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A Randomized Open Label Parallel Clinical Study to Evaluate the Safety and Efficacy of Clevira Syrup against Common Cold and Cough

Anoop Austin[1*], Abiraamasundari[2] and Esekia Raja Selvan[1]

[1]Apex laboratories private limited R&D, B/59, SIPCOT, Industrial Park, Irungattukottai, Kancheepuram District
[2]SpinoS Life Science and Research Private limited, Door No. 29 A, Krishna Madura Vanam, Coimbatore

[*]**Corresponding author:** Anoop Austin, Apex laboratories private limited R&D, B/59, SIPCOT, Industrial Park, Irungattukottai, Kancheepuram District- 602 117

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Abstract

Objective: To compare the efficacy of Clevira Syrup in Human adult patients, with common cold and cough.

Methods: An Open Label, Balanced, Randomized, Multi-Dose, Two-Treatment, Parallel, Comparative Phase III Clinical trial to determine the safety and efficacy of Clevira syrup. 20 Patients were enrolled and received Clevira syrup along with Standard Treatment for common cold. Before enrolling in the Haematology, Biochemistry, Serology, RT-PCR and Chest X-Ray were done to the patients for Diagnostic purpose/Confirmation of infection.

Results: All the patients demonstrated safety measures with respect to Blood pressure and Pulse rate. Also, statistically significant ($p<0.0001$) improvement showed in temperature from baseline (101.74± 0.60) and at the end of the study treatment (97.71 ± 0.92).

Conclusion: The study demonstrated an expedited clinical cure with normal vital signs & hematological results, which validated that Clevira is safe and efficacious in patients with common cold and cough. The data further entrusted that Clevira syrup can be used in patients with common cold and cough and relieve the signs and symptoms, with a rapid recovery, without any adverse side effects.

Keywords

Bronchitis; Clevira Syrup; Common Cold; Cough; Emphysema; RT -PCR.

Introduction

Clevira is a Proprietary Ayurvedic Medicine. The individual herbal ingredients used are known to have variety of medicinal properties against fever of viral origin and proven to have effective antipyretic, analgesic, anti-viral and immune-modulatory properties [1].

Clevira Syrup, a polyherbal formulation from apex laboratories, is a combination of ten ingredients, used in traditional medicine for management of viral infection and other disease conditions. The formulation is made out of Papaya leaf (*Carica papaya*), Persian Neem leaf (*Melia azedarach*), King of bitters plant (Andrographis paniculata), Khus Khus root (*Vetiveria zizanioides*), Pointed Guard plant (*Trichosanthes dioica*), Nutgrass (*Cyperus rotundus*), Ginger (*Zingiber officinale*), Black Pepper (Piper nigrum), Carpet Weed (Mollugo cerviana) and Heart-leaved Moonseed stem (*Tinospora cordifolia*). These ingredients were found to have anti-inflammatory, anti-pyretic, antibacterial, anti-microbial, anti-cancer, antihelmintic, larvicidal, hepatoprotective, anti-diabetic, anti-obesity and hypolipidemic activity [2,3].

Respiratory infection pertaining to cold and cough are seasonal infections, predominant in winter season. Antibiotics are widely prescribed and drug resistance and allergy is a common clinical situation. To overcome this clinical challenge, Clevira Syrup was evaluated based upon the activity pertaining to its safety and efficacy in Viral infections [2]. With this rationale the study was conducted in Human Patients diagnosed with the above signs and symptoms. Further the outcome of the study could help in developing a new additional benefit in treating the patients, which is a common clinical situation.

Methodology

Study design

This study was an Open Label, Balanced, Randomized, Multi-Dose, Two-Treatment, Parallel, Comparative Phase III Clinical Trial to Determine the Safety and Efficacy of Clevira Syrup [2].

Ethical conduct of the study

The study was conducted as per the Ethical guidelines for biomedical research on human participants, ICMR (2017), ICH (Step 5) 'Guidance on Good Clinical Practice. The study was initiated after obtaining

proper ethical committee approvals and registered in Clinical trial registry of India (CTRI/2023/02/050004).

Patient information and consent

Patients were asked to read the informed consent document which was followed by a presentation by the trained study personnel. All the queries of the patients were resolved before obtaining their consent. Copy of the informed consent documents (English and vernacular language versions) used for obtaining consent for participation in the study. Patients were under medical supervision throughout their stay in the clinical facility to ensure safety and wellbeing of the patients.

