06	0.24	0.10	
	SD	0.25	1.32	0.95	0.24	0.72	0.11	**0.54**
	Min.	0	0	0.00	0	0	0.00	
	Max.	1	9	3	1	4	2	
Monocytes	**Mean**	2.35	2.49	2.62	2.48	2.55	2.70	
	SD	1.28	1.31	1.21	1.31	1.40	1.05	**0.32**
	Min.	1	1	1	1	1	1.00	
	Max.	5	6	6	5	6	4.00	

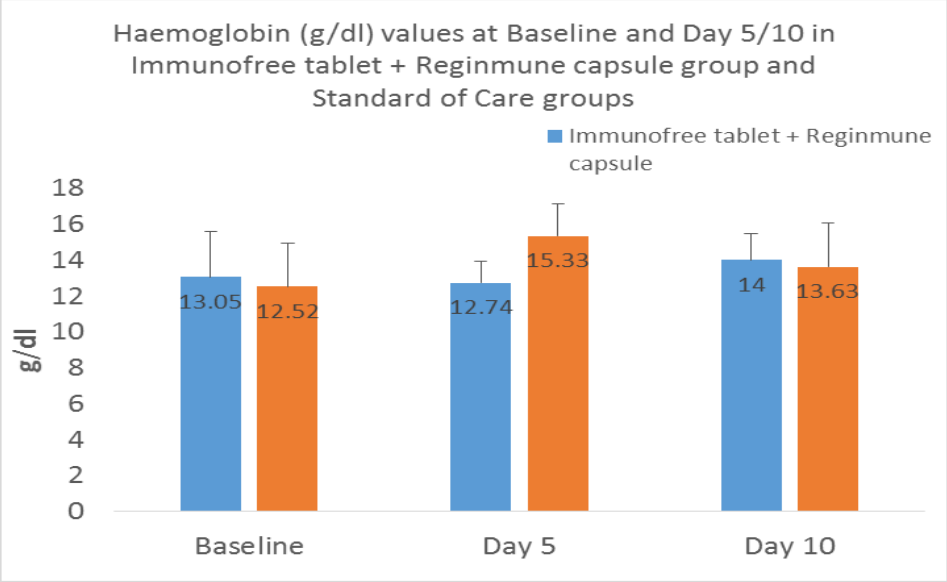


Figure 15.1: Haemoglobin (g/dl) values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

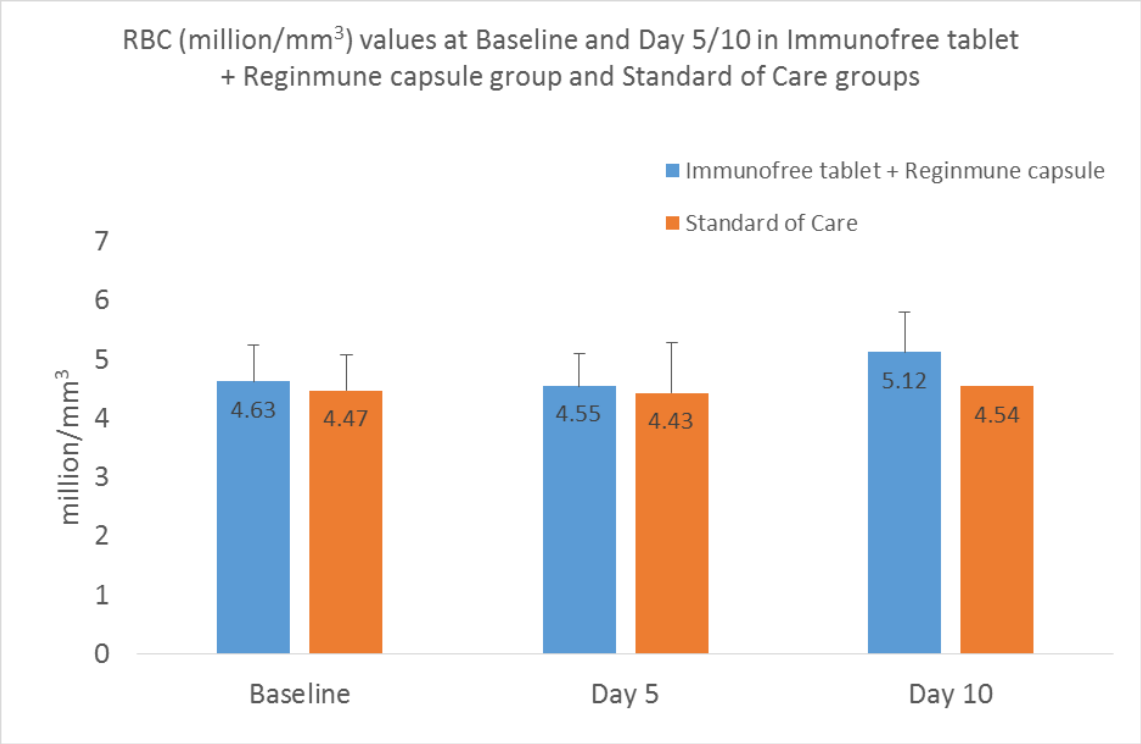


Figure 15.2: RBC (million/mm^3) values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

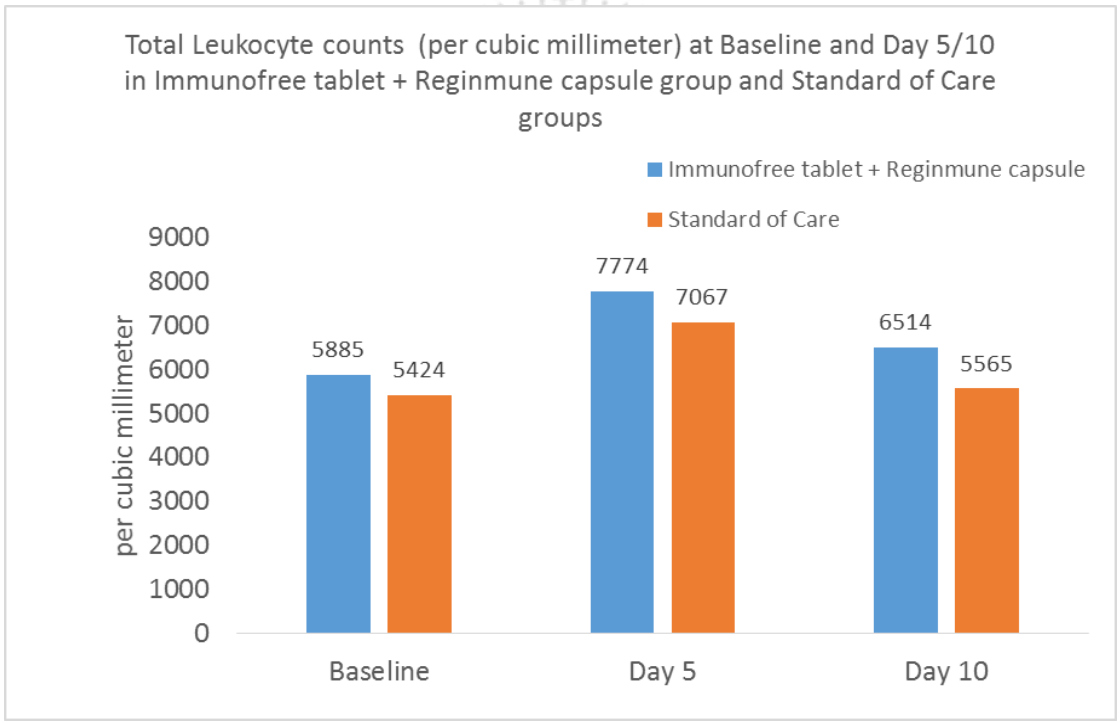


Figure 16: Total Leukocyte counts (per cubic millimeter) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

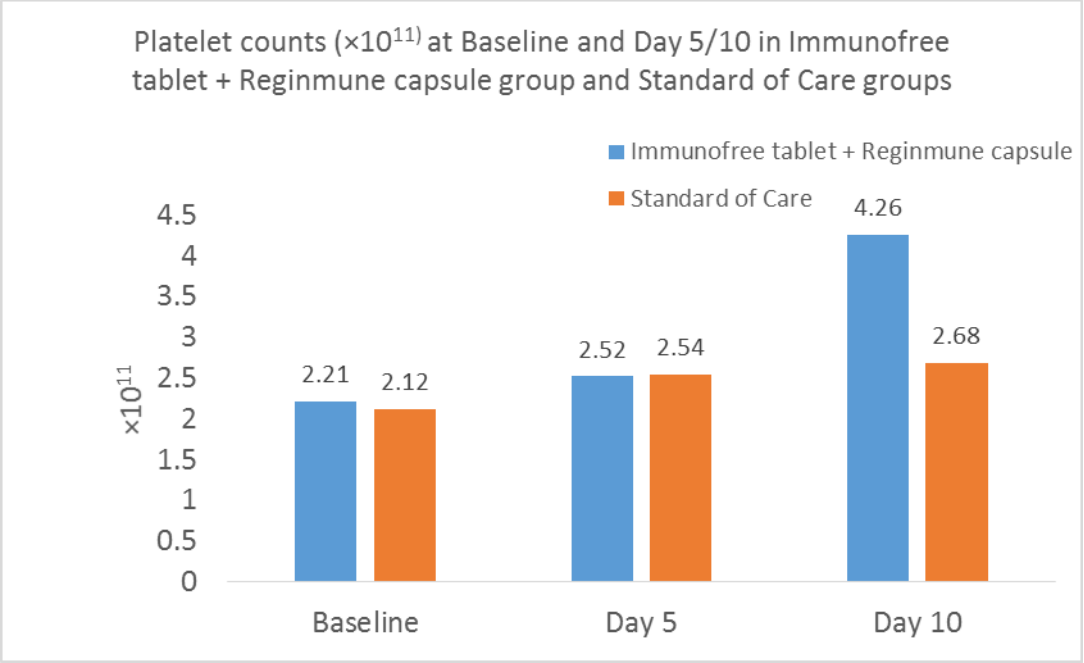


Figure 17: Platelet counts (×10[11]) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

