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RESEARCH ARTICLE

A Randomized Open Label Parallel Clinical Study to Evaluate the Safety and Efficacy of Clevira Tablets against Influenza Viruses

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ABSTRACT

Objective: The aim of the study was to compare the efficacy of Clevira tablets in Human adult patients, with Influenza A&B and Vital flu. **Methods**: This study was an open label, balanced, randomized, multi-dose, two-treatment, parallel, and comparative Phase III clinical trial to determine the safety and efficacy of Clevira Tablets. Twenty patients were enrolled and received Clevira Tablet along with Standard Treatment for Influenza A&B and other respiratory viral infections. Enrollment was based on the diagnosis of hematology, biochemistry, serology, RT-PCR, and chest X-ray and inclusion, and none of the exclusion criteria and included in the study. **Results:** All the patients demonstrated safety measures with respect to blood pressure and pulse rate. Furthermore, statistically significant ($P < 0.0001$) improvement showed in temperature from baseline (102.03 ± 0.64) and at the end of the study period (98.14 ± 0.70). **Conclusion:** The study demonstrated an expedited clinical cure with normal vital signs and hematological results which validated that Clevira is safe and efficacious in patients with Influenza A&B and Viral flu. The data further entrusted that Clevira can be used in infected patients with Influeza A&B and Viral Flu, and relieve the signs and symptoms, with a rapid recovery, without any adverse side effects.

Keywords: Adverse events, Clevira, Influenza virus, Phase III clinical trial, RT-PCR

INTRODUCTION

In recent days, the usage of many herbal formulations for various illnesses has increased. Clevira is one among them, which is a polyherbal formulation consisting of many ingredients, which has antiviral activity against HSV-1 and HSV-2. Pre-clinical, clinical, and docking studies have also shown its antiviral activity against, fever of viral origin.

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

Clevira tablet is made out of *Carica papaya*, *Melia azedarach*, *Andrographis paniculata*, *Vettivera zizanoides*, *Tricosanthus dioica*, *Cyperus rotundus*, *Zingiber officinale*, *Piper nigrum*, *Mollugo cerviana* and *Tinospora cordifolia*, which is a proprietary ayurvedic medicine. The individual herbal drugs used are known to have a variety of medicinal values, against fever of viral origin and proven to have effective antipyretic, analgesic, anti-viral, and immunity-boosting properties.[2]

These ingredients were found to have anti-inflammatory, anti-pyretic, antibacterial, anti-microbial, anti-cancer, antihelmintic, larvicidal, hepatoprotective, antidiabetic, antiobesity, and hypolipidemic activity.[3]

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METHODS

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 tablets.

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.[4] The study was initiated after obtaining proper ethical committee approvals and registered in the Clinical Trial Registry of India (CTRI/2023/02/050004).[5]

Patient Information and Consent

Patients were asked to read the informed consent document which was followed by a presentation by the trained study personnel.[6] 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.[7]

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, and RT-PCR were done done to the patients for diagnostic purpose/ confirmation of infection.[8]

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 and 75 years, with an oral temperature of more than 38.0°C (100.4° F) with or without associated rash, body pain and joint pain, severe headache especially behind the eyes, nausea, and vomiting.
- Mild to moderate cases of Influenza and other respiratory viral infections associated disease as defined by the WHO.
- With Viral fever accompanied by thrombocytopenia with a platelet count between 80,000/μL and 100,000/μL, along with stable vitals like pulse and blood pressure.
- Female patients who tested negative for pregnancy (up to 2 weeks before the study).

Exclusion Criteria

The following criteria were excluded from the study:

- Patients with dengue hemorrhagic fever grades III and IV
- Patients with platelet count <80,000/μL
- Pregnant or lactating women
- Patients who have received blood or blood products transfusion, during the current illness
- Patients with thrombocytopenia purpura (ITP), leukemia, and 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.[9] Patient enrollment was confirmed by RT-PCR/CT value with symptoms of Influenza and other respiratory viral infections.

Sample Size and Treatment

Totally, 22 patients were screened and 20 patients were enrolled and received, Clevira Tablet along

with standard treatment for Influenza A&B, Viral Flu. Twenty patients were received the daily dose of 01 or 02 Clevira tablets along with standard treatment, twice a day for 7–10 days, based on the severity of infection.

