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Efficacy and Safety of Inosine Pranobex in COVID-19 Patients: A Multicenter Phase 3 Randomized Double-Blind, Placebo-Controlled Trial

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Inosine pranobex (IP), an immunomodulatory agent, is used in the treatment of various viral infections. The results of a phase 3 randomized controlled trial are reported, evaluating the efficacy and safety of IP in the treatment of mild to moderate COVID-19. It includes 416 symptomatic patients with confirmed SARS-CoV-2 infection. In addition to a defined standard of care, patients randomly (1:1) receive either IP 500 mg tablet (IP group) or a matching placebo (placebo group) at 50 mg kg^{-1} body weight/day rounded to the nearest 500 mg dose (maximum 4 g day^{-1}) administered in 3–4 divided doses for 10 days. Compared to the placebo group, IP group shows significantly higher rates of clinical response (CR) and clinical cure (CC) on Day-6 for both non-hospitalized patients and the total population. IP group shows significantly earlier CR and CC with fewer adverse events and no mortality. Based on these findings and the fact that IP increases natural killer cell-mediated cytotoxicity of virus-infected cells as an early immune response to viral infection and enhances NKG2D ligand expression, it is concluded that IP should be started early to maximize the benefit in mild to moderate COVID-19 patients. (Trial registration number: CTRI/2021/02/030892).

1. Introduction

The COVID-19 pandemic created a global health crisis and led to an accelerated search for drugs and vaccines to reduce morbidity, mortality, and spread of the disease. In this paper, we share our experiences gained during the repurposing of inosine pranobex (IP), also known as inosine acedoben dimepranol, Isoprinosine, or methisoprinol, to treat COVID-19 patients.

The drug is an immunomodulatory agent with broad spectrum antiviral properties and is licensed since 1971 in several countries for the treatment of various viral infections.[1,2] Based on the results of this current study, IP has been approved in India for restricted emergency use in the management of mild to moderate COVID-19; IP has also been approved for the management of Influenza and other acute respiratory viral infections, Mucocutaneous herpes

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simplex, Genital wart, and subacute sclerosing panencephalitis.[3]

It enhances both innate and adaptive immunity and controls viral infections including those by coronaviruses.[1,4]

In the first line of defense against any viral infection, natural killer (NK) cells kill infected cells rapidly and directly, without waiting for antigen presentation or recognition.[2] IP promotes an early and sustained increase in the NK cell component of circulating lymphocytes,[5] and enhances the synthesis of purine nucleotide, expression of NKG2D ligand, and cellular susceptibility to NKG2D-dependent NK cell cytotoxicity in metabolically active cells.[6] It potentiates neutrophil, monocyte, and macrophage chemotaxis and phagocytosis.[1] Soon after the occurrence of a viral infection, the cellular RNA and protein synthesis is markedly depressed. IP enhances host RNA synthesis while diminishing viral RNA synthesis.[1]

Moreover, IP modulates adaptive immunity as well by triggering a surge in the number of IgG and complement surface markers.[1] This, in turn, enhances the NK activity of eosinophils.

This suggests IP may offer therapeutic benefits in the management of COVID-19, especially during this pandemic.

In a phase 2 proof-of-concept study,[7] in mild/moderate COVID-19 patients, a sub-group analysis showed that IP, when added to standard of care, produced significantly higher clinical response (CR) at Day-14 than standard of care only (100.00% vs 69.23%; P = 0.03). IP was well-tolerated without any serious adverse events or new safety concerns.

Therefore, this double-blind phase-3 study aimed to evaluate the efficacy and safety of IP 500 mg tablets (50 mg kg^{-1} body weight/day) compared to a matching placebo when added to a defined standard of care (DS), in symptomatic COVID-19 patients with mild to moderate severity. Results of this study were presented to the office of the Drugs Controller General of India (DCGI) and the DCGI has granted permission to manufacture and market IP for restricted emergency use as an add-on therapy for the treatment of COVID-19 patients.[3]

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2. Results

2.1. Demographics

Figure 1 shows the CONSORT flow diagram of the study population. **Table 1** shows the demographic characteristics of 416 enrolled patients. The commonest comorbidities were diabetes [29 (6.97%)] and hypertension [17 (4.09%)] (Table S1, Supporting Information). In Total Population (TP), 206 were randomized to IP and 210 to placebo.

Patient compliance for the treatment was 100% in IP group and 99.71% in placebo group (Table S2, Supporting Information). Early discontinuation was 2.16% and discontinuation due to adverse events was 1.2% (Table S3, Supporting Information). Twenty-one patients (10.19%) on IP and seventeen patients (8.10%) on placebo discontinued from the study. Nine patients (4.37%) on IP and eight (3.81%) on placebo were lost to follow-up. Six patients (2.91%) on IP and four (1.90%) on placebo discontinued due to high uric acid (Table S4, Supporting Information). Summary of the population set for TP and Non Hospitalized Patients (NHP) is provided in Tables S5 and S6, Supporting Information, respectively.

2.2. Primary Endpoints

CR on Day-6 in NHP (**Table 2**, **Figure 2**a) was significantly higher in IP group than in placebo group [Intention to treat (ITT): **Δ 23.71%**, $P < .001$; per protocol (PP) population: **Δ 27.79%**, $P < .001$]. However, CR on Day-11 in TP was similar between the two groups both in ITT and PP analysis (Table 2).

Figure 2a,b shows that the CR on Day 6 was significantly higher in IP group than in placebo group in both nonhospitalized and total population, respectively.

2.3. Secondary Endpoints

2.3.1. Clinical Response (CR)

CR on Day-6 in TP was significantly higher in IP than in placebo group both in the ITT and PP populations (Δ 17.09%, $P < .001$ and Δ 19.83%; $P < .001$ respectively, Figure 2b, Table 2). CR on Day-11 in NHP showed no significant difference between the two groups either in ITT or PP analysis (Table 2).

2.3.2. Clinical Cure (CC)

CC on Day-6 (Table 2, **Figure 3**a,b) was significantly higher in IP group than in placebo group among ITT-NHP (Δ22.96%; $P < 0.001$) as well as ITT-TP (Δ14.6%; P = 0.003)]. CC on Day-11 (Table 2) in ITT-TP and in ITT-NHP showed no significant difference between the two groups. Similar results were seen in PP population.

Figure 3a,b shows that the CC on Day 6 was significantly higher in IP group than in placebo group in both nonhospitalized and total population, respectively.