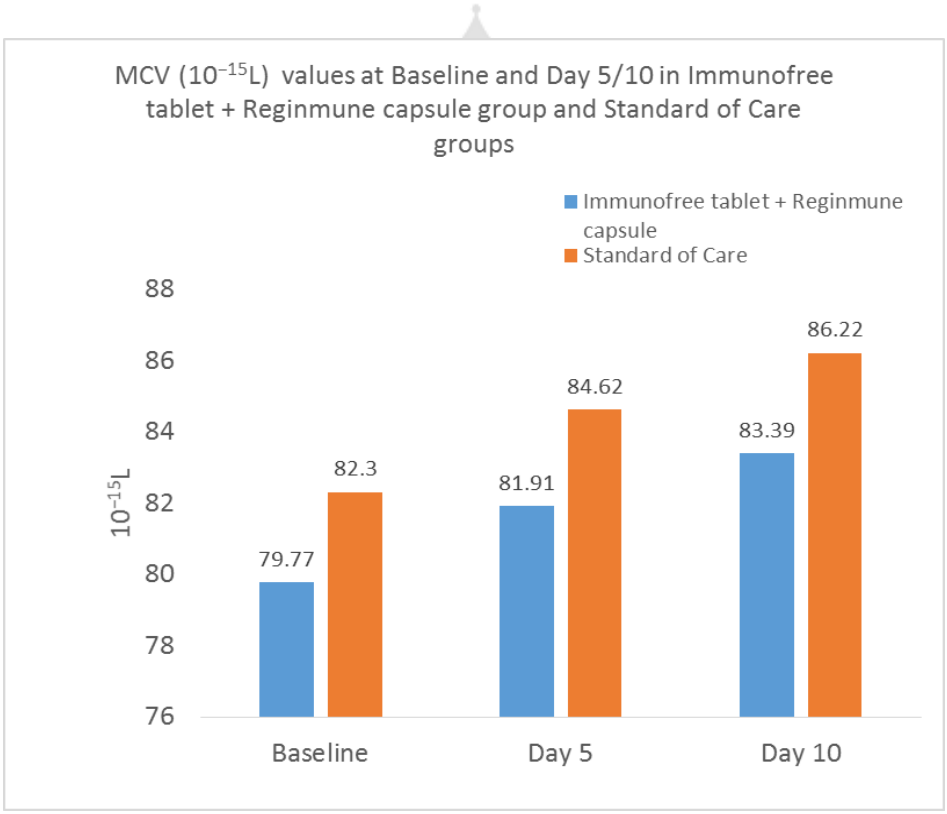


Figure 18: MCV (10−15L) values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

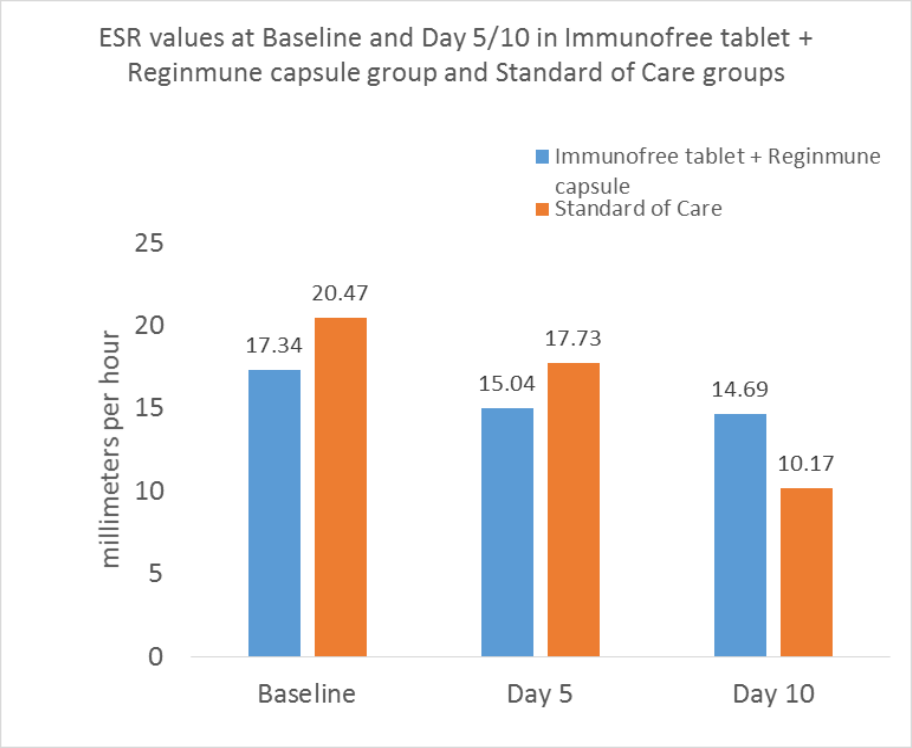


Figure 19: ESR values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

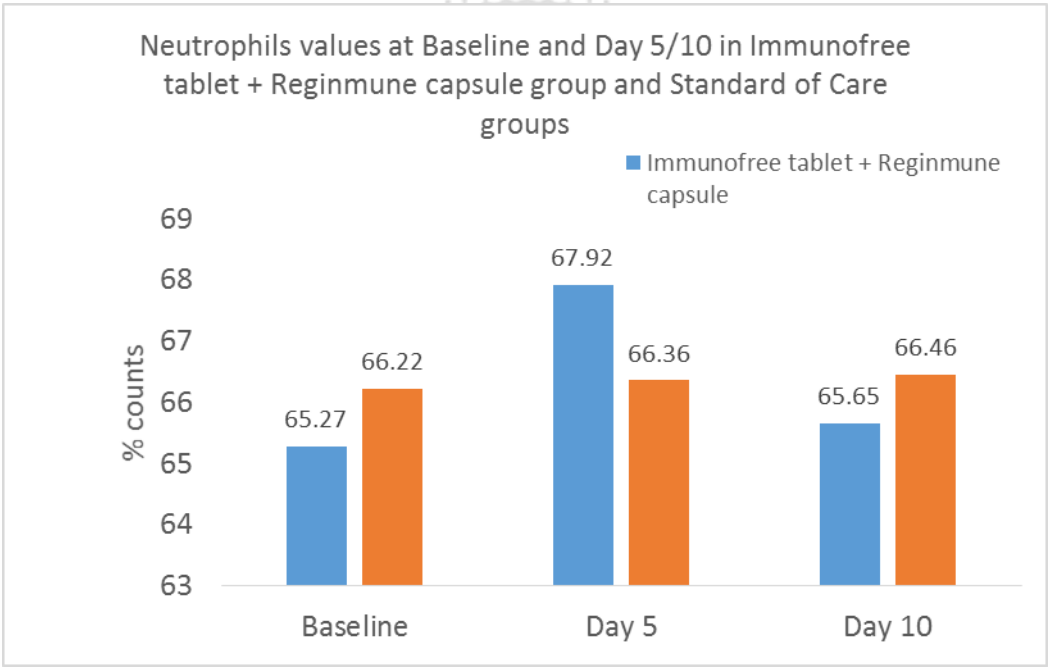


Figure 20: Neutrophils values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

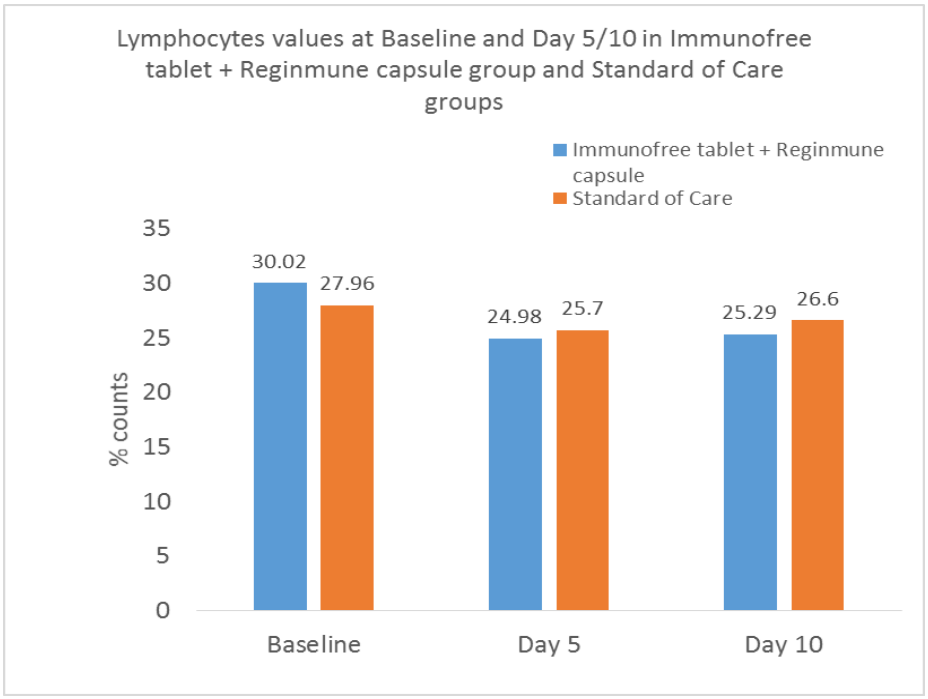


Figure 21: Lymphocytes values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