Data Analysis

Analysis sets

The statistical evaluation was performed using Chi-square test or Fisher's exact test between the treatment groups. The proportion of patients with Influenza and Flu, a contagious respiratory illness caused by Influenza viruses that infect the nose, throat, and sometimes the lungs on day 10 and the percentage of patients receiving rescue therapy during the treatment period were analyzed using Pearson correlation coefficient or Spearman rank correlation. Statistical analysis was performed using the appropriate software.[10]

Safety analysis

A total of 20 patients were dosed and 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, for example, frequency and percent for recovered days, and mean changes from baseline as appropriate. Frequency and percentage of patients were to be provided for each categorical variable by treatment group.

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 subdivided into two, namely, (i) evaluation visit on day 01–10 (Treatment Arm 0) and (ii) evaluation visit for 1 month (Treatment Arm 03) if required and followed by the final fourth visit (Visit 04) which is a follow-up visit after 1 month, if required. The visit is based on 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, two were found to be negative for RT-PCR, out of 20 enrolled patients 15 were positive for Influenza A virus, four were positive for Influenza B virus and one was diagnosed with viral fever [Figure 1].

Some common symptoms were observed from the patients, such as fever runny nose, headache, fatigue, sneezing, cough, sore throat, body ache, weakness, loss of appetite, nasal congestion, and stuffy nose.

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 1].

All patients included in the study were Asians. Table 2 explains the summarized demographic details of patients who were enrolled in the study.

Efficacy Evaluation

Statistical analysis of phase III clinical trial of Clevira tablet

Primary and secondary end-point efficacy evaluations were performed for Clevira Tablet. Primary and secondary end point of recovery analysis data from Day 01 to Day 10 and safety

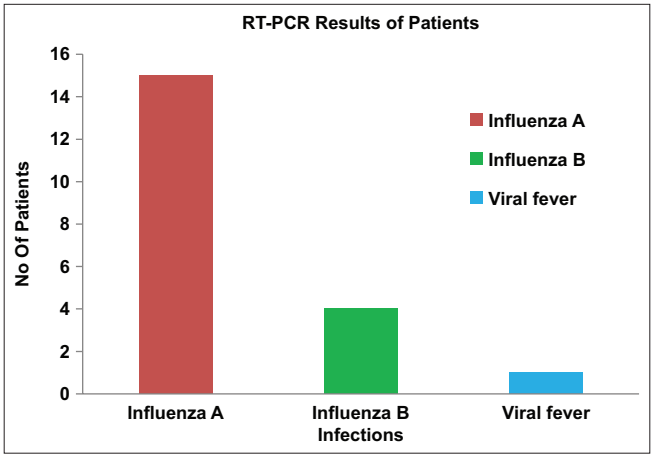

Figure 1: RT-PCR interpretation of the patients

Table 1: Demographic details of patients enrolled

S. No	Patient enrolment code	Gender	Race	Age (years)	Height (cm)	Weight (Kg)	BMI (Kg/m^2)
1	S002-01-001	F	Asian	42	158.0	62.0	24.8
2	S002-01-002	F	Asian	29	149.0	56.0	25.2
3	S002-01-003	F	Asian	32	153.0	60.0	25.6
4	S002-01-004	F	Asian	58	158.0	58.0	23.2
5	S002-01-005	M	Asian	27	160.0	65.0	25.3
6	S002-01-006	F	Asian	28	155.0	59.0	24.5
7	S002-01-007	M	Asian	71	159.0	60.0	23.7
8	S002-01-008	F	Asian	41	151.0	59.0	25.8
9	S002-01-009	F	Asian	19	148.0	48.0	21.9
10	S002-01-010	M	Asian	21	162.0	66.0	25.1
11	S002-01-011	F	Asian	49	157.0	56.0	22.7
12	S002-01-012	M	Asian	20	155.0	58.0	24.1
13	S002-01-013	M	Asian	57	158.0	60.0	24.0
14	S002-01-014	F	Asian	29	151.0	53.0	23.2
15	S002-01-015	M	Asian	53	157.0	61.0	24.7
16	S002-01-016	F	Asian	43	153.0	58.0	24.7
17	S002-01-017	M	Asian	65	159.0	59.0	23.3
18	S002-01-018	F	Asian	19	145.0	44.0	20.9
19	S002-01-019	M	Asian	27	160.0	57.0	22.2
20	S002-01-020	M	Asian	62	155.0	56.0	23.3

measure analysis data for the all the patients (Demographic data, hematology, and vital signs) were performed by SAS software.