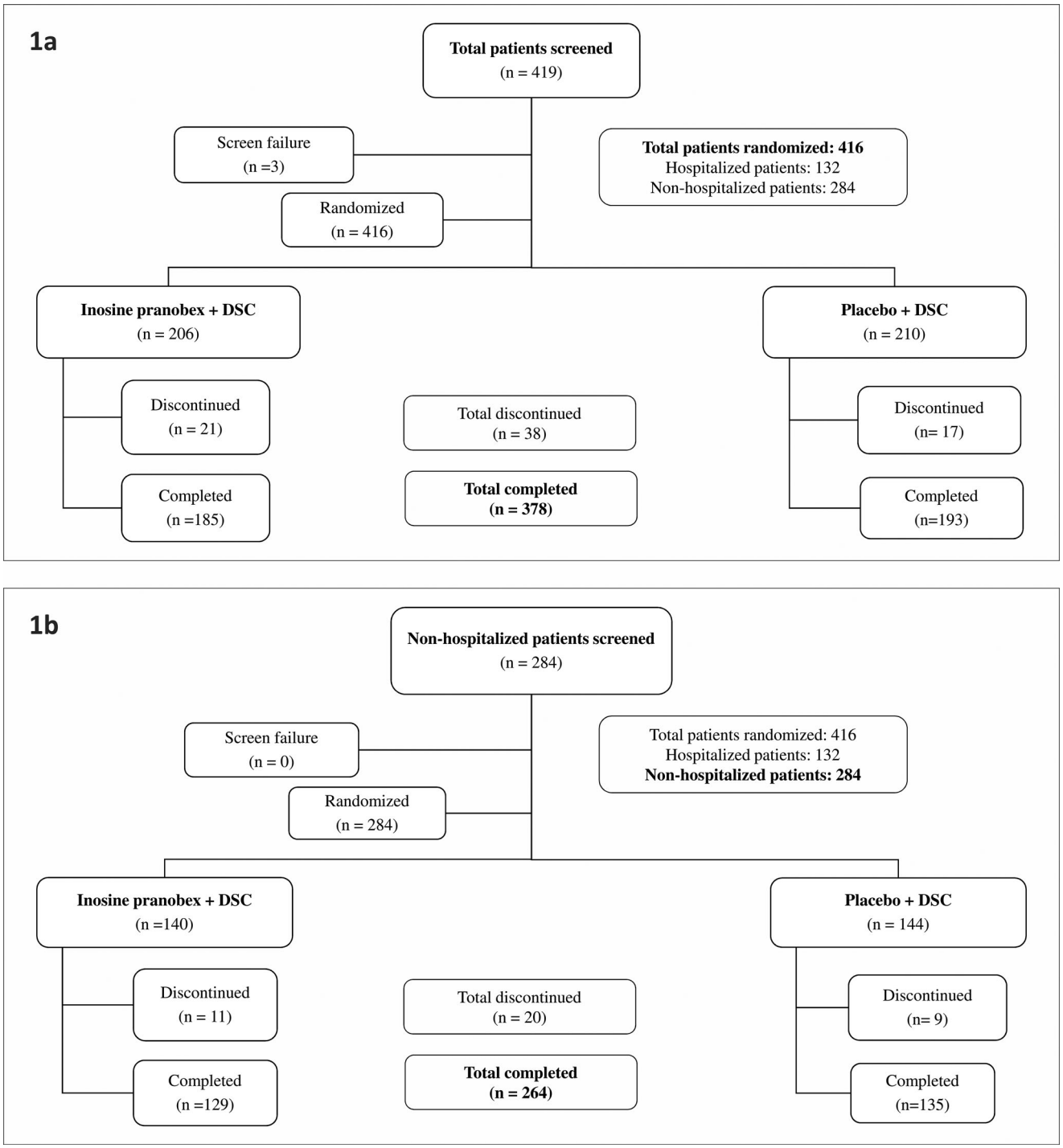

Figure 1. CONSORT Flow diagram showing patient disposition and randomization; a) total patients including both hospitalized and non-hospitalized patients. b) The non-hospitalized patient cohort. DSC = defined standard of care.

2.3.3. Time to CR and CC

Median time to CR was significantly earlier in IP than in placebo group (Table 2) among both ITT-NHP (6 vs 7 days; $P < 0.001$) and ITT-TP (6 vs 8 days; $P < 0.001$). Median time to CC was also significantly earlier in IP than in placebo group (Table 2) among both NHP (6 vs 7 days; $P < 0.001$) and TP (6 vs 8 days; $P < 0.001$). **Figure 4** shows the Kaplan–Meier plots for time to CR and time to CC. Similar results were seen in PP population (Table 2).

Figure 4 shows Kaplan–Meier plot for Time to CR and Time to CC in ITT population (n = 414); 4a shows median time to CR was significantly earlier in the IP group than that in the placebo

Table 1. Summary of patient demographics for the including both hospitalized and non-hospitalized coronavirus disease-19 patients.

Demographic characteristic	IP + DSC (n = 206)	Placebo + DSC (n = 210)	Total (n = 416)
Gender			
Male [n [%]]	136 (66.02)	134 (63.81)	270 (64.90)
Female [n [%]]	70 (33.98)	76 (36.19)	146 (35.10)
Age [years]			
Mean (SD)	43.0 (13.98)	44.4 (13.54)	43.7 (13.76)
Median	42.0	43.0	42.0
Range	18.0–74.0	18.0–74.0	18.00–74.0
Height [cm]			
Mean (SD)	166.7(6.91)	165.9(6.29)	166.3(6.61)
Median	167.0	167.0	167.0
Range	125–190	146–188	125–190
Weight [kg]			
Mean (SD)	65.66 (10.15)	65.49 (8.43)	65.57 (9.31)
Median	65.00	65.00	65.00
Range	45.00–102.00	42.00–85.30	42.00–102.00
BMI [kg m^{-2}]			
Mean (SD)	23.65 (3.55)	23.81 (2.98)	23.73 (3.27)
Median	23.30	23.63	23.51
Range	15.03–38.40	16.00–32.46	15.03–38.40
Medical History [n[%]]			
Asthma	1 (0.49)	0 (0.00)	1 (0.24)
Cardiovascular Disease	1 (0.49)	0 (0.00)	1 (0.24)
Diabetes	7 (3.40)	22 (10.48)	29 (6.97)
Hyperlipidemia	0 (0.00)	1 (0.48)	1 (0.24)
Hypertension	10 (4.85)	7 (3.33)	17 (4.09)
Seizures	1 (0.49)	0 (0.0)	1 (0.24)
Sickle Cell Anemia	0 (0.00)	1 (0.48)	1 (0.24)
Thyroid	1 (0.49)	1 (0.48)	2 (0.48)

Note: Percentage (%) was calculated from the respective header counts. IP: Inosine pranobex; DSC: defined standard of care; n = number of patients; SD: standard deviation; BMI: body mass index.

group (6 days vs 8 days; $p < 0.001$). 4b shows median time to CC was significantly early in IP group as compared to the placebo group (6 days vs 8 days, $p < 0.001$).