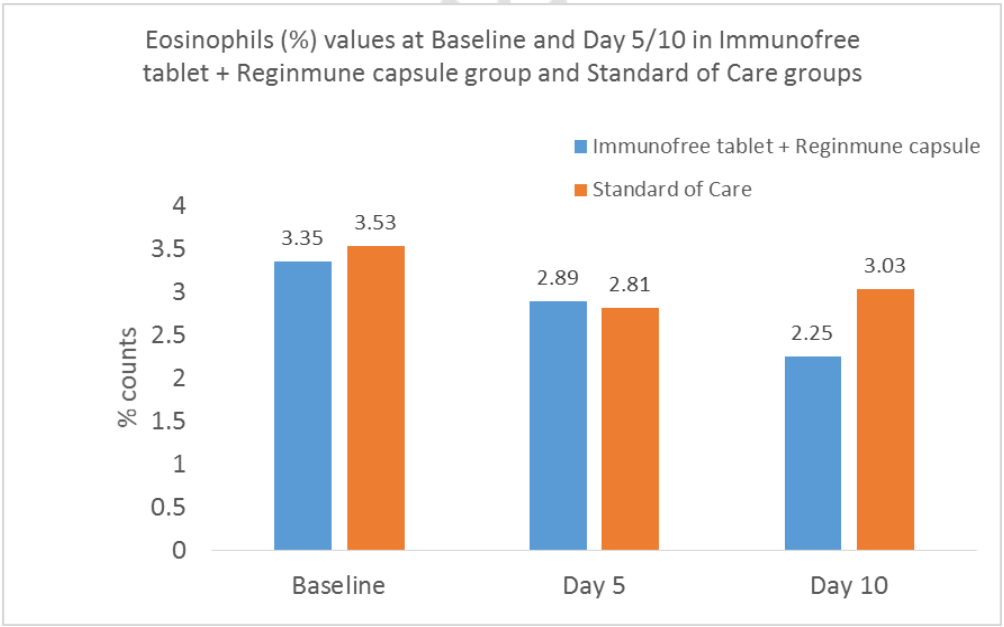


Figure 22: Eosinophils (%) values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

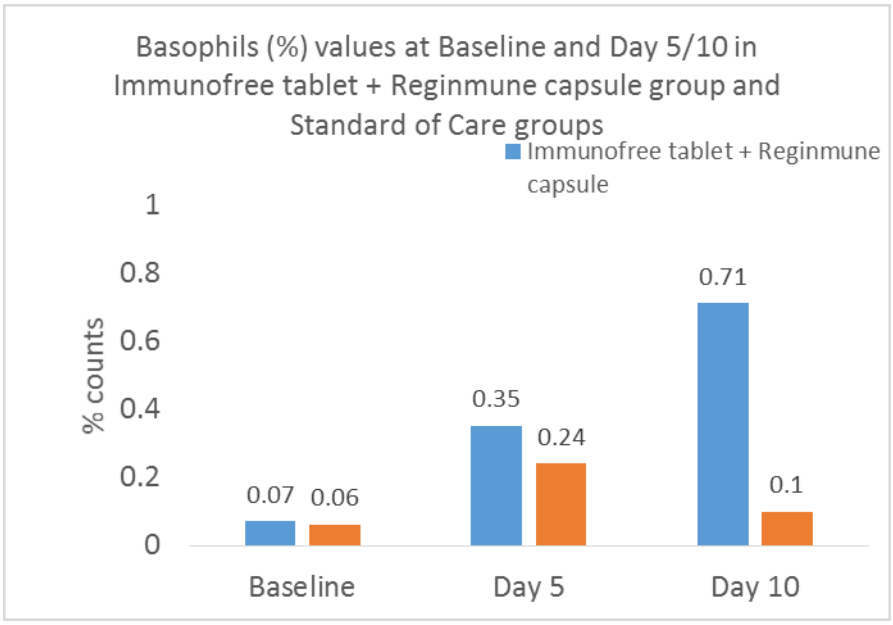


Figure 23: Basophils (%) values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

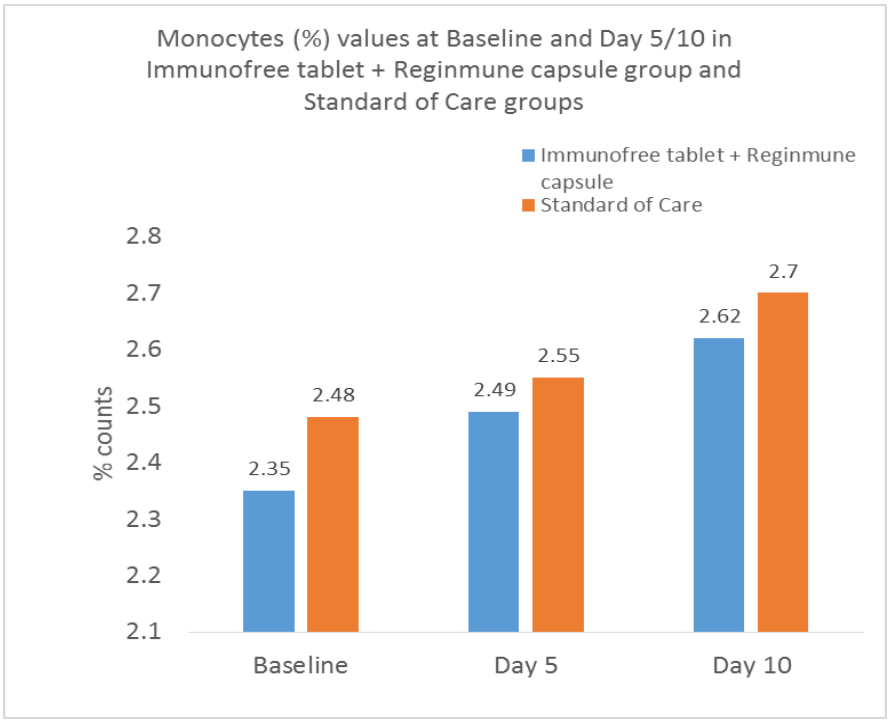


Figure 24: Monocytes (%) values at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

BIOCHEMISTRY LAB ASSESSMENT:

Table 18: Biochemistry assessments between Immunofree tablet + Reginmune capsule and Standard of Care groups

		Immunofree tablet + Reginmune capsule			Standard of Care		
Lab Tests	**Variable**	**Baseline (N=50)**	**Day 5 (N=50)**	**Day 10 (N=6)**	**Baseline (N=50)**	**Day 5 (N=50)**	**Day 10 (N=14)**
Serum Sodium mEq/L	**Mean**	133.15	137.83	135.17	138.40	139.71	137.37
	SD	25.39	7.71	7.50	4.57	4.87	3.11
	Min.	13.9	101	123	128	125	134.00
	Max.	146	147	145	148	148	141.00
Serum Potassium mEq/L	**Mean**	4.09	4.01	3.93	4.09	3.92	3.77
	SD	0.43	0.48	0.63	0.43	0.79	0.93
	Min.	3.4	2.8	2.8	3.2	1.01	2.20
	Max.	5.4	5.21	4.9	5.03	5.25	4.60
BUN mg/dL	**Mean**	17.51	17.37	12.12	16.53	19.60	13.12
	SD	20.99	13.98	3.97	10.30	19.91	5.52
	Min.	0.4	2.5	7.15	4.67	5.14	5.50
	Max.	144	67	18.2	49	128	21.00
AST (SGOT) units/L	**Mean**	37.90	40.88	31.16	38.67	47.00	28.87
	SD	23.28	29.17	6.62	54.56	60.62	8.68
	Min.	12	12	21.11	11	18	15.00
	Max.	161	177	48.26	391	391	38.00
ALT (SGPT) units/L	**Mean**	40.96	39.45	33.67	38.09	39.74	28.23
	SD	15.65	16.87	15.21	23.92	21.58	6.15
	Min.	19	16	12.24	14	20	17.00
	Max.	107	104	66.1	151	151	35.00
Serum Creatininemg/dL	**Mean**	0.94	0.95	0.80	0.91	0.89	0.88
	SD	0.21	0.17	0.24	0.20	0.22	0.25
	Min.	0.5	0.61	0.52	0.5	0.3	0.53
	Max.	1.32	1.31	1.39	1.49	1.47	1.14
ALP (IU/L)	**Mean**	60.67	55.56	45.45	65.45	59.74	58.53
	SD	14.65	15.77	15.31	23.82	31.58	36.45
	Min.	26	36	24	34	24	27.00
	Max.	80	89	83	110	125	135