Demographic data

There is no statistically significant (P = 0.6006) difference observed between Clevira tablet (39.60 ± 16.82) of age [Tables 3 and 4].

Hematology parameters

All hematology parameters were found to be normal and within limits, and at the end of the study period of day 10 [Tables 5].

Vital signs

During the course of study at day 01 and day 10, blood pressure, radial pulse rate, temperature, and well-being status were enquired and recorded, [Table 7]. Paired sample t-test example baseline versus end of treatment comparison is given in Table 8.

Patients in treatment with Clevira tablets clearly illustrated the safety aspects with respect to blood pressure and pulse rate. Furthermore, statistically significant (P < 0.0001) improvement showed in temperature from baseline (102.03 ± 0.64) to end of the study treatment (98.14 ± 0.70) [Figure 2].

Table 2: Demographic details of patients

Parameters	Mean	SD	Min	Max	CV%
Age (years)	39.60	16.82	19.00	71.00	42.47
Height (cm)	155.15	4.53	145.00	162.00	2.92
Weight (kg)	57.75	5.06	44.00	66.00	8.76
BMI (kg/m^2)	23.91	1.32	20.90	25.80	5.53

Table 3: Mean value for age and BMI

Treatments	(Clevira tablet along with standard treatment) Day 10
No of Subjects	20
Gender (Female: Male)	11 F: 09 M
Mean Age	39.60±16.82
Mean BMI	23.91±1.32

Table 4: The ANOVA procedure for dependent variable: Age and BMI

Source	DF	Anova SS	Mean square	F-value	Pr >F
(Clevira Tablet)	1	75.62500000	75.62500000	0.28	0.6006

Recovery Analysis

Mean recovery day (Mean ± SD) of treatment (Clevira tablet was found to be 8.00 ± 1.30) [Table 9]. The

Table 5: Comparison of hematology parameter between baseline and end line (Day 00 vs. Day 10)

Patient Enrolment Code	Time of evaluation	Hematology								
		RBC count ($\times10^{12}/\mu L$)	Packed Cell Volume (%)	Total WBC count (/μL)	Lymphocytes (%)	Neutrophils (%)	Eosinophil (%)	Monocyte (%)	Basophils (%)	Platelet count ($\times10^{9}/L$)
S002-01-001	Day 00	4.4	36.8	10000	45	50	2	3	0	139
	Day 10	5.3	38.1	6650	39	59	1	1	0	184
S002-01-002	Day 00	4.6	37.2	9710	37	59	1	2	1	125
	Day 10	5.2	39.3	6920	38	56	2	4	0	178
S002-01-003	Day 00	4.3	39.5	10307	32	60	0	8	0	152.3
	Day 10	5.6	40.8	7900	39	54	1	5	1	245
S002-01-004	Day 00	4.4	40.7	9950	36	57	1	5	1	164
	Day 10	4.62	41.2	6542	36	57	3	3	1	214.3
S002-01-005	Day 00	5.1	42.4	10850	54	40	3	3	0	160.7
	Day 10	5.01	43.9	7843	37	56	0	6	1	210
S002-01-006	Day 00	4.94	36.6	10763	58	38	0	3	1	154
	Day 10	5.1	39.2	7204	38	56	1	5	0	204.6
S002-01-007	Day 00	4.3	41.8	8612	52	44	2	2	0	98.1
	Day 10	4.92	43.4	6250	34	63	0	2	1	122
S002-01-008	Day 00	4.23	39.7	9624	37	57	1	4	1	160
	Day 10	5.3	41	6471	35	59	2	3	1	219
S002-01-009	Day 00	4.7	40.9	8007	51	39	3	6	1	151
	Day 10	5.6	42.3	5913	37	57	1	5	0	207
S002-01-010	Day 00	4.1	43.6	8730	43	46	5	5	1	120.4
	Day 10	5.32	43.2	5849	33	63	1	3	0	191
S002-01-011	Day 00	4	38.9	8040	44	51	1	4	0	134
	Day 10	5.21	42.7	5981	38	59	0	3	0	235
S002-01-012	Day 00	4.6	41.6	9562	52	43	2	2	1	164
	Day 10	4.8	42.4	6007	34	62	1	2	1	217
S002-01-013	Day 00	5.2	42.2	9145	50	46	0	3	1	167
	Day 10	4.92	44.7	6143	31	66	1	2	0	227