2.3.4. Other Secondary Endpoints

For all the remaining secondary endpoints, the difference between IP and placebo groups was not statistically significant.

2.4. Safety Endpoints

Adverse events were mild and fewer in IP group (12 in 11 patients vs 23 in 21 patients in placebo group; **Table 3**). No new/unexpected adverse event was reported. By Day-14, there were no deaths in IP group while there were two deaths in the placebo group. (Table S7, Supporting Information). Uric acid elevation was in similar frequencies in both IP and placebo groups (Table S8, Supporting Information). No patient in either group received any steroids.

2.5. Subgroup Analysis

In the subgroups <45 years (Table S9, Supporting Information) and body mass index (BMI) <30 kg m^{-2} (Table S10, Supporting Information), CR on Day-6 in PP-NHP was significantly higher with IP than with placebo. No significant difference was seen between IP and placebo groups in the subgroups ≥45 years (Table S9, Supporting Information) and BMI ≥30 kg m^{-2} (Table S10, Supporting Information). In PP-NHP, both genders had significantly higher CR on Day-6 with IP than with placebo (Table S11, Supporting Information).

3. Discussion and Conclusion

Both in TP and NHP, a significantly higher percentage of patients on IP than on placebo showed CR and CC on Day-6 though there was no significant difference seen on Day-11 with respect to CR, CC, virological cure (VC), or any other parameters. The addition of IP to the D resulted in earlier improvement and complete resolution of symptoms (clinical cure) both in TP and NHP. This may help in minimizing the severity of COVID-19 course. In TP, the median time to both CR and CC was two days earlier in IP group. Even among NHP, the addition of IP reduced the time for third quartile to CR and CC by two days (Table 2).

These results confirm the efficacy of IP in early improvement and resolution of the clinical symptoms in patients with mild/moderate COVID-19.

A higher percentage of patients in IP group of NHP achieved CR and CC compared with patients in IP group of TP (Table 2). Even in subgroup analysis (Tables S9–S11, Supporting Information), IP group showed a higher CR and rate of recovery, especially in outpatients.

Treatment-emergent complications have been a concern while treating COVID-19.[8] A suppressed immune system may lead to complications such as mucormycosis.[9] IP was well-tolerated and there was no serious adverse event or death in IP group. The adverse events reported were unlikely to be related to IP, were mild in severity, and resolved without sequelae after the administration of concomitant medication. The most common adverse event reported was nausea (2.16%). This suggests that IP can safely be used with standard care in an at-home setting and can reduce patient load in hospitals, ensure patient safety, and fulfill the current unmet need in this ongoing pandemic.

Most respiratory viral infections are self-limiting; nonetheless, reducing the duration of symptoms (morbidity) by using IP helps in reducing the overall disease burden, health-related productivity loss, and healthcare cost. Earlier, a phase-4 randomized controlled trial had shown the efficacy and safety of IP in treating patients with confirmed acute respiratory viral infections.[4] Patients treated with IP showed faster resolution of influenza-like symptoms than those treated with placebo. Similarly, our study showed earlier improvement and cure from mild/moderate COVID-19 symptoms in IP group with a good safety profile.

In a Czech study on 301 elderly (75–95 years) residents with COVID-19, IP 500 mg, two tablets given three times a day for

Table 2. CR, time to CR, Clinical Cure (CC), and time to CC in total population and non-hospitalized patients.

		ITT Population				PP Population			
		Total population		Non-hospitalized patients		Total population		Non-hospitalized patients	
		IP + DSC (N = 204)	Placebo + DSC (N = 210)	IP + DSC (N = 140)	Placebo + DSC (N = 144)	IP + DSC (N = 173)	Placebo + DSC (N = 180)	IP + DSC (N = 121)	Placebo + DSC (N = 126)
CLINICAL RESPONSE									
Day 06	n [%]	132 (64.71)	100 (47.62)	110 (78.57)	79 (54.86)	116 (67.05)	85 (47.22)	97 (80.17)	66 (52.38)
	95% CI	57.73–71.25	41.12–55.09	70.84–85.05	46.36–63.16	59.51:74.00	39.75:54.79	71.94:86.86	43.30:61.35
	P-value	**<.001**		**<.001**		**<0.001**		**<0.001**	
Day 11	n [%]	194 (95.10)	201 (95.71)	136 (97.14)	141 (97.92)	173 (100)	180 (100)	121 (100)	126 (100)
	95% CI	91.17–97.62	92.02–98.02	92.85–99.22	94.03–99.57	97.89:100.0	97.97:100.0	97.00:100.0	97.11:100.0
	P-value	0.765		0.674		-		-	
TIME TO CLINICAL RESPONSE									
Event, n [%]	194 (95.10)	201 (95.71)	136 (97.14)	141 (97.92)	173 (100)	180 (100)	121 (100)	126 (100)	
Censored, n [%]	10 (4.90)	9 (4.29)	4 (2.86)	3 (2.08)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Quartile estimate for event (in days)									
	25th percentile (95% CI)	5.00 (4.00–6.00)	6.00 (5.00–6.00)	5.00 (4.00–5.00)	6.00 (4.00–6.00)	5.00 (5.00–6.00)	6.00 (5.00–6.00)	5.00 (4.00–5.00)	6.00 (5.00–6.00)
	Median (95% CI)	6.00 (NE)	8.00 (7.00–8.00)	6.00 (NE)	7.00 (7.00–8.00)	6.00 (NE-NE)	8.00 (7.00–9.00)	6.00 (NE-NE)	7.00 (7.00–8.00)
	75th percentile (95% CI)	9.00 (8.00–9.00)	9.00 (9.00–10.00)	7.00 (6.00–8.00)	9.00 (9.00–10.00)	9.00 (8.00–9.00)	9.50 (9.00–10.00)	7.00 (6.00–8.00)	9.00 (9.00–10.00)
	P-value	**0.0002**		**<.0001**		**0.0002**		**<0.0001**	
CLINICAL CURE									
Day 06	n [%]	125 (61.27)	98 (46.67)	107 (76.43)	77 (53.47)	109 (63.01)	83 (46.11)	94 (77.69)	64 (50.79)
	95% CI	54.22–68	39.77–53.66	68.52–83.19	44.98–61.82	55.35:70.21	38.67:53.68	69.22:84.75	41.74:59.81
	P-value	**0.003**		**<.001**		**0.001**		**<.001**	
Day 11	n [%]	194 (95.10)	199 (94.76)	136 (97.14)	136 (97.14)	173 (100)	178 (98.89)	121 (100)	125 (99.21)
	95% CI	91.17–97.62	90.82–97.36	92.85–99.22	93.04–99.24	97.89:100	96.04:99.87	97:100	95.66:99.98
	P-value	0.876		0.968		0.164		0.326	
TIME TO CLINICAL CURE									
Event, n [%]	194 (95.10)	199 (94.76)	136 (97.14)	140 (97.22)	173 (100)	178 (98.89)	121 (100)	125 (99.21)	
Censored, n [%]	10 (4.90)	11 (5.24)	4 (2.86)	4 (2.78)	0(0.00)	2 (1.11)	0(0.00)	1 (0.79)	
Quartile estimate for event									
	25th percentile (95% CI)	6.00 (5.00:6.00)	6.00 (NE)	5.00 (4.00:6.00)	6.00 (5.00:6.00)	6.00 (NE-NE)	6.00 (6.00–7.00)	6.00 (4.00–6.00)	6.00 (5.00–6.00)
	Median (95% CI)	6.00 (6.00:7.00)	8.00 (7.00:8.00)	6.00 (NE)	7.00 (7.00:8.00)	6.00 (6.00–7.00)	8.00 (7.00–9.00)	6.00 (NE-NE)	7.00 (7.00–9.00)
	75th percentile (95% CI)	9.00 (8.00:9.00)	10.00 (9.00:10.00)	7.00 (6.00:8.00)	9.00 (9.00:10.00)	9.00 (8.00–9.00)	10.00 (9.00–10.00)	7.00 (7.00–8.00)	10.00 (9.00–11.00)
	P-value	**0.0006**		**<.0001**		**0.0006**		**<.0001**	