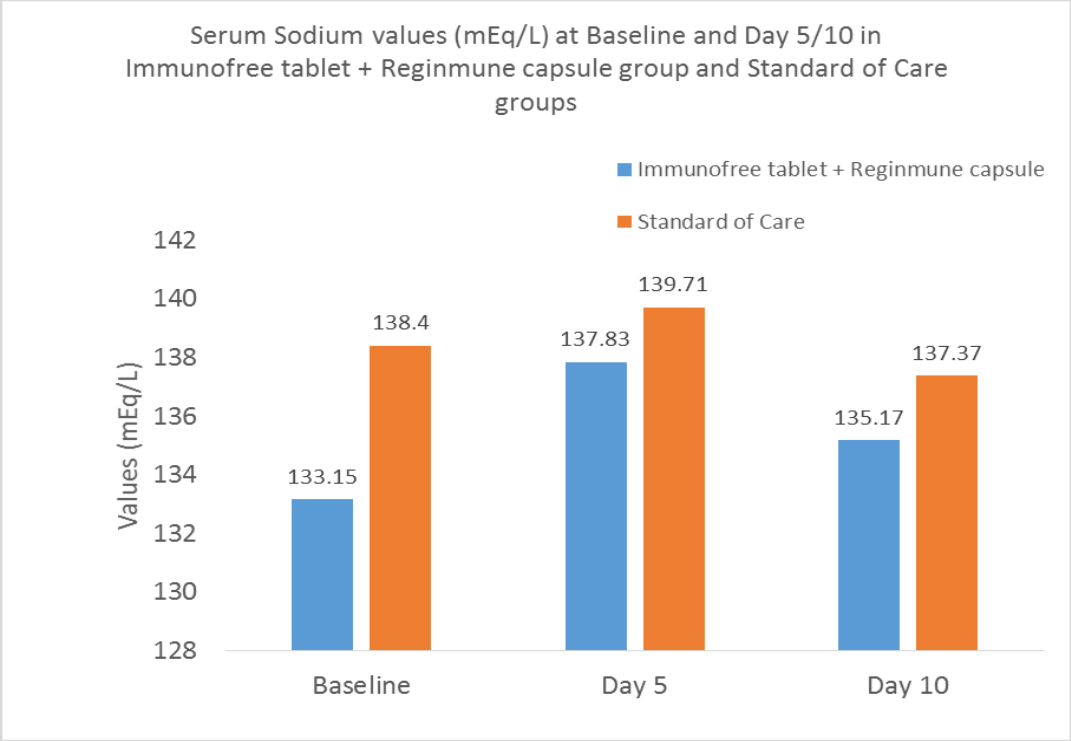


Figure 25: Serum Sodium values (mEq/L) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

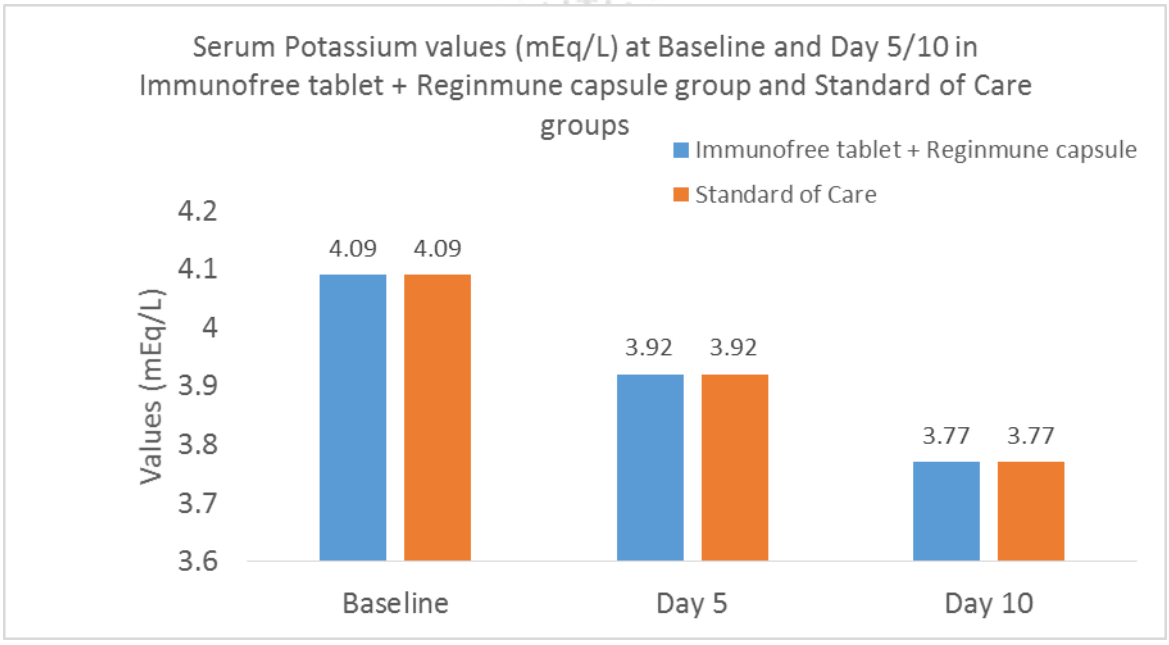


Figure 26: Serum Potassium values (mEq/L) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

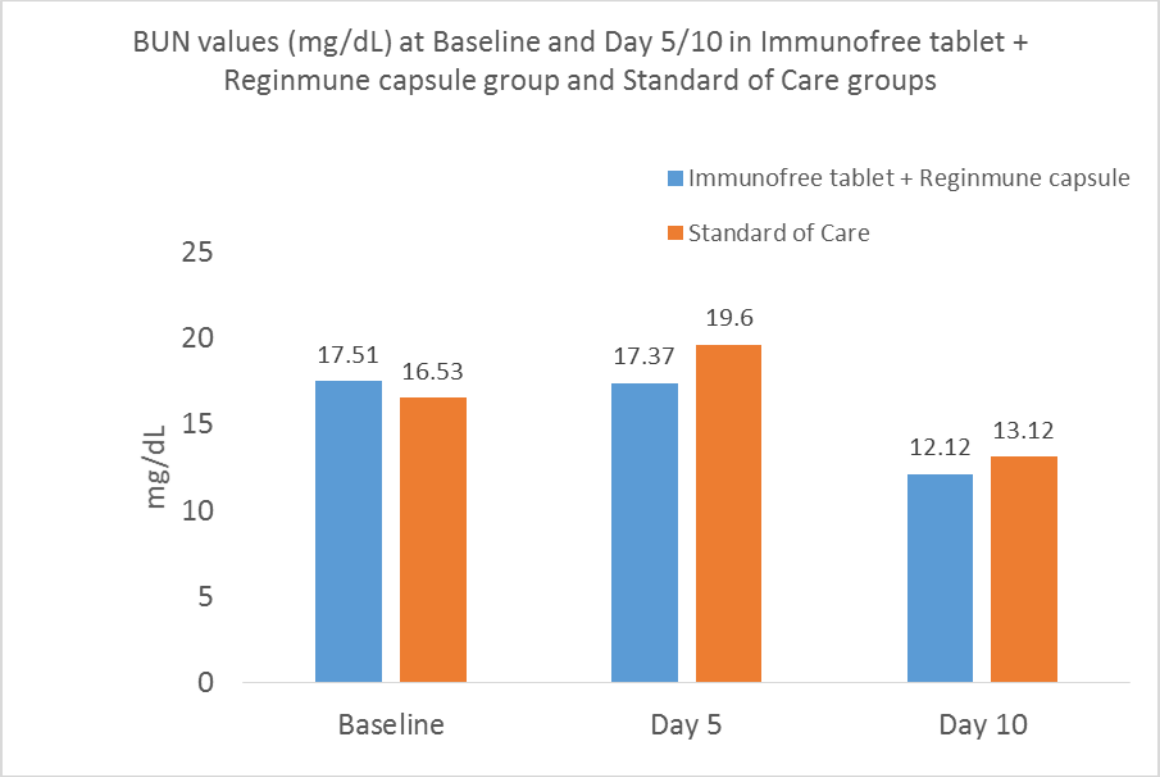


Figure 27: BUN values (mg/dL) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

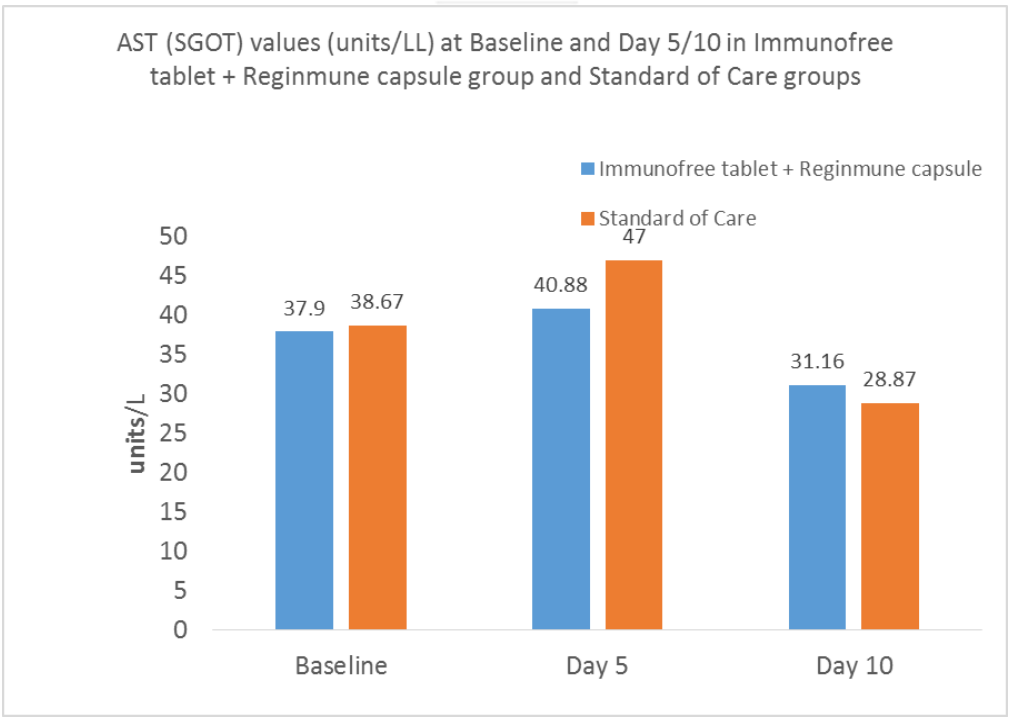


Figure 28: AST (SGOT) values (units/L) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