Day 00-screening baseline

overall clinical efficacy shows a healthy recovery rate found from 20 patients.

DISCUSSION

The main objectives of this study were compared the efficacy of Clevira tablets with tandard supportive care treatment in human adult patients with Influenza A&B and Flu, a contagious respiratory illness caused by Influenza viruses infect the nose, throat, and sometimes the lungs and monitor the safety and tolerability of Clevira in patients with Influenza A&B and Flu, a contagious respiratory illness caused by Influenza viruses at infect the nose, throat, and sometimes the lungs**.**

Influenza is commonly called the flu. At present, the efforts of various countries are focused on the rapid diagnosis and isolation of patients, as well as to find a cure for Influenza, to combat the serious impact of the disease and contagious respiratory illness. It is vital to study the promising effects of various existing approved antivirals drugs for SARS-CoV-2 like Clevira, which has been suggested to be an effective and safe for respiratory infections.[1] The pharmacological properties of *C. papaya, M. azedarach, A. paniculata, V. zizanoides, T. dioica, C. rotundus, Z. officinale, P. nigrum, M. cerviana,* and *T. cordifolia* plants have a concrete approach for developing healthy therapeutic options against respiratory virus infection caused by Influenza A, Influenza B and contagious respiratory illness.

Table 6: Vital signs (Blood pressure, radial pulse rate, and temperature day 00 vs. Day 10)

S. No.	Patient Enrolment Code	Treatment Group	Day 01			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.	S002-01-001	Influenza A	116/80	78	102.2	121/79	79	98.24
02.	S002-01-002	Influenza A	121/76	74	101.6	119/82	75	98.78
03.	S002-01-003	Influenza A	130/76	70	102.38	126/80	72	97.88
04.	S002-01-004	Influenza A	114/80	65	102.02	118/83	68	98.96
05.	S002-01-005	Influenza A	120/80	80	102.2	120/84	83	98.06
06.	S002-01-006	Influenza A	127/85	82	101.84	125/81	78	98.42
07.	S002-01-007	Viral fever	122/80	87	103.1	123/78	76	98.6
08.	S002-01-008	Influenza A	128/87	81	102.2	126/85	82	97.7
09.	S002-01-009	Influenza B	129/78	79	102.38	130/80	80	99.14
10.	S002-01-010	Influenza A	126/79	71	101.46	129/82	75	98.24
11.	S002-01-011	Influenza A	126/81	84	102.32	124/82	81	98.42
12.	S002-01-012	Influenza B	132/84	80	102.2	130/80	83	96.98
13.	S002-01-013	Influenza A	124/84	76	102.38	125/83	80	97.16
14.	S002-01-014	Influenza A	130/81	72	102.74	127/79	77	98.42
15.	S002-01-015	Influenza A	120/86	81	101	122/85	83	98.78
16.	S002-01-016	Influenza A	126/79	77	101.9	128/78	79	98.24
17.	S002-01-017	Influenza A	132/81	78	100.9	131/80	84	96.26
18.	S002-01-018	Influenza B	120/82	82	102.46	122/83	80	98.42
19.	S002-01-019	Influenza B	119/81	74	102.74	120/78	78	97.7
20.	S002-01-020	Influenza A	123/84	76	100.6	125/85	81	98.42

Table 7: Paired sample t-test example (Baseline vs. end of treatment comparison) Clevira Tablet

Difference	DF	t-value	Pr> |t|
Systolic blood pressure	19	−0.55	0.5906
Diastolic blood pressure	19	−0.24	0.8142
Pulse rate	19	−1.54	0.1391
Temperature	19	19.26	<0.0001