For clinical response and clinical cure, P-value was calculated by using Chi-Square at 5% level of significance and percentage was calculated by using header count. For time to clinical response and time to clinical cure, the percentage was calculated by respective treatment group and P-value was calculated by using Log-rank test. Significant P values are in bold. IP: Inosine pranobex; DSC: defined standard of care; CI: confidence interval; n = number of patients; ITT: intention-to-treat; PP: Per protocol; NE: not estimable.

seven days, significantly reduced the case fatality rate.[2] IP seems to be safe for the elderly. As aging impacts both innate and adaptive immunity to viral infection,[10] and IP is known to enhance both types of immunity, it may be particularly useful in the elderly to fight viral infections. However, in our study, subgroup analysis of patients ≥45 years did not show any difference in CR between IP and placebo groups. But IP was more efficient than placebo irrespective of gender and in patients aged <45 years or with BMI <30 kg m^{-2}. Similar results were also seen by Beran et al.[4] This may be due to the fact that the immune system in young and non-obese patients is more amenable to favorable modulation by IP in fighting respiratory viral disease infections. Future larger studies on the elderly may help in elucidating the results.

In our study, 6.97% of patients had diabetes and 4.09% had hypertension and this low sample size may be the reason why the

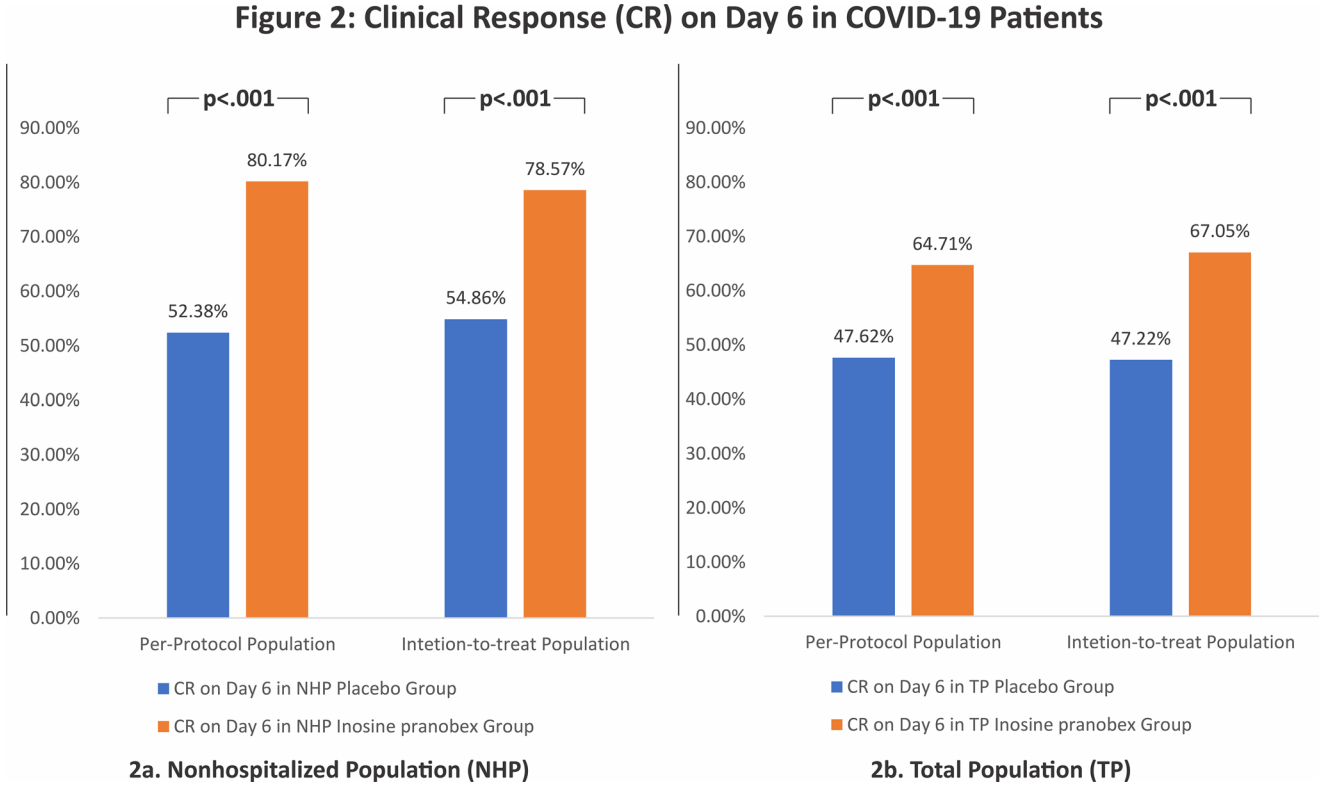

Figure 2. CR on Day 6 in a) nonhospitalized population and b) total population

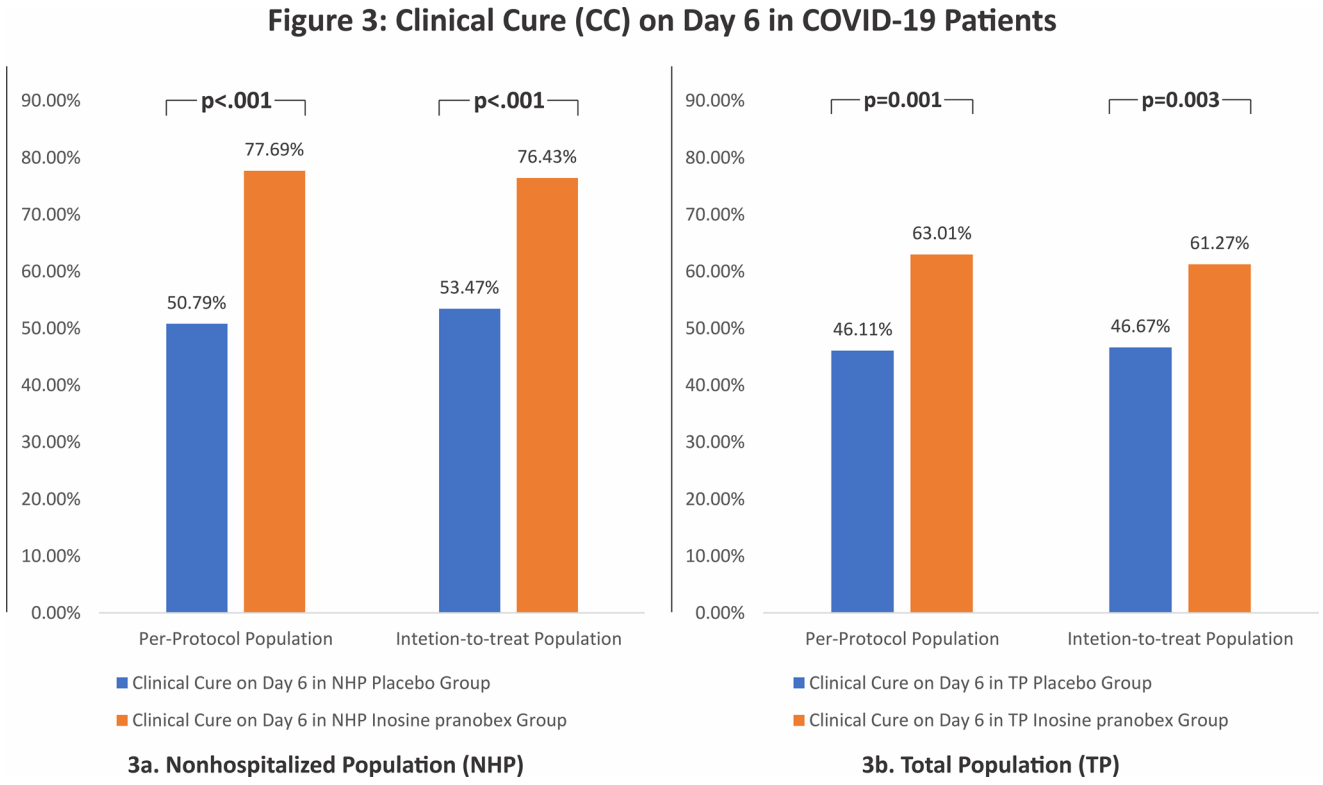

Figure 3. CC on Day 6 in a) nonhospitalized population and b) total population

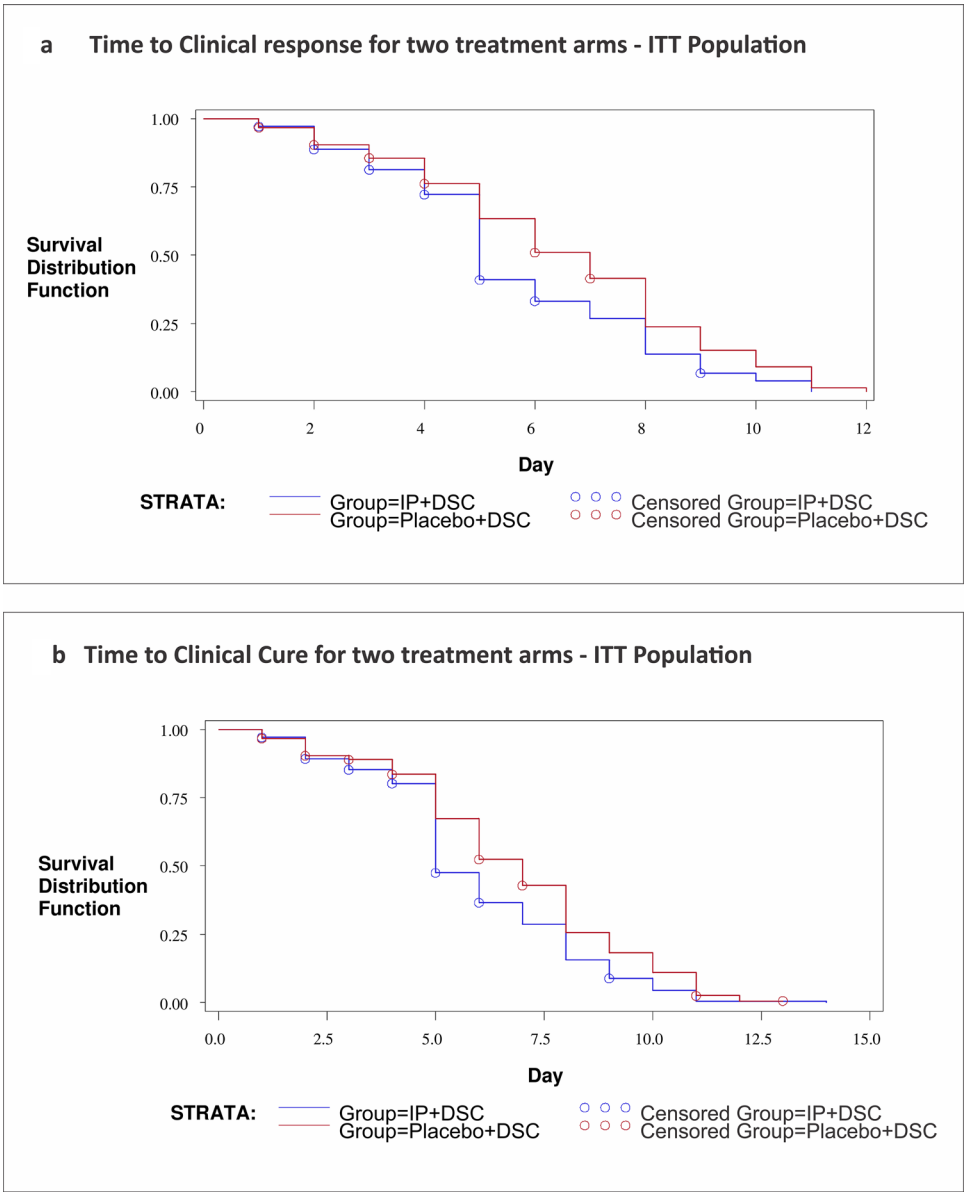

Figure 4. Time to CR and CC in ITT population (n = 414); a) Kaplan–Meier plot for time to CR; median time to CR: 6 days versus 8 days; $p < 0.001$. b) Kaplan–Meier plot for time to CC; median time to CC: 6 days versus 8 days, $p < 0.001$. ITT population is the set of all randomized patients in the trial. ITT: Intention-to-treat; IP: Inosine pranobex; DSC: defined standard of care.

subgroup analysis with diabetes and hypertension did not show a significant difference between IP and placebo groups. Future studies may focus on determining the predictors of treatment success and on different dosing strategies in different patient populations especially in those with comorbidities as it may affect the drug plasma levels and drug-related effects.