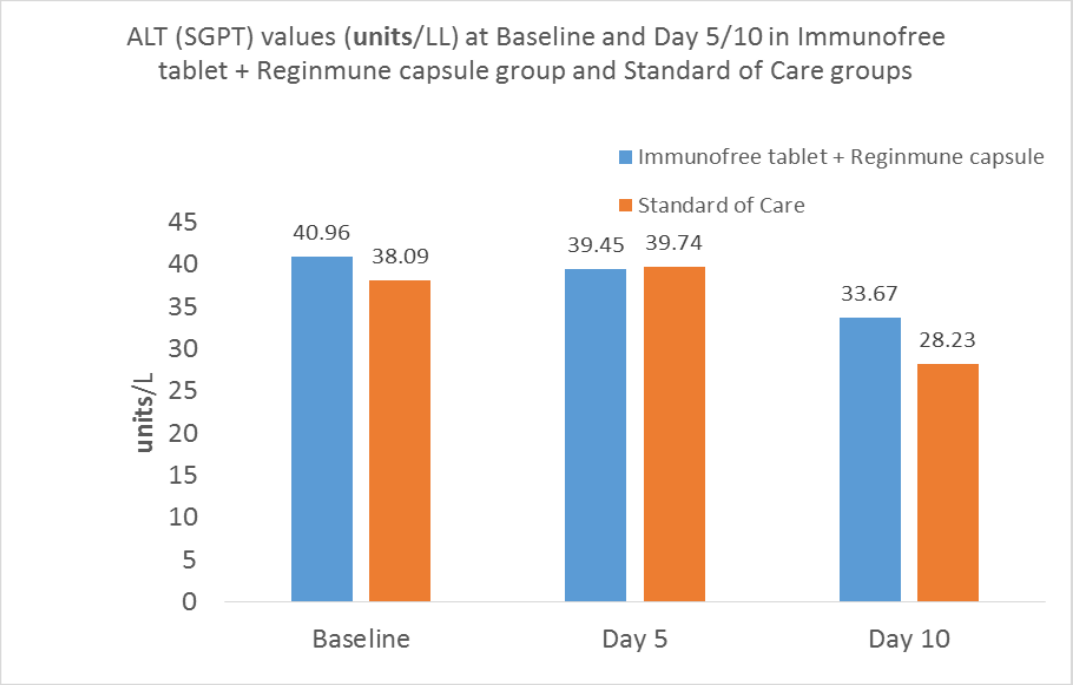


Figure 29: ALT (SGPT) values (units/LL) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

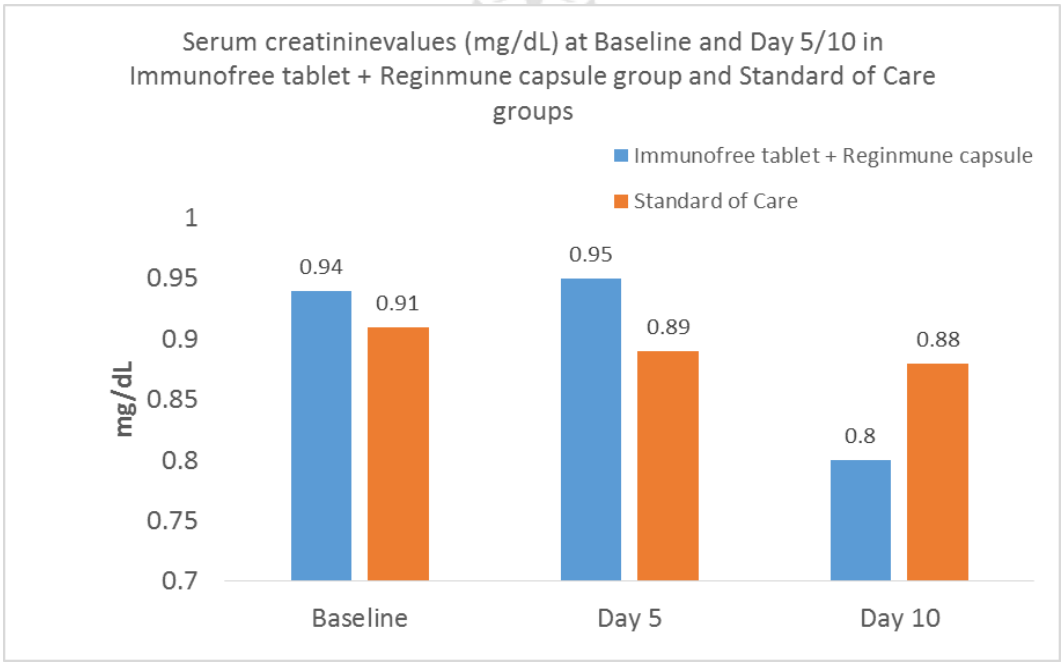


Figure 30: Serum creatinine values (mg/dL) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

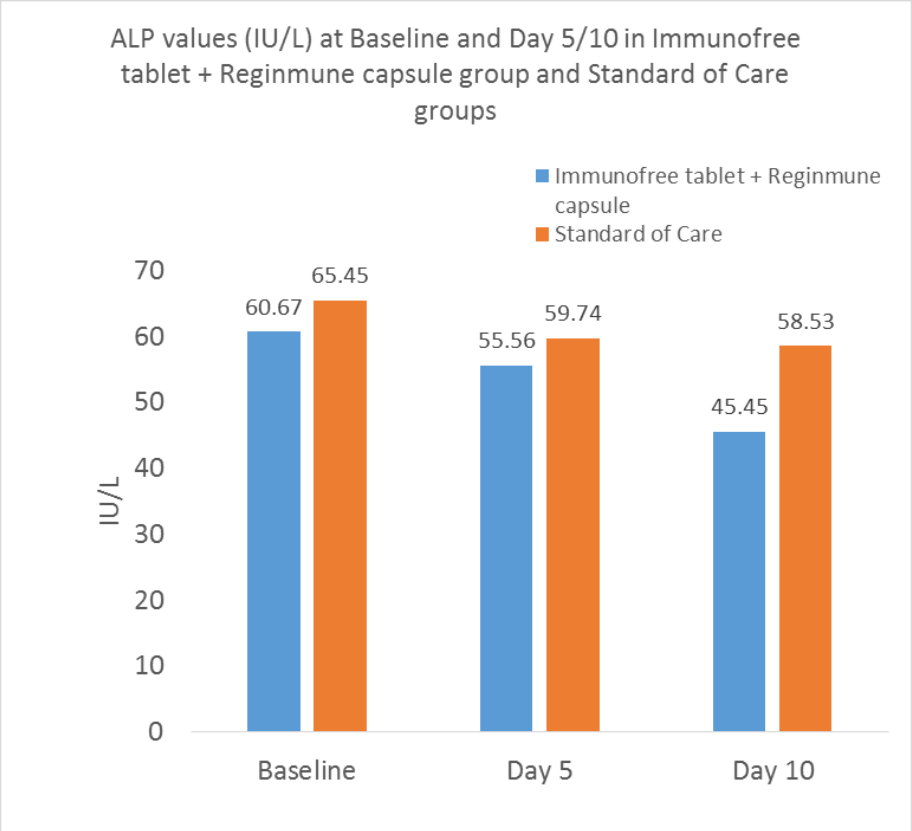


Figure 31: ALP (IU/L) at Baseline and Day 5/10 in Immunofree tablet + Reginmune capsule group and Standard of Care groups

URINALYSIS:

Table 19: Urine analysis results between Immunofree tablet and Reginmune capsule + and Standard of Care

	Parameter	Immunofree tablet and Reginmune capsule			Standard of Care		
		Baseline	Day 5	Day 10	Baseline	Day 5	Day 10
Colour	Pale yellow	50/50	50/50	4/4	50/50	50/50	14/14
Appearance	Clear	50/50	50/50	4/4	50/50	50/50	14/14
Specific gravity	Mean	1.02	1.01	1.02	1.02	1.01	1.02
	SD	0.02	0.00	0.02	0.02	0.00	0.02
	Min	1.01	1.01	1.01	1.01	1.01	1.01
	Max	1.10	1.02	1.11	1.10	1.02	1.10
PH	Mean	6.31	6.11	6.15	6.67	6.19	6.18
	SD	0.38	0.27	0.33	1.52	0.34	0.34
	Min	6.00	6.00	5.80	6.00	6.00	6.00
	Max	7.10	7.00	7.20	12.00	7.10	7.00
Glucose	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Protein	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Bile salts	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Bile pigments	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Ketones	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Urobillinogen	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Occult blood	Negative	50/50	50/50	4/4	50/50	50/50	14/14
Epithelial cells	Absent	50/50	50/50	4/4	50/50	50/50	14/14
Pus cells	0-2	40	38	2	30	32	10
	2-3	6	6	0	12	6	4
	4-6	4	6	2	8	12	0
Red cells	0-2	44	46	4	36	40	10
	2-4	4	2	0	10	4	4
	4-6	2	0	0	4	6	0
Casts	Absent	50/50	50/50	4/4	50/50	50/50	14/14
Crystals	Absent	50/50	50/50	4/4	50/50	50/50	14/14
Bacteria	Absent	50/50	50/50	4/4	50/50	50/50	14/14
UPT	Positive	0	0	0	0	0	0

ECG EVALUATION:

Table 20: ECG evaluation between Immunofree tablet and Reginmune capsule and Standard of Care groups

Parameter	Immunofree tablet and Reginmune capsule (N=50)		Standard treatment (N=50)		P-value*
ECG	Baseline	Day 5/10	Baseline	Day 5/10	0.02
Normal	26	46	23	38	
% improvement	76.9		65.2		

*The result is significant at p < .05 when compared to Day 5/10 results.