Diagnosis and main criteria for inclusion and exclusion

Patients who met all of the following criteria were considered for enrollment in the study:

Before enrolling in the study Hematology, Biochemistry, Serology, RT-PCR will be done to the patients for Diagnostic purpose/Confirmation of infection.

Inclusion criteria

Patients meeting all of the following criteria were considered for enrollment in the study:

Patients from either sex, at an age between 18-75 years, with an oral temperature of more than 38.0°C (100.4° F) without associated rash, body pain, Malaise, Lassitude, Bronchitis, Productive Cough, Cold, Running nose, Nasal Catarrh and Sneezing. Female patients, who tested negative for pregnancy (up to two weeks prior to the study).

Exclusion criteria

- Patients with Dengue hemorrhagic fever grade III and IV
- Patients with platelet count less than 80,000/micro litre.
- Pregnant or lactating women
- Patients who have received blood or blood products transfusion, during the current illness
- Patients with Thrombocytopenia purpura (ITP), Leukemia, Hemophilia
- Patients with serum ALT level 3 times higher than the upper limit of the normal range (>165 U/L) and Impaired renal function with serum creatinine> 1.5 mg/dl (males) and > 1.4 mg/dl (females).
- Patients who were hypersensitive, to any of the components of the formulation.

Primary selection of patients

The primary selection was to assess the efficacy of Clevira from day one of enrollment/treatment initiation, soon after the confirmation of illness, which is defined as time taken for clinical recovery. Patients enrolled based on chest X-ray report. Due to common cold and cough, patient pulmonary imaging interference was evaluated by radiologist and physician. Hence 20 patients were enrolled in for treatment with Clevira syrup.

Common pulmonary report finding for patients:

- Hyperinflation of the lungs
- Air trapping
- Increased lung markings
- Flattening of the diaphragm

Sample size and treatment

Totally 22 patients were screened and 20 Patients were enrolled and received Clevira Syrup along with Standard Treatment for common cold and cough, 20 patients were received the daily dose of Clevira Syrup 10 ml twice or thrice daily for 7 to 10 days based on the severity of infection.

Data Analysis

Analysis sets

The statistical evaluation was performed using Chi-square test or Fisher exact test between the treatment groups. The proportion of patients with cold and cough on Day 10 and the percentage of patients receiving rescue therapy during the treatment period were analysis by using Pearson correlation coefficient or Spearman rank correlation. Statistical analysis was performed using XLSTAT/SAS softwares.

Safety analysis

A total of 20 patients involved in this study were successfully recovered from the infections. There were no adverse events and serious adverse events reported during course of the study. The planned safety analyses consisted of descriptive summaries of the data as relevant to the scale of data, e.g., frequency and percent for recovered days, and mean changes from baseline as appropriate. The details are provided in Table 6 and 7, respectively.

Efficacy and safety assessment

Evaluation Schedule

The first visit (Visit 01) is the screening Visit, followed by the second visit (Visit 02) which is a randomization visit/Study enrollment visit (Day 00). The third visit (Visit 03) is evaluation visit on Day 01 to 10. (Visit 04) is follow up visit after One month, if required. The visit is based upon the patient's signs and symptoms, which are reduced between the treatment days and based on the Investigator's decision.

Results

Out of 22 patients, 2 were found to be Negative for RT- PCR, hence 20 patients were enrolled for the study. Based on RT PCR results infections with the patients has been identified. Some common symptoms were observed from the patients like cough, cold, running nose, head ache, body ache and stuffy nose etc. (Figure 1).