The protocol of this study got approved in January 2021 and the study started in February 2021. In spite of the issuance of the revised COVID guidelines later that year,[11] both hydroxychloroquine and azithromycin were widely prescribed for COVID-19 in 2021. Also, our study compared the use of IP to that of a placebo and not to the DSC.

Enrolment was paused for interim analysis as pre-specified in the protocol. However, this was during the peak of the second wave of COVID-19 pandemic in India. We resumed the trial during the continuing second wave while maintaining the double-blinding and randomization to avoid any possible bias based on change in virus strain.

Overall, our study showed that IP 500 mg tablets in combination with standard care benefits COVID-19 patients with mild/moderate disease severity. Its legal re-classification from prescription-only medicine to over-the-counter category in some countries[12] further reiterates its efficacy and safety. When used early in COVID-19 patients, IP reduces the disease progression

Table 3. Summary of adverse events by system organ class and preferred term in total population.

	IP + DSC(N = 206)		Placebo + DSC(N = 210)		Total population(N = 416)	
Parameter	n [%]	(E)	n [%]	(E)	n [%]	(E)
At least one adverse event	11 (5.34)	-	21 (10.00)	-	32 (7.69%)	-
Gastrointestinal disorders	6 (2.91)	6	8 (3.81)	8	14 (3.37)	14
Abdominal distension	1 (0.49)	1	0 (0.00)	0	1 (0.24)	1
Dyspepsia	0 (0.00)	0	2 (0.95)	2	2 (0.48)	2
Nausea	4 (1.94)	4	5 (2.38)	5	9 (2.16)	9
Vomiting	1 (0.49)	1	1 (0.48)	1	2 (0.48)	2
General disorders and administration site conditions	0 (0.00)	0	4 (1.90)	4	4 (0.96)	4
Death	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Disease progression	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Pyrexia	0 (0.00)	0	2 (0.95)	2	2 (0.48)	2
Infections and infestations	1 (0.49)	1	0 (0.00)	0	1 (0.24)	1
Urinary tract infection	1 (0.49)	1	0 (0.00)	0	1 (0.24)	1
Metabolism and nutrition disorders	2 (0.97)	2	4 (1.90)	4	6 (1.44)	6
Hyperglycemia	2 (0.97)	2	4 (1.90)	4	6 (1.44)	6
Musculoskeletal and connective tissue disorders	1 (0.49)	1	1 (0.48)	1	2 (0.48)	2
Myalgia	1 (0.49)	1	0 (0.00)	0	1 (0.24)	1
Pain in extremity	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Nervous system disorders	0 (0.00)	1	1 (0.48)	3	1 (0.24)	4
Dizziness*	0 (0.00)	1	0 (0.00)	2	0 (0.00)	3
Headache	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Respiratory, thoracic and mediastina disorders	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Acute respiratory distress syndrome	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Skin and subcutaneous tissue disorders	1 (0.49)	1	1 (0.48)	1	2 (0.48)	2
Pruritus	1 (0.49)	1	1 (0.48)	1	2 (0.48)	2
Investigations	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1
Alpha tumor necrosis factor increased	0 (0.00)	0	1 (0.48)	1	1 (0.24)	1

Note 1: Percentage (%) was calculated by using overall count as denominator. Note 2: The patients who had dizziness* suffered more than one adverse event, so it is already counted once in the subject count. n: number; E: event; IP: Inosine pranobex; DSC: defined standard of care

while ensuring patient safety. It does so by NK cell-mediated cytotoxicity of virus-infected cells as an early immune response to viral infection. We conclude that IP should be used at the early stage of viral infection to get maximum benefit.

4. Experimental Section

Study Design: A phase 3, double-blind, placebo-controlled, prospective, randomized, comparative, parallel-group, and multicentric study was conducted from February 8, 2021 to June 16, 2021 at eleven sites across India (trial registration number: CTRI/2021/02/030892).

Necessary approvals were obtained from the Central Drugs Standard Control Organization (CDSCO, the drug regulatory authority of the Government of India) and the respective institutional ethics committees (IECs). All patients voluntarily signed informed consent. Additional information is provided in the Supporting Information.

Patients (n = 416, inpatients and outpatients) aged 18–75 years with laboratory-confirmed COVID-19 with mild/moderate severity (Ministry of Health and Family Welfare, India, guidelines),[13] that is, oxygen saturation ≥90%, and respiratory rate ≤30 min^{-1} presenting with WHO listed symptoms of COVID-19 (complains of fever, headache, myalgia, cough, throat pain or shortness of breath) were enrolled with a score 3–5 on the Modified World Health Organization (WHO) Ordinal Scale for Clinical Improvement.[14]

Patients were excluded from participation in the study if they had known hypersensitivity to any of the ingredients of the study drug; were pregnant and lactating women; had known history of gout or hyperuricemia (serum uric acid level >8 mg dl^{-1}), urolithiasis, nephrolithiasis, or any degree of renal dysfunction; had history of diagnosed primary congenital immunodeficiency, or acquired immunodeficiency like Human Immunoeficiency V, or any genetic or developmental anomaly like cerebral palsy, coeliac disease, lactose intolerant, cancer in nonremission stage; were undergoing treatment with xanthine oxidase inhibitors, uricosuric agents, diuretics, immunosuppressive agents or zidovudine; had a severe cardiac, hepatic, gastrointestinal, renal, pulmonary or skin diseases; were simultaneously participating in another clinical study; had medical or psychological conditions deemed by the investigators to interfere with successful participation in the study; or were judged by the investigator as inappropriate to participate in the study for any reason other than those mentioned above.