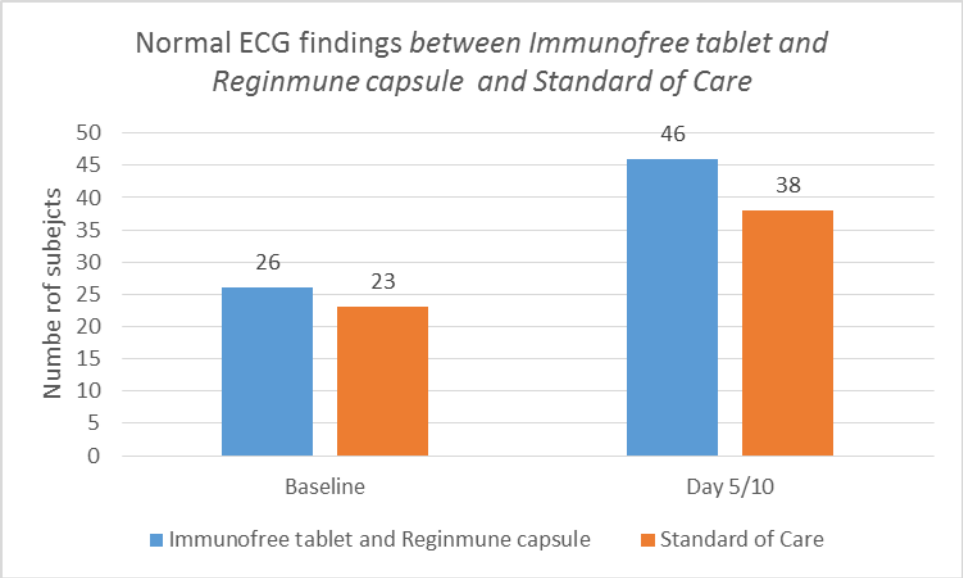


Figure 32: Number of subjects with normal ECG on baseline (day1) and day 5/10 in Immunofree tablet and Reginmune capsule and Standard of Care groups

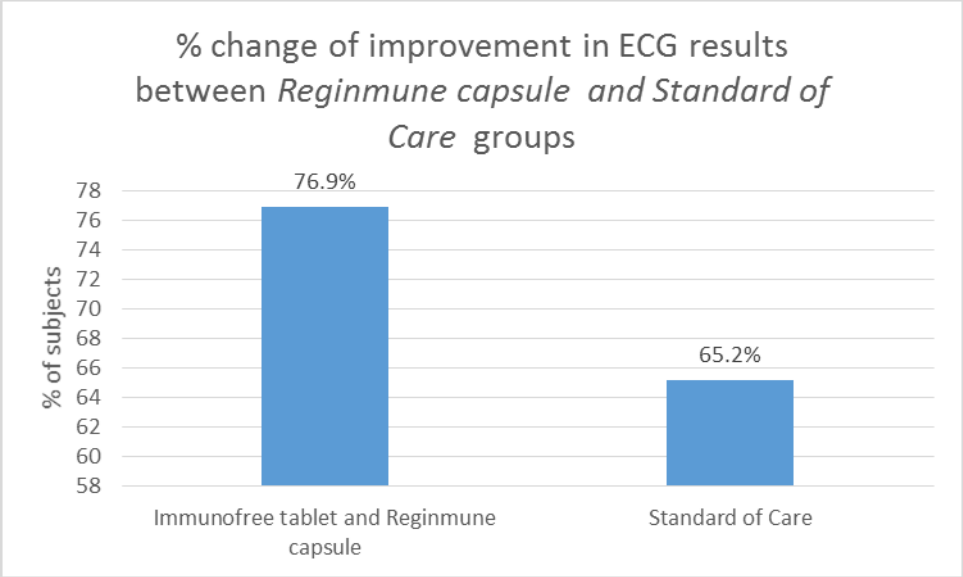


Figure 33: % change of improvement from baseline in ECG results between in Immunofree tablet and Reginmune capsule and Standard of Care groups

ADVERSE EVENTS:

Total Adverse Events

S. No.	AE	Immunofree tablet and Reginmune capsule group (N=50)	Standard of care (N=50)
1	No. of AEs	1	6

Immunofree tablet and Reginmune capsule group:

Table 21: Adverse events in Immunofree tablet and Reginmune capsule treatment group

S. No.	Sub. No.	AE	Intensity	AE treatment	Action Taken	Outcome
1.	03	Mouth Ulcers	Mild	None	None	Self-resolved

Standard of care group:

Table 22: Adverse events in Standard of care group

S. No.	Sub. No.	AE	Intensity	AE treatment	Action Taken	Outcome
1.	4	Vertigo	Mild	Non-Pharmacological treatment	None	Self-resolved
	12	Mouth Ulcers	Mild	None	None	Self-resolved
2.	13	Dizziness	Moderate	None	None	Self-resolved
3.	27	Drowsiness	Mild	None	None	Self-resolved
4.	31	Nausea and vomiting	Mild	None	None	Self-resolved
5.	42	Nausea and vomiting	Mild	None	None	Self-resolved
6	58	Vertigo	Mild	None	None	Self- resolved

VITAL SIGNS EVALUATION:

Table 23: Vital signs evaluation in Immunofree tablet and Reginmune capsule group from screening and Day 1 to Day 11.

		Immunofree tablet and Reginmune capsule group											
	Day	0 (N=50)	1 (N=50)	2 (N=50)	3 (N=50)	4 (N=50)	5 (N=50)	6 (N=6)	7 (N=6)	8 (N=6)	9 (N=6)	10 (N=6)	Day 11 (N=6)
Pulse (per minute)	**Mean**	81.18	86	81.60	84.38	82.36	81.60	81.86	79.50	82.67	79.20	93.67	78.53
	SD	9.83	81.64	6.66	8.00	8.59	7.41	8.29	5.47	8.05	5.40	10.12	3.75
	Min	66	8.50	70	69	67	68	70.00	68.00	76.00	70.00	82.00	70.00
	Max	110	69	98	100	100	100	100.00	88.00	99.00	84.00	100.00	88.00
Respiratory rate (per minute)	**Mean**	22.86	22.14	20.96	20.46	20.00	19.78	20.29	19.92	21.11	22.20	21.00	18.72
	SD	2.71	2.36	2.21	1.39	1.94	2.00	2.46	2.11	2.52	2.86	4.36	2.19
	Min	18	18	17	18	16	16	16.00	18.00	18.00	19.00	18.00	17.00
	Max	28	26	25	24	25	24	25.00	24.00	26.00	26.00	26.00	25.00
Systolic blood pressure (mm/Hg)	**Mean**	119.44	118.92	117.22	121.04	120.90	121.08	119.14	121.75	121.78	116.00	114.00	121.47
	SD	8.01	7.89	15.76	7.59	7.60	6.92	9.98	8.25	8.86	5.48	5.29	12.16
	Min	110	101	20	110	110	110	100.00	109.00	110.00	110.00	110.00	110.00
	Max	140	134	132	138	140	134	140.00	130.00	136.00	120.00	120.00	170.00
Diastolic blood pressure (mm/Hg)	**Mean**	77.06	75.78	78.26	77.76	77.14	76.96	76.29	78.83	78.67	79.20	75.33	77.68
	SD	6.20	6.01	7.79	7.16	5.38	7.18	5.97	6.63	6.00	1.79	6.11	3.07
	Min	68	60	60	60	60	40	70.00	70.00	70.00	76.00	70.00	70.00
	Max	90	87	112	100	90	90	90.00	90.00	90.00	80.00	82.00	82.00
Temperature (^{0}F)	**Mean**	95.31	97.38	97.92	97.64	96.43	96.15	97.52	97.40	97.44	96.23	96.26	97.08
	SD	2.24	2.11	1.08	2.80	1.94	1.22	1.64	1.20	0.73	2.11	2.25	2.14
	Min	95.88	96.88	96	94	95.55	96.66	94.00	94.80	96.00	36.77	36.77	36.74
	Max	102	99	101	101	98	97	99.60	99.00	98.00	98.40	98.00	98.00

Table 24: Vital signs evaluation in Standard of care group from screening and Day 1 to Day 11.