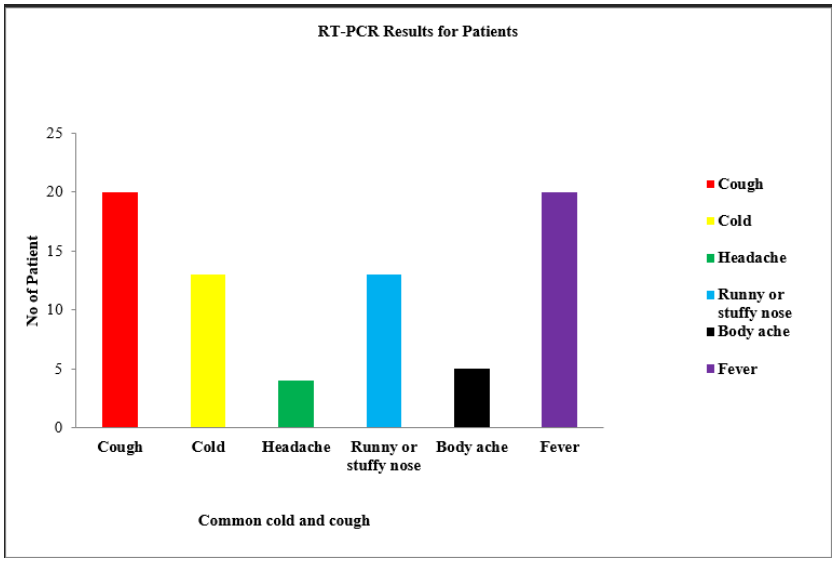

Figure 1: Identification of the infection by RT-PCR results.

X-Ray Findings and Observation

Emphysema was observed radiologically in 3 patients, where the inner walls of the alveolar sacs were found weaken and rupture, which resulted in larger air spaces, instead of many small ones. This reduces the surface area of the lungs and, in turn, the amount of oxygen that reaches your bloodstream. Postnasal drip is the annoying sensation of mucus dripping down your throat, making you cough and clear your throat frequently. In 9 patients had post nasal drip findings. Bronchitis, was observed in 7 patients, where cough was also associated symptom. One patient had inflammation in airways and respiratory tract infection (Table 1).

S.No	Patient Enrolment Number	Gender	Race	Age (years)	Chest X-Ray
1	S002-02-001	F	Asian	37	post nasal drip was found
2	S002-02-002	M	Asian	35	post nasal drip was found
3	S002-02-003	M	Asian	29	emphysema was found
4	S002-02-004	F	Asian	20	post nasal drip was found
5	S002-02-005	M	Asian	53	Bronchitis

6	S002-02-006	F	Asian	32	post nasal drip was found
7	S002-02-007	F	Asian	58	emphysema was found
8	S002-02-008	F	Asian	45	Bronchitis
9	S002-02-009	M	Asian	68	emphysema was found
10	S002-02-010	F	Asian	70	post nasal drip was found
11	S002-02-011	M	Asian	65	post nasal drip was found
12	S002-02-012	F	Asian	41	Inflammation in airways was found
13	S002-02-013	F	Asian	58	Bronchitis
14	S002-02-014	F	Asian	33	Bronchitis
15	S002-02-015	F	Asian	61	Bronchitis
16	S002-02-016	M	Asian	23	Bronchitis
17	S002-02-017	M	Asian	30	Bronchitis
18	S002-02-018	F	Asian	24	post nasal drip was found
19	S002-02-019	F	Asian	29	post nasal drip was found
20	S002-02-020	F	Asian	36	post nasal drip was found

Table 1: Chest X-ray reports for patients.

Demographic and other baseline characteristics

A total of 20 patients were enrolled into the study and their mean age, height, weight and BMI were recorded (Table 2).

S.No	Patient Enrolment Number	Gender	Race	Age (years)	Height (cm)	Weight (Kg)	BMI (Kg/m2)
1	S002-02-001	F	Asian	37	159.0	60.0	23.7
2	S002-02-002	M	Asian	35	166.0	63.0	22.8
3	S002-02-003	M	Asian	29	162.0	58.0	22.1
4	S002-02-004	F	Asian	20	153.9	52.1	21.9
5	S002-02-005	M	Asian	53	159.0	61.0	24.1
6	S002-02-006	F	Asian	32	156.0	55.0	22.6
7	S002-02-007	F	Asian	58	153.0	55.0	23.4
8	S002-02-008	F	Asian	45	150.0	53.0	23.5
9	S002-02-009	M	Asian	68	160.0	63.0	24.6
10	S002-02-010	F	Asian	70	159.0	60.0	23.7
11	S002-02-011	M	Asian	65	159.0	58.0	22.9
12	S002-02-012	F	Asian	41	154.0	56.0	23.6
13	S002-02-013	F	Asian	58	158.0	60.0	24.0
14	S002-02-014	F	Asian	33	155.0	57.0	23.7
15	S002-02-015	F	Asian	61	151.0	54.0	23.6
16	S002-02-016	M	Asian	23	161.0	62.0	23.9
17	S002-02-017	M	Asian	30	165.0	64.0	23.5
18	S002-02-018	F	Asian	24	156.0	59.0	24.2
19	S002-02-019	F	Asian	29	159.0	62.0	24.5
20	S002-02-020	F	Asian	36	157.0	59.0	23.9

Table 2: Demographic details of patients.