In a computer-generated randomization (1:1), in blocks of four, patients in the TP received either "tablet IP 50 mg kg^{-1} body weight/day rounded to the nearest 500 mg dose (max 4 mg day^{-1}) with DSC" (IP group) or "matching placebo with DSC" (placebo group) for 10 days. Each group included hospitalized and NHP. The dose of IP was determined based on available clinical literature[1,2,4,5] and the phase 2 proof-of-concept study of IP in mild/moderate COVID-19 patients.[7] The standard of care for

COVID-19 was defined based on the commonly used treatment protocols followed in various hospitals across India during the study at that time, in agreement with the study investigators. It included tablets of azithromycin (500 mg once daily for five days) and hydroxychloroquine (400 mg twice daily for one day followed by 200 mg twice daily for four days). It also included tablets of zinc 50 mg twice daily, vitamin C 1000 mg day^{-1}, and vitamin D3 2000 IU/day, each for 10 days.

Efficacy of IP was assessed by measuring the number of patients who achieved CR, CC, or VC. The safety of IP was evaluated by assessing the incidence and severity of adverse events and mortality rates.

Definitions: CR referred to 2-point improvement or becoming asymptomatic (Grade-2 or less) on the modified WHO ordinal scale.[14] CC was becoming asymptomatic (Grade-2 or less) on the modified WHO ordinal scale. VC was two consecutive (within 48 h) negative COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal or oropharyngeal test (equivalent to Grade-1 on modified WHO ordinal scale).

Sample Size: In phase 2 (proof-of-concept) study,[7] patients who received standard care (azithromycin + hydroxychloroquine) + IP showed better CR (100% vs 50%, $P < 0.05$) than those who received only standard care. Assuming a 65% CR rate for standard care + IP, 332 patients should complete the study to detect a 30% effect size with 80% power. Anticipating a 20% dropout rate, it was planned to enroll 416 patients (208/arm) in phase 3 study. Enrolment was paused from March 3, 2021 to May 17, 2021 for a pre-specified interim analysis to be conducted by a part of the study team who were not directly involved in the treatment or assessment of the subjects.

Interim analysis was performed after the enrolment of 216 patients [ITTpopulation: n = 214; IP: inpatients = 64, outpatients = 42; Placebo: inpatients = 66, outpatients = 42; total inpatients = 130 (61%), total outpatients = 84 (39%)]. Based on interim analysis, with effect size (proportion) of 0.8333 in IP group and 0.6429 in placebo group, a total sample size of 220 outpatients was required to detect the difference with 90% of power. Thus, another 136 (= 220–84) outpatients were needed and considering 20% dropout, 170 more outpatients were needed. As this was less than the previously calculated sample size, 200 more outpatients were enrolled.

Procedures: Patients were assessed on Day-6 (+1 day) and Day-11 (+1 day). A telephonic follow-up visit for safety assessment was done on Day-14 (±1 day). Physical and systemic examinations were performed on a daily basis for inpatients. The modified WHO ordinal scale for Clinical Improvement and the modified Medical Research Council (mMRC) scale,[15] were administered daily in person for inpatients and telephonically for outpatients to assess the severity of dyspnea. Physical examination, systemic examination, vital signs, laboratory tests, X-ray chest, and electrocardiogram were done at every visit.

Use of antiviral drugs such as Favipiravir, Remdesvir, Itolizumab, Tocilizumab, Oseltamavir, etc. was not allowed as concomitant or rescue medication. If required for the patient's clinical management; such cases were considered a major protocol deviation and such patients were discontinued from the study.

All clinical assessments were done by the designated blinded investigational team who did not handle IP. The designated unblinded pharmacist, who did not perform or participate in any clinical assessment, dispensed IP. If serum uric acid level was >8 mg dL^{-1} during the study, IP was stopped and patient was followed up till Day-14. Such a patient continued to receive the DS.

Protocol Amendment after Interim Analysis: At interim analysis, CR on Day-11 in TP (primary endpoint) was similar in both groups (93.40% vs 93.52%; P = 0.971). Interestingly, CR on Day-6 in TP (a secondary endpoint) occurred in higher proportion of patients on IP, although not statistically significant (52.83% vs 46.30%; P = 0.339). However, CR on Day-6 in NHPs was significantly higher in IP group (83.33% vs 64.29%; P = 0.047) than in placebo. No difference was seen in hospitalized patients.

As a result, CDSCO was approached with a proposal to amend the protocol. Amended protocol was approved by CDSCO and respective IECs before resuming enrollment.

CR at Day-6 in NHP was added as an additional primary endpoint. Only NHPs were enrolled thereafter to achieve the target sample size and to ensure adequate power to detect any difference with respect to this second primary endpoint, that is, CR at Day-6, and to have robust unbiased data to assess the benefit-risk profile of IP, especially in the NHPs.

The researchers also proposed to amend the acceptable upper limit of uric acid levels to 8 mg dL^{-1} (from 6 mg dL^{-1}) in the exclusion criteria as even this range was considered safe by the study team as well as other researchers,[16,17] and the hyperuricemia were generally reversible.[1]

Endpoints: Primary endpoints after interim analysis were CR on Day-6 in NHP and CR on Day-11 in TP. Secondary endpoints were:

- CR on Day-6 in TP
- CR on Day-11 in NHP
- CC on Day-6 and Day-11 in TP and NHP
- VC on Day-11 in TP and NHP
- Time to CR and CC in TP and NHP
- Mortality rate at Day-11 in TP and NHP
- Severity of dyspnea on Day-6 and Day-11 in TP and NHP
- Duration of hospitalization for inpatients
- Rate of hospitalization in NHP
- Rate of steroid use
- Percentage of patients requiring oxygen inhalation (non-assisted)
- Duration of oxygen use/duration of requiring ventilation on Day-6 and Day-11
- Change in blood levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) between the groups on Day-6 and Day-11

Safety endpoints included the incidence and severity of adverse events.

Statistical Analysis Plan: Qualitative data were expressed as numbers and percentages. Continuous data were expressed using mean, standard deviation, median, range, and 95% confidence interval (CI), wherever applicable. Change from the baseline in each group and mean changes from baseline between the groups were compared (Change from baseline = post visit value – baseline value). Wherever appropriate, two-sided 95% CI for means and p-values have been provided. Analysis of endpoints was done in both TP and NHP. Chi-square test was used to compare IP and placebo groups with respect to CR, CC, VC, and mortality. Time to event (CR, CC) for both groups were compared using Kaplan–Meier plot and Log Rank test. Descriptive statistics and T-test were used for other endpoints, wherever appropriate. A $P < 0.05$ was considered significant.

Subgroup Analysis: As predetermined, a subgroup analysis (including hospitalized and non-hospitalized subgroups) was performed to better understand the outcome of the study treatments based on the following factors: age (<45 and ≥45 years), gender, BMI (<30 and ≥30 kg m^{-2}), diabetes, and hypertension.