		Standard of care group											
	Day	0 (N=50)	1 (N=50)	2 (N=50)	3 (N=50)	4 (N=50)	5 (N=50)	6 (N=14)	7 (N=14)	8 (N=14)	9 (N=14)	10 (N=14)	Day 11 (N=14)
Pulse (per minute)	**Mean**	81.38	81.16	82.28	83.56	81.43	80.55	79.43	87.33	77.20	87.33	77.00	79.25
	SD	8.85	8.59	7.76	7.61	7.71	6.60	24.56	11.02	4.15	11.02	1.15	5.70
	Min	62	62	68	68	60	68	82	80	70	80	76	72
	Max	108	106	104	102	100	100	102	100	80	100	78	100
Respiratory rate (per minute)	**Mean**	22.94	22.50	24.22	20.06	21.80	19.90	18.15	22.00	20.60	21.00	17.50	18.25
	SD	2.85	2.19	12.80	1.60	8.15	1.77	5.37	4.00	1.34	1.73	1.00	1.68
	Min	18	18	18	16	16	16		18.00	19.00	19.00	16.00	16.00
	Max	29	26	88	24	76	26	25	26	22	22	18	24
Systolic blood pressure (mm/Hg)	**Mean**	118.86	118.62	118.12	121.18	120.43	122.29	111.76	119.33	128.00	123.33	120.00	119.50
	SD	7.35	8.05	15.96	7.22	6.99	6.70	33.89	9.02	13.04	11.55	0.00	2.24
	Min	108	108	20	109	109	109	9.98	110.00	110.00	110.00	120.00	110.00
	Max	132	136	134	138	134	144	140.00	128.00	140.0	130.00	120.00	120.00
Diastolic blood pressure (mm/Hg)	**Mean**	75.98	75.30	78.26	77.18	76.27	77.67	68.35	78.00	82.00	80.67	76.50	77.70
	SD	5.10	5.91	9.32	7.28	6.38	4.97	21.04	2.00	8.37	9.02	4.43	3.33
	Min	60	60	70	60	60	70	60	76	70	72	70	70
	Max	86	88	100	100	90	90	90	80	90	90	80	84
Temperature (^{0}F)	**Mean**	96.33	96.13	95.10	96.66	94.91	94.84	88.90	98.00	98.00	97.00	95.25	93.52
	SD	12.59	12.63	12.76	9.07	12.52	12.31	27.54	0.00	0.71	1.73	1.50	13.59
	Min	36.66	35.55	35.5	35.11	34.44	35.56	1.64	98.00	97.00	95.00	94.00	36.00
	Max	103	103	105	102	102	100	99.60	98.00	99.00	98.00	97.00	98.00

TELEPHONIC FOLLOW-UP VISIT ON DAY 21:

Table 25: Telephonic Follow up visit findings at Day 21

Variables	Variable	Immunofree tablet and Reginmune capsule (N=50)	Standard of Care Group (N=50)
Subject's health status	Normal	50	50
	Abnormal	0	0
Adverse events	Yes	0	0
	No	50	50
Did the AE resulted in	Yes	0	0
Death	No	50	50
Worsening sign/symptoms/	Yes	0	6
Or showing no improvement after the end of treatment	No	50	50
Protocol violations	Yes	0	0
	No	50	50
Patient withdrew informed	Yes	0	0
Consent	No	50	50
The patient lost to follow up	Yes	0	0
	No	50	50

DISCUSSION

Beginning in December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. Thus far, there are no specific therapeutic agents for

coronavirus infections. The endpoints so far tested in the literature for Covid-19 so far were all-cause mortality, length of hospital stay, Time to clinical improvement, clinical status on the ordinal scale, % of participants with clinical response, Changes in PaO2/FiO2 ratio, and change in viral load. In this study, the primary endpoint was the time to clinical improvement, defined as the time from randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live discharge from the hospital, whichever came first.

Out of 112 patients were screened, 12 were found screen failures. 10 patients of screen failures were severe covid-19 patients and 2 subjects were admitted to ICU. 100 patients who underwent randomization, 50 patients were assigned to receive Immunofree tablet + Reginmune capsule, and 50 patients to the standard of care as per randomization chart. The mean age of the subjects was 43.2 and 41.76 in Immunofree tablet and Reginmune capsule and Standard of Care groups. The mean height of the subjects was 164.93 and 163.95 in Immunofree tablet and Reginmune capsule and Standard of Care groups. The mean weights of the subjects were 62.46 and 61.78 in Immunofree tablet and Reginmune capsule and Standard of Care groups. The BMI of the subjects was 23.02 and 23.05 in Immunofree tablet and Reginmune capsule and Standard of Care groups. There were no important between-group differences in other demographic characteristics between Immunofree tablet and Reginmune capsule and Standard of Care. Data from all 100 patients who completed the study were analyzed.

The primary endpoint time to clinical improvement was estimated based on 2 point improvement (from time of enrolment) in disease severity rating on the 7-point ordinal scale. 88% of subjects in the Immunofree tablet + Reginmune capsule group were shown clinical improvement and discharged from the hospital at Day 5 when compared to 72% of subjects in the standard of care group at Day 5. 100% of subjects were clinically improved 2-point improved and discharged at Day 10 from the hospital in both Immunofree tablet +Reginmune capsule group and Standard of care groups. The odds ratio for clinical improvement was 1.418 with 95% confidence intervals of 0.9433-2.133). The P-value is 0.0020 and significant at $p<.05$. Hence the time to clinical improvement results were favouring the Immunofree tablet + Reginmune when compared to the standard of care.

Real-Time Polymerase Chain Reaction, commonly known as RT-PCR test, is the most effective test for detecting COVID-19 virus in human cells. In the RT-PCR test, a small

amount of DNA is taken and specific sequences of the genetic material are amplified to diagnose acute infection. The RT-PCR test can detect acute infection. In the RTPCR test, at Day 5 of treatment 88% of patients were virologically cured in Immunofree tablet + Reginmune capsule when compared to 72% of patients in the Standard of Cure at Day 5 of treatment. On Day 10 of treatment, all patients were virologically cured in Immunofree tablet + Reginmune capsule when compared to 88% of patients cured in the Standard of Cure at Day 10 of treatment.

Symptomatic monitoring efforts may allow for understanding the epidemiological situation of the spread of coronavirus disease 2019 (COVID-19). Studies have shown that COVID-19 could induce fever, dry cough, dyspnoea, and fatigue in infected patients. In more severe cases, infections caused viral pneumonia and could lead to severe acute respiratory distress syndrome (ARDS) and even death. Pharyngodynia, nasal congestion, and rhinorrhea have been reported in patients with COVID-19. Recently, the European Rhinology Society reported that "a significant part of the COVID-19 patients (20-60%) appear to have a loss of smell. Loss of smell can be the presenting symptom before other symptoms like coughing/fever occur. We assessed the covid-19 related symptoms at baseline and daily till hospital discharge.

In clinician global symptoms assessment, the reduction of mean symptoms (0-3 score) where 0 is nil, 1 is Mild, 2 is Moderate and 3 is severe) for cough, fever with or without chill, shortness of breath, nasal congestion, Neuro disorders, Anosmia, Ageusia, and fatigue was reduced in Immunofree tablet + Reginmune capsule group when compared to baseline and also when compared to standard of care group. However, the results were not significant between the groups.

The mean symptoms scores for cough were 1.3, 0.1, 0.9, 0.88, 0.5, 0.3, 0.1, 0.1 and 0.1 in Immunofree tablet + Reginmune group and 1.4, 1.3, 1.1, 1.0, 0.98, 0.9, 0.8, 0.6, 0.4 and 0.3 in Standard of care group (N=50) at Day 1 to 10, respectively. The mean symptoms scores for fever with or without chill were 1.4, 1.1, 0.9, 0.88, 0.7, 0.55, 0.3, 0.1, 0.1 and 0.2 in Immunofree tablet + Reginmune group and 1,4, 1,3, 1,2, 1, 0.98, 0.9, 0.9, 0.7, 0.5 and 0.4 in Standard of care group at Day 1 to 10, respectively. The mean symptoms scores for shortness of breath were 1.1, 0.8, 0.8, 0.78, 0.6, 0.4, 0.2, 0, 0.2 and 0.1 in Immunofree tablet + Reginmune group and 1.2, 1.2, 1.1, 1, 0.88, 0.8, 0.8, 0.6, 0.4, and 0.3 in Standard of care group at Day 1 to 10, respectively. The mean symptoms scores for nasal congestion were 0.9,

0.6, 0.4, 0.38, 0.1, 0.02, 0.02, 0.02 and 0 in Immunofree tablet + Reginmune group and 0.9, 0.8, 0.7, 0.5, 0.48, 0.40.4, 0.2, 0 and 0.1 in Standard of care group at Day 1 to 10, respectively. The mean symptoms scores for neuro disorders were 0.9, 0.6, 0.3, 0.28, 0.1, 0.07, 0.07, 0.07, and 0 in Immunofree tablet + Reginmune group and 1, 0.7, 0.7, 0.4, 0.38, 0.3, 0.3, 0.1, 0.1 and 0.1 in Standard of care group at Day 1 to 10, respectively. The mean symptoms scores for Anosmia were 0.8, 0.5, 0.4, 038, 0.2, 0.04, 0.04, 0.04, 0.04, 0.03 in Immunofree tablet + Reginmune group and 0.8, 0.7, 0.5, 0.4, 0.38, 0.3, 0.3, 0.3, 0.1, 0.1 and 0.3 in Standard of care group (N=50) at Day 1 to 10, respectively. The mean symptoms scores for Aguesia were 0.8, 0.5, 0.4, 0.38, 0.2, 0.04, 0.04, 0.04, 0.04 and 0.03 in Immunofree tablet + Reginmune group and 0.9, 0.8, 0.6, 0.5, 0.48, 0.4, 0.4, 0.4, 0.3, 0.1 and 0.3 in Standard of care group (N=50) at Day 1 to 10, respectively. The mean symptoms scores for fatigue were 1.4, 1.1, 1, 0.98, 0.8, 0.6, 0.4, 0.4, 0.3, 0.2 and 0.1 in Immunofree tablet + Reginmune group and 1.5, 1.4, 1.2, 1.1, 1.08, 1, 0.9, 0.7, 0.5 and 0.4 in Standard of care group at Day 1 to 10, respectively.