All patients included in the study were Asians. Table 3 explains the summarized demographic details of patients who were enrolled in the study.

Parameter	Mean	SD	Min	Max	CV%
Age (years)	42.35	16.11	20.00	70.00	38.05
Height (cm)	157.65	4.19	150.00	166.00	2.66
Weight (kg)	58.56	3.51	52.10	64.00	5.99
BMI (kg/m^2)	23.51	0.72	21.90	24.60	3.08

Table 3: Summarized Demographic details.

Efficacy Evaluation

Statistical analysis of Phase III Clinical trial of Clevira syrup

Primary and secondary end point efficacy evaluations were performed for Clevira Syrup. Primary and secondary end point of recovery analysis data from Day 1 to Day10 and safety measure analysis data for the all the patients (Demographic data, Haematology and vital signs) were performed by SAS software.

Demographic data

There is no statistically significant (p = 0.2424) difference was observed between Clevira Syrup (42.35 ± 16.11) of age and BMI (23.51 ± 16.11) (Table 4,5).

Treatments	Clevira Syrup (Day 10)
No of Subjects	20
Gender (Female: Male)	13 F: 07 M
Mean Age	42.35 ± 16.11
Mean BMI	23.51 ± 0.72

Table 4: Mean Age and BMI Average.

Source	DF	Anova SS	Mean Square	F Value	Pr> F
Treatment (Clevira Syrup)	1	1.60000000	1.60000000	1.41	0.2424

Table 5: A NOVA for Dependent Variable: Age and BMI

Hematology parameters

All hematology parameters were found to be normal and within limits, and at the end of the study period of day 10 (Table 6,7).

Patient Enrolment Number	Time of evaluation	Haematology								
		RBC count ($x10^{12}$/ µL)	Packed Cell Volume (%)	Total WB C count (/ µl)	Lymphocytes (%)	Neutrophils (%)	Eosinophils (%)	Monocyte (%)	Basophils (%)	Platelet count (× 10^9 / L)
S002-02-001	Day 00	4.1	37.2	7412	46	49	2	2	1	181.2
	Day 10	4.3	38.1	5330	38	59	0	2	1	190
S002-02-002	Day 00	4.3	41.4	7520	46	48	1	4	1	184
	Day 10	4.4	42.9	5743	34	61	0	4	1	185
S002-02-003	Day 00	4	42.3	7864	45	50	2	3	0	175
	Day 10	4.35	43.4	5672	31	65	0	3	1	182
S002-02-004	Day 00	4.6	39.6	7120	43	48	3	5	1	188.9
	Day 10	4.6	41.5	6120	32	63	0	4	1	191

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S002-02-005	Day 00	4.2	42.5	8045	41	54	1	4	0	207
	Day 10	4.5	43.3	6258	29	66	1	4	0	210.3
S002-02-006	Day 00	3.9	38.1	7680	40	52	2	6	0	182.3
	Day 10	4.6	40.2	5632	33	61	1	5	0	180
S002-02-007	Day 00	4.05	40.9	8140	49	47	0	3	1	211
	Day 10	4.45	41.7	6020	40	56	0	3	1	215.1
S002-02-008	Day 00	4.7	39.7	8365	48	44	2	5	1	190.2
	Day 10	4.6	41.4	6100	37	57	1	4	1	191
S002-02-009	Day 00	5.1	42.8	8452	51	43	3	3	0	194.3
	Day 10	5	44.7	6146	33	63	1	3	0	194.7
S002-02-010	Day 00	4.4	38.3	7968	53	42	0	3	2	213.6
	Day 10	4.7	40.6	5972	32	64	0	3	1	215
S002-02-011	Day 00	4.1	42.5	7840	48	43	2	6	1	224
	Day 10	4.3	42.7	5869	39	56	0	4	1	230.6
S002-02-012	Day 00	4	40.4	7600	52	41	3	4	0	196
	Day 10	4.2	42	5460	33	62	1	4	0	201
S002-02-013	Day 00	4.9	39.7	8000	50	48	0	2	0	184.6
	Day 10	4.8	41.3	6220	31	67	0	2	0	200
S002-02-014	Day 00	4.2	41.2	7561	52	40	1	5	2	218
	Day 10	4.4	43.6	5766	36	58	1	3	2	223
S002-02-015	Day 00	3.8	38.8	6946	49	44	2	4	1	210
	Day 10	4.7	40.7	5210	32	63	0	4	1	206.7
S002-02-016	Day 00	4.6	42.3	7455	47	46	4	3	0	207
	Day 10	5.1	44.6	5478	33	63	0	3	1	210
S002-02-017	Day 00	4.4	42	7800	48	47	2	2	1	193.4
	Day 10	4.8	43.8	5590	39	58	0	2	1	195
S002-02-018	Day 00	4.5	40.6	7645	51	42	3	4	0	198.4
	Day 10	4.9	42.1	5020	37	59	0	3	1	203.7
S002-02-019	Day 00	4.8	39.4	7459	55	37	4	4	0	196
	Day 10	5.3	41.9	5349	35	60	1	4	0	194.2
S002-02-020	Day 00	4.2	38.7	7400	54	42	1	3	0	209
	Day 10	4.6	40.5	5275	30	66	0	3	1	207