Institutional Review Board Statement: Inosine pranobex 500 mg tablets Protocol no: TML/IAD//2020/02 version 3.1. Dated 13 May 2021 (A phase 3, double-blind, placebo-controlled, prospective, randomized, comparative, parallel-group, multi-center, study to assess the efficacy and safety of inosine pranobex added to a defined standard of care in covid-19 patients)

These are the details of the approvals by the IRBs of the centers where the study was conducted (**Table 4**).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Table 4. Details of IRB Aprovals.

SN.	Principal Investigator	Site	IEC Details
1	Dr. Sumer Sanjiv Choudhary	N. K. P. Salve Institute of Medical Sciences & Research Centre and Lata Mangeshkar Hospital, Nagpur	Institutional Ethics Committee, N. K. P. Salve Institute of Medical Sciences & Research Centre and Lata Mangeshkar Hospital, Digdoh Hills, Hingna Road, Nagpur 440019. **EC Regn No**: ECR/88/Inst/MH/2013/RR-19 **Ref**: NKPSIMS & RC and LMH/Pharmacology IEC/16/2021 dt26.5.2021
2	Dr. Mohd. Saif Khan	Rajendra Institute of Medical Sciences (RIMS), Ranchi	Institutional Ethics Committee, RIIMS Ranchi, Jharkhand-834009 **IEC Regn No**: ECR/769/INST/JH/2015/RR-18
3	Dr. Manish Patel	VS General Hospital & Sardar Vallabhbhai Patel Institute of Medical Sciences & Research, Ahmedabad	Institutional Ethics Committee. Smt NHL Municipal College, Ellisbridge, Ahmedabad 380 006 **IEC Regn No**: ECR/245/Guj/2013 **Ref**: NHLIEC/2021/July/22/no1 dt 22.7.2021
4	Dr. Dnyaneshwar Halnor	Vijay Vallabh Hospital & Research Centre, Mumbai	Institutional Ethics Committee, Vijay Vallabh Hospital,423 Tirupati Nagar, Phase I, Bolinj, Virar West 401303 **EC Regn No**: ECR/880/Inst/MH/2017/R-R 2020
5	Dr. C R Jayanthi	Victoria Hospital, Bangalore Medical College, Bangalore	Ethics Committee of Bangalore Medical College and Research Institute(An autonomous Institute of Govt. of Karnataka), KR Road, Fort, Bangalore 560 002
6	Dr. Ranganath T Ganga	All India Institute of Medical Sciences (AIIMS), Raipur	All India Institute of Medical Sciences (AIIMS), Academic Section,2nd floor, Medical College Complex, Gate No 5, Tatibhand, G E Road, Raipur-492099(CG) **EC Regn No**: ECR/714/Inst/CT/2015/RR-21
7	Dr. Shubhangi Despande	GMERS Medical College and General Hospital, Vadodara	Institutional Human Ethics Committee, GMERS Medical College and General Hospital, Vadodara 390021, Gujarat **EC Regn No**: ECR/28/Inst/GJ/2013/RR-19 Approved up to 15 April 2021 **Outward No**: IHEC/21/OUT/CT011 Approval Date 12.10.2021
8	Dr. Ayan Ghosh	College of Medicine & JNM Hospital, Kalyani, Kolkata	Office of the Institutional Ethics Committee, College of Medicine & JNM Hospital, West Bengal University of Health Sciences, Kalyani, Nadia, West Bengal 741235. **IEC Regn No**: ECR/674/Inst/WB/2014 **Ref No**: F24/PR/COMJNMH/IEC/66 Dated17 May 2021
9	Dr. Krishna Prasad Anne	Pranaam Hospitals Pvt Ltd, Hyderabad	Institutional Ethics Committee, Pranaam Hospitals Pvt Ltd, 1–58/6/40&41, Madinaguda Miyapur, R R Dist, Hyderabad 500050, Telangana **IEC Regn No**: ECR/1460/Inst/TG/2020 **Ref No**: IEC/PRNM/003 dated 15.5.2021
10	Dr. Ajit Avhad	Family Care Hospitals, P.K. Road Opposite Seven Square Academy, Mira Road (East), Thane, Maharashtra 401107	Institutional Ethics Committee, Vijay Vallabh Hospital,423 Tirupati Nagar, Phase I, Bolinj, Virar West 401303. **EC Regn No**: ECR/880/Inst/MH/2017/R-R 2020
11	Dr. Anand Yannawar	Sonali Memorial Hospitals, Near Dange Chowk, Near Dhanije School, Gujar Nagar, Jai Hind Nagar, Thergaon, Pune Maharashtra 411033	Institutional Ethics Committee, SAi Sneha Hospital and Diagnostic Centre, Opp PMT Bus Depot, Pune Satara Road, Katraj, Pune, Maharashtra, 411046 **EC Regn No**: ECR/989/Inst/MH/2017/RR20 **Ref**: IECSSH170521 dt 17.5.2021

management, clinical operations, study monitoring, data management, statistical analysis, and medical writing. Gedeon Richter Polska provided the study drug (Groprinosin 500 mg, tablets) for the Phase 2 study. IP used in the phase 3 study was manufactured by Themis Medicare Ltd, based on the technology of Gedeon Richter Polska, Poland.

Conflict of Interest

All the authors, except for A.S. and Y.B., acted as investigators in the clinical trial and have received their investigator's fees for this study. They have received no other funding related to the study. A.S. is an employee of Themis Medicare Limited, India, the sponsor of the study. Y.B. was an employee of Themis Medicare Limited, India when the study was conducted and when the first draft of the manuscript was prepared. He has checked and approved the final version of the manuscript being submitted. M.S.K. has received an honorarium from Themis Medicare Limited, India as a Speaker. All the authors report that they have no other disclosures to make.

Author Contributions

Conceptualization, Resources, Supervision: A.K.S. Methodology: A.K.S., C.R.J., R.T.G., M.S.K., and S.S.C. Investigation: C.R.J., R.T.G., D.H., A.A., M.S.K., A.G., S.S.C., A.N.Y., S.D., M.P., and K.P.A. Data Curation and Project Administration: Y.B. Writing – Review & Editing: C.R.J., A.K.S., R.T.G., D.H., A.A., M.S.K., A.G., S.S.C., A.N.Y., S.D., M.P., K.P.A., and Y.B. All authors provided critical inputs to revise the manuscript drafts, approved the final version of the manuscript, and agreed to be accountable

for all aspect of the work in ensuring that questions related to any part of the work are adequately resolved.

Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to data ownership and intellectual property rights.

Keywords

antiviral, COVID-19, efficacy, inosine acedoben dimepranol, inosine pranobex, safety

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