In Subject's global assessment of symptoms for cough, fever with or without chill, difficulty in breath, body pain, nasal congestion, GI symptoms, fatigue, and headache from Day 1 to Day 10 were reduced in Immunofree tablet + Reginmune capsule group when compared to baseline and also when compared to standard of care group. The results were not significant between the groups.

Chest radiographs are usually of limited value in the diagnosis of early stages especially in mild disease courses; however, the CT findings may be present early even before the onset of the symptoms. Chest radiographs are very helpful in the intermediate to advanced stages of COVID-19 with features of acute respiratory distress syndrome (ARDS) as well as the follow-up. In this study, % of patients have improved chest findings in Immunofree tablet + Reginmune capsule group and Standard of care groups. The % of normal chest radiographs were 44, 80, and 96 in the Immunofree tablet + Reginmune capsule group and 50, 70, and 88 in the Standard of care group at baseline, Day 5, and Day 10, respectively. However, the changes in the chest findings between both groups were not statistically significant at Day 5 and Day 10.

Predicting the course of a COVID-19 patient's disease after hospital admission is essential to improving treatment. Brigham and Women's Hospital researchers analyzed patients' levels of inflammation, known to be associated with severity of illness, by looking at C-reactive

protein (CRP) trends in 100 COVID-19 patients admitted to the hospital. They found that a rapid rise in CRP levels during the first 48-to-72 hours of hospitalization was predictive of subsequent respiratory deterioration and intubation, while steadier CRP levels were observed in patients whose condition remained stable. Brigham and Women's Hospital researchers analyzed patients' levels of inflammation, known to be associated with severity of illness, by looking at C-reactive protein (CRP) trends. They found that a rapid rise in CRP levels during the first 48-to-72 hours of hospitalization was predictive of subsequent respiratory deterioration and intubation, while steadier CRP levels were observed in patients whose condition remained stable. We analyzed the CRP values at baseline and day of discharge at day 5/10. The % reduction of CRP values was 65.14% in Immunofree tablet + Reginmune capsule when compared 47.3% in the standard of care group at Day 5 from baseline. The % reduction of CRP values was 67.55% in Immunofree tablet + Reginmune capsule when compared 47.3% in the standard of care group at Day 10 from baseline.

Procalcitonin (PCT) is a widely used biomarker to assess the risk of bacterial infection and disease progression. Early evidence suggests that PCT may also be a valuable tool in identifying COVID-19 patients at high risk for clinical deterioration or patients at risk for bacterial co-infection.PCT helps to discriminate between milder cases and more severe cases. PCT also helps to distinguish between severe bacterial pneumonia and mild viral pneumonia. If a patient has bacterial co-infection, his prognosis, and his mortality risk increase if early antibiotic treatment is not initiated. Recent clinical findings show that unnecessary antibiotic use can be safely reduced in patients with a low likelihood of bacterial co-infection indicated by low PCT values. In our study, the reductions of Procalcitonin values significantly differed in the Immunofree tablet + Reginmune capsule group and standard of care group from baseline. The mean values of Procalcitonin values were 0.2 and 0.01 in Immunofree tablet + Reginmune capsule and 0.19 and 0.03 in the standard of care at baseline and Day 10, respectively. The differences were not significant between the groups.

The blood oxygen saturation levels were improved in the Immunofree tablet + Reginmune capsule group and Standard of care group when compared to baseline. The mean results of Blood oxygen saturation values ($SpO_{2)}$ were 94.57 and 97.33 and 98.36 in Immunofree tablet + Reginmune capsule and 94.53, 96.57, and 97.33 in the standard of care group at day 0, day 5, and Day 10, respectively. The results were significant when compared to the baseline in both groups but the differences were not significant between the groups.

Regarding the hematology tests, total leukocyte test, platelets, neutrophils, and lymphocytes and the reduction rate of erythrocyte sedimentation rate were favorable to Immunofree tablet + Reginmune capsule group when compared with Standard of Care. All hematology laboratory parameters within normal range. However, the results were not significant between both groups.

The hemoglobin values were 13.05, 12.74, and 14.0 in the Immunofree tablet + Reginmune capsule group and 12.52, 15.33, and 13.63 in Standard of care at baseline, Day 5, and Day 10, respectively. The values in both groups were within the normal range.

The RBC values were 4.63, 4.55, and 5.12 in the Immunofree tablet + Reginmune capsule group and 4.47, 4.43, and 4.54 in Standard of care at baseline, Day 5, and Day 10, respectively. The values in both groups were within the normal range.

The Total leukocytes values were 58885, 7774, and 6513 in the Immunofree tablet + Reginmune capsule group and 5423, 7066, and 5565 in Standard of care at baseline, Day 5 and Day 10, respectively. The counts were increased in Immunofree tablet + Reginmune capsule and Standard of care groups but the results were not significant.

The ESR values were 17.34, 15.04, and 14.69 in the Immunofree tablet + Reginmune capsule group and 20.47, 17.73, and 10.17 in Standard of care at baseline, Day 5 and Day 10, respectively. The values were reduced in Immunofree tablet + Reginmune capsule and Standard of care groups but the results were not significant.

All Biochemical lab tests results were within the normal range between Immunofree tablet + Reginmune capsule and Standard of Care groups. There were no significant differences in the Immunofree tablet + Reginmzune capsule group when compared to the baseline and also when compared to the standard of care group.

The biochemical test SGOT values were 37.9, 40.8, and 31.16 in the Immunofree tablet + Reginmune capsule group and 38.67, 47.0, and 28.87 in Standard of care at baseline, Day 5 and Day 10, respectively. All the SGOT values were in the normal range in both groups.

The biochemical test SGPT values were 40.96, 39.45, and 33.67 in the Immunofree tablet + Reginmune capsule group and 38.09, 39.74, and 28.23 in Standard of care at baseline, Day 5 and Day 10, respectively. All the SGPT values were in the normal range in both groups.

The biochemical test Creatinine values were 0.94, 0.95, and 0.80 in Immunofree tablet + Reginmune capsule group and 0.91, 0.89, and 0.88 in Standard of care at baseline, Day 5 and Day 10, respectively. All the Creatinine values were in the normal range in both groups.

The serum sodium values were 133.15, 137.83, and 135.17 in the Immunofree tablet + Reginmune capsule group and 138.4, 139.71, and 137.37 in Standard of care at baseline, Day 5 and Day 10, respectively. All the values were in the normal range in both groups.

The serum potassium values were 4.09, 4.01, and 3.93 in the Immunofree tablet + Reginmune capsule group and 4.09, 3.92, and 3.77 in Standard of care at baseline, Day 5 and Day 10, respectively. All the values were in the normal range in both groups.

The BUN values were 17.51, 17.37, and 12.12 in the Immunofree tablet + Reginmune capsule group and 16.53, 19.6, and 13.12 in Standard of care at baseline, Day 5, and Day 10, respectively. All the values were in the normal range in both groups.

The adverse events reported were 1 and 6 in the Immunofree tablet and Reginmune capsule group and standard of care group respectively. The reported adverse events were mouth ulcers in Immunofree tablet and Reginmune capsule group and Dizziness, Drowsiness and Nausea, Vertigo and vomiting in Standard of Care, respectively. All AEs were mild and self-resolved.

ECG monitoring is advisable especially when patients experience electrolyte disturbances and use concomitant QTc-prolonging drugs. Therefore, ECG monitoring upholds a critical role in patient safety during the dose adjustment of medications used in the management of COVID-19.76.9% of subjects were improved the ECG results in the Immunofree tablet and Reginmune capsule group when compared to the standard treatment group. The results were significant between the groups.

All the vital signs were found normal at baseline, Day 5, and Day 10.

Concomitant medications were administered to the study subjects in Standard of Care as deemed necessary by the Investigator as per hospital policy.

The subjects were maintained healthy normal at a follow-up visit on Day 21 in Immunofree tablet and Reginmune capsule group and Standard of Care groups.

There were no protocol violations and deviations reported.

There were no patients lost to follow-up.

There were no patients were withdrawn their consent.

CONCLUSION

In conclusion, the time to 2-point clinical improvement as per 7 points ordinal WHO scale was seen favor in Immunofree tablet + Reginmune capsule group when compared to the standard of care. The results were significant. The Immunofree tablet + Reginmune capsule treatment was very effective in virological results. Immunofree tablet + Reginmune capsule treatment reduced the Covid 19 symptoms when compared to the baseline. It reduces the Inflammatory marker CRP levels when compared to the baseline and also when compared to the standard of care. It increases the Immune parameters of Total leukocyte counts, Platelets, Neutrophils, and Lymphocytes when compared to Standard of care. It improves the blood oxygen saturation levels. It improved the chest findings in Chest X-Ray. All the biochemical tests were normal at baseline and post-study. There were no serious adverse events reported in the study. Overall Immunofree tablet + Reginmune capsule group was very effective in treating the Covid-19 patients. The Immunofree tablet + Reginmune capsule group was tolerated very well in Covid-19 patients. The overall results in the Intervention are encouraging for Mild to Moderate Covid19 cases. A larger sample size study is suggested to confirm its effect on Moderate-Severe cases.

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