Table 6: Comparison of Hematology parameter between baseline and end line (Day 0 Vs Day 10).

Vital signs

During the course of study at Day 01 and Day 10, blood pressure, radial pulse rate, temperature and wellbeing status was enquired and recorded (Table 7). Paired sample t-test example baseline vs end of treatment comparison are dealt in (Table 8).

S.No.	Patient Enrollment Number	Treatment Group No.02	Day 0			Day 10		
			Blood pressure (mm Hg)	Radial pulse rate (Per min)	Body temperature (°F)	Blood pressure (mm Hg)	Radial pulse rate (Per min)	Body temperature (°F)
01.	S002-02-001	Common cold & cough	118/82	80	101.48	112/78	77	96.98

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02.	S002-02-002	Common cold & cough	120/77	76	101.66	123/82	81	98.96
03.	S002-02-003	Common cold & cough	124/78	73	102.38	121/82	70	96.98
04.	S002-02-004	Common cold & cough	116/83	70	101.3	118/80	74	96.62
05.	S002-02-005	Common cold & cough	121/84	79	102.2	125/81	83	97.52
06.	S002-02-006	Common cold & cough	125/81	77	100.76	119/78	81	98.96
07.	S002-02-007	Common cold & cough	127/79	82	101.12	125/80	80	98.24
08.	S002-02-008	Common cold & cough	122/86	85	101.66	124/81	81	97.7
09.	S002-02-009	Common cold & cough	130/78	77	102.56	127/83	79	98.42
10.	S002-02-010	Common cold & cough	116/84	84	102.38	123/82	80	96.26
11.	S002-02-011	Common cold & cough	124/85	87	101.84	119/77	83	98.96
12.	S002-02-012	Common cold & cough	131/78	82	102.2	127/76	79	96.8
13.	S002-02-013	Common cold & cough	126/85	78	101.3	128/80	81	97.7
14.	S002-02-014	Common cold & cough	130/80	76	102.92	125/76	78	97.52
15.	S002-02-015	Common cold & cough	124/87	80	101.3	123/86	84	98.06
16.	S002-02-016	Common cold & cough	128/79	71	100.94	125/82	76	98.78
17.	S002-02-017	Common cold & cough	131/76	73	101.48	128/79	78	97.34
18.	S002-02-018	Common cold & cough	124/75	81	101.84	126/81	84	96.26
19.	S002-02-	Commo	119/86	77	102.38	122/	80	97.1

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	019	n cold & cough				83		6
20.	S002-02-020	Common cold & cough	127/76	82	101.12	130/80	76	98.96

Table 7: Vital signs (Blood pressure, Radial pulse rate, Temperature Day 0 vs Day 10).

Difference	DF	t Value	Pr> |t|
Systolic Blood pressure	19	0.76	0.4571
Diastolic Blood pressure	19	0.65	0.5216
Pulse Rate	19	-0.88	0.3913
Temperature	19	13.87	<.0001

Table 8: Paired t-test (Baseline vs End of treatment comparison).

Patients in treatment with Clevira Syrup clearly illustrated the safety aspects with respect to Blood pressure and Pulse rate. Also, statistically significant ($p<0.0001$) improvement showed in temperature from baseline (101.74 ± 0.60) to end of the study treatment (97.71 ± 0.92) (Figure 2).