Availability of potential phytochemicals of flavonoids, alkaloids, lignan, and coumarins are targeting the viral infections and arrest the spreading of infections. Flavonoid components of quercetin[4] have significant inhibitory activity against NS2B-NS3 serine protease,[5] particularly against dengue virus serotype 2, and exert its antiviral property by preventing viral assembly.[6] Coumarins in *T. dioica* are effective in inhibiting the viral growth and it provides faster relief in conditions of viral fever[7] in chikungunya[8] and dengue[9] and other respiratory illness. However, the present study has shown that there was a significant improvement in the patients recovery on day 7 to day 10, who got treated with Clevira tablets along with standard treatment.

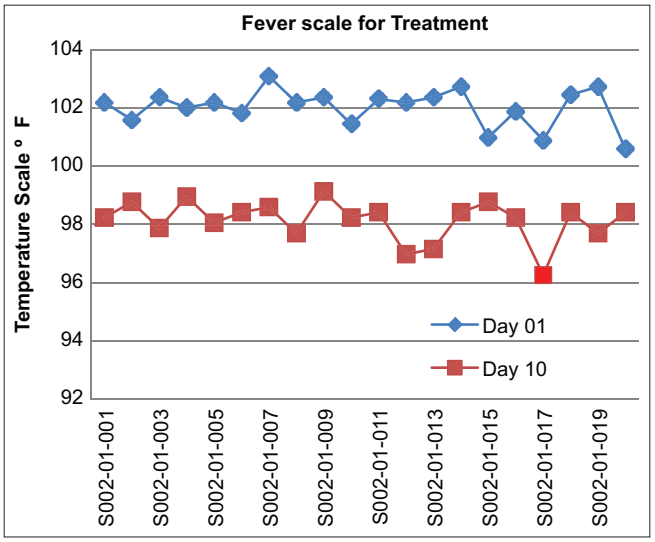

Figure 2: Comparison of fever scale between baseline and end line (Day 01 vs. Day 10)

From the study results, it is clear that the normalization of body temperature was evident on day 5 onward in Clevira treated group. Thus, Clevira is having a good antipyretic activity. It is also evident that Clevira is having a significant improvement ($P < 0.001$*) in the Arthralgia and

Table 8: Analysis variable: Recovery day

Analysis variable: Recovery day						
Treatment	**N Obs**	**Mean**	**Std Dev**	**Minimum**	**Maximum**	**Coeff of Variation**
Treatment (Clevira Tablet) Day 10	20	8.00	1.30	6.00	10.00	16.22

Myalgia score on day 3, 4, and 5, suggesting a good analgesic and antipyretic activity of Clevira. All the hematological and biochemical parameters were within the normal range with significant reduction in hematocrit and WBC count, suggesting the anti-viral property and immune-modulatory capacity of Clevira against dengue infections and other viral infectious fever conditions. Unaltered renal and liver function tests suggest the safety of Clevira tablets at the recommended dose.[1]

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,[10] compared to that of baseline and control group. The overall response of Clevira group showed remarkable improvement and was 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]

CONCLUSION

This randomized, Phase III, and multicenter study has shown that Clevira is clinically effective and safe as contagious respiratory illness by Influenza virus A&B that infect the nose, throat, and sometimes the lungs. The overall clinical efficacy shows that a high recovery percentage was observed in infected patients for treatment Clevira tablet. However, the Clevira tablet was showed expedited cure clinically on day 07 to day 10 showing the marked improvement of cure status.

All hematology laboratory parameters were found to be normal and within limit at the end of the study period (Day 10) and all patients in treatment with Clevira Tablet (n = 20) showed no safety issues with respect to blood pressure, pulse rate, and temperature.

As there is an expedited clinical cure and normal vital signs and hematological results showed that Clevira is safe and efficacious in patients with Influenza and Flu, a contagious respiratory illness caused by influenza viruses. Henceforth, Clevira can be used in infected patients with Influenza A&B and Viral Flu to relieve the signs and symptoms of the viral infection and for a rapid recovery without any adverse effects.

CONFLICTS OF INTEREST

There are no conflicts of Interest.

ACKNOWLEDGMENTS

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