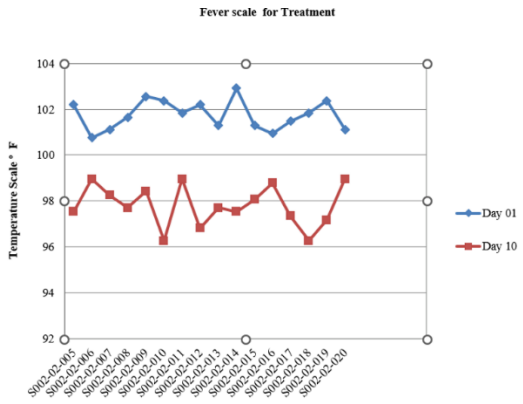

Figure 2: Comparison of fever scale between baseline and end line (Day 1 vs Day 10).

Recovery Analysis

Mean recovery day (Mean ± SD) of Treatment (Clevira Syrup were found to be 7.90 ± 1.21) (Table - 9). The Overall Clinical efficacy shows healthy recovery rate found from 20 patients.

Treatment	N Obs	Mean	Std Dev	Minimum	Maximum	Coeff of Variation
Clevira Syrup- Day 10	20	7.90	1.21	6.00	10.00	15.31

Table 9: Analysis Variable: Recovery Day.

Discussion

The main objectives of this study was to compare the efficacy of Clevira Syrup with Standard Supportive Care Treatment in Human Adult Patients with common cold and cough that affects nose, throat, and sometimes the lungs and monitor the safety and tolerability of Clevira in patient. There was a significant improvement in the quality of life of subjects in Clevira syrup related to the signs and symptoms of fever, sneezing, cough, headache, sore throat, runny nose, trouble in swallowing, compared to that of baseline.

From the study results of treatment with Clevira syrup, it is evident that the normalization of body temperature, cold symptoms, decrease in cough and infectious symptoms were down to significant levels in the treated Clevira syrup group from Day 1 to Day 10. This effect is probably due to the presence of antiviral property of *A. paniculata, C. papaya, T. cordifolia* and *T. dioica* which are the active ingredients of Clevira and it is proactive process of inhibit the viral growth [4,5]. It is clear that rapid recovery observed on Day 7 onwards in Clevira syrup group patients and herbal ingredients can boost to block [6,7] the spread of virus and prevent initial replication cycles [8] due to presence of *M. azedarach* [9] in Clevira. Thus, our present studies demonstrated that, Clevira is having a good anti-allergic activity [10]. It is also evident that Clevira is having a significant improvement from common cold and cough from Day 7 to Day 10 and it elucidated best recovered at end of the study Day 10 for 20 patients.

There was a significant improvement in the quality of life of subjects in Clevira group related to the fatigue, sense of feeling week, dizziness and sense of feeling depressed, compared to that of baseline and control group [11]. The overall response of Clevira group showed remarkable improvement [12] and were completely free from viral symptoms and very good subject compliance was also observed. There were no clinically significant adverse events during the entire study period [1].

Clevira, with its polyherbal ingredients showed a significant antiviral action against coronavirus, when given in addition to the standard of care medications suggested by Indian Council of Medical Research (ICMR), which is also an recommended formulation for mild to moderate COVID-19 patients [1].

The antiviral property is also elucidated by the presence of 52 major phyto-constituents [2], which was identified by in silico studies, further substantiating its antiviral properties. From the Clinical study, it is clearly evaluated that all the hematological parameters were found to be normal and within normal limits at the end of the study period (Day 10) and all patients in treatment with Clevira Syrup (N = 20) showed no side effects and safety issues with respect to the parameters tested in this study.

Hence, this Phase III clinical study clearly demonstrates its clinical cure and normal vital signs & hematological results, to understand that Clevira Syrup is safe and efficacious in patients with Common cold signs and symptoms of the viral infection and for a rapid recovery without any adverse effects.

Conclusion

The Overall Clinical efficacy clearly demonstrates it good recovery percentage, which was observed among the infected patients for treatment with Clevira Syrup. Moreover, Clevira Syrup demonstrated, expedited

cure, clinically on Day 7 to 10, showing the marked improvement of cure status, from the clinical signs and symptoms.

This randomized, Phase III clinical study has shown that Clevira is as clinically effective and safe as Contagious Respiratory Illness by Viruses causing cold and cough that infect the nose, throat, and respiratory track.

Conflict of Interest

There is no conflict of Interest.

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