ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 4, August - 2023, Page No. : 40 - 51

Efficacy and safety of oral molnupiravir as an add on to standard of care in the early treatment of COVID – 19 : An open label phase 3 clinical trial

[1]Piyush Agarwal, [1]Shradhanand Singh, [1]Brajesh Kumar Jha, [1]Jaganmohan Somagoni, [2]Ram Gupta, [3]Bhupesh Dewan, [4]Rajesh S. Nachankar, [5]Jaideep Gogtay

[1]Dr. Reddy's Laboratories Ltd, [2]Torrent Pharmaceuticals Ltd Research Center, [3]Zuventus Healthcare Ltd, [4]Viatris Ltd, [5]Cipla Ltd.

Corresponding Author: Dr. Piyush Agarwal, Global Clinical Management, IPDO, Dr. Reddy's Laboratories Pvt. Ltd., Hyderabad, India.

How to citation this article: Piyush Agarwal, Shradhanand Singh, Brajesh Kumar Jha, Jaganmohan Somagoni, Ram Gupta, Bhupesh Dewan, Rajesh S. Nachankar, Jaideep Gogtay, "Efficacy and safety of oral molnupiravir as an add on to standard of care in the early treatment of COVID – 19 : An open label phase 3 clinical trial", IJMACR- August - 2023, Volume – 6, Issue - 4, P. No. 40 – 51.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background and Objectives: Molnupiravir received the emergency use authorization (EUA) in India for the treatment of coronavirus disease (COVID-19). We aimed to evaluate the efficacy and safety of molnupiravir in patients with COVID-19.

Methods: Participants (N=1218) with mild COVID-19 disease across 22 centres from India were randomised to receive 800 mg Molnupiravir twice daily for 5 days plus standard of care (SoC) or SoC alone. Efficacy and safety endpoints included clinical improvement at Day 5, 10 &14, time to clinical improvement, change in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load, rate of SARS-CoV2 real-time reverse transcription–polymerase chain reaction (RT-PCR) negativity and incidence and severity of adverse events.

Results: Time to clinical improvement based on World Health Organisation (WHO) ordinal scale was 5 days in the Molnupiravir+SoC arm as compared to 10 days for SoC arm. Participants of Molnupiravir+SoC showed statistically significant results in two- point and one-point improvements in WHO ordinal score at Day 5 [P<0.0001, P<0.0001] and Day 10 [P<0.0001, P<0.0001]. Significant difference in SARS-CoV-2 viral load was observed in Molnupiravir+SoC arm [p=<.0001, p=<0.0001] at Day 5 and Day 10 respectively. Also, significant difference in RT-PCR negative test results were observed at Day 5 (P=0.0001), 10 (P<.0001) and 14 (P=0.0002). Severity of all adverse events were mild

in intensity. No serious adverse events (SAE) and deaths were observed in Molnupiravir+SoC.

Interpretation and Conclusions: Oral Molnupiravir along with SoC was found to increase the effectiveness of the treatment without any safety concerns in subjects with mild Covid-19.

Keywords: COVID-19, Molnupiravir, SARS-CoV2, RT-PCR, Standard of Care, Viral load.

Introduction

As of September 25, 2022, there were 613,410,796 confirmed cases of COVID-19 worldwide, with 6,518,749 deaths reported to WHO.1 Infection with SARS-CoV-2 virus can cause an array of illness and they are divided into four major categories: asymptomatic, mild, moderate, and severe illness.2 Asymptomatic infections, minor upper respiratory symptoms, severe viral pneumonia with respiratory failure, and even mortality are among the clinical manifestation of COVID 19 virus infection.3 The second week after the onset of viral infection symptoms is the time when the development from prodromes (often fever, exhaustion, and cough) to severe pneumonia, acute respiratory distress syndrome (ARDS), or extracorporeal membrane oxygenation (ECMO) are most frequently observed.4 Many SARS-CoV-2 patients, especially the more severe ones, experience sequelae such ARDS, shock, acute renal injury, acute cardiac injury and secondary infection. It has been reported that mild COVID-19 disease patients with underlying co-morbidities are at high risk for progressing to severe COVID-19.5Molnupiravir, a direct oral antiviral drug, is an orally active inhibitor of RNA-dependent RNA polymerase (RdRp). RdRp is used by coronavirus for its RNA replication and transcription.6 Molnupiravir driven mutagenesis results in decline of viral load by error catastrophe.7Several phase 1 and 2 trials evaluated Molnupiravir.8,9,10 Based on exposure– response analyses from phase 2 trials, an 800-mg dose of Molnupiravir was selected for further investigation,11 including the remarkable phase 3 MOVe-OUT trial in nonhospitalized adults in whom the onset of signs or symptoms of Covid-19 had occurred not more than 5 days earlier.For the treatment of mild-to-moderate COVID-19 in adults who are at high risk for developing severe COVID-19, including hospitalisation or death, Molnupiravir has received EUA in three different countries.12The most effective medical intervention to reduce the chances of hospitalisation and death from Covid-19 is still vaccination, 13,14,15 however, early treatment soon after the onset of symptoms has also been demonstrated to be successful.16 Thus, the thrust for the new treatments to reduce the risk of progression of coronavirus disease 2019 (Covid-19) continues.Regardless of vaccine availability, pharmaceutical industries are devoting sustained efforts in developing new mitigations of COVID-19.3 Additionally, thousands of people are immunocompromised and may not be able to acquire utmost immune response post vaccination.17 Hence, there is an emergent need for easily administered oral anti-viral drugs having potent activity against SAR-CoV-2.Considering the unmet need for affordable medication in India, the present study was planned to evaluate the efficacy and safety of Molnupiravir+ SoC in mild COVID-19 patients.

Material & Methods

Trial Design and Randomization: This was a prospective, randomized, multicentre, open label, parallel group study to evaluate the clinical efficacy and safety of oral Molnupiravir capsules as add on to

Standard of Care (SoC) in mild COVID-19 patients. The study protocol was reviewed and approved by Drug Controller General of India (DCGI) and Independent Ethics Committee (IEC) of clinical sites. Study was conducted according to the guidelines of Declaration of Helsinki and Principles of Good Clinical Practices and was registered on Clinical Trial Registry of India (CTRI) (CTRI/2021/06/033938). The study was conducted at 22 centres across different geographical locations in India. Each patient agreed to participate in screening procedures by signing the most recent IEC approved Informed Consent Form (ICF). The total duration of study participation was 28 days from the day of randomization.

Patients

Patients of age 18-60 years were enrolled to evaluate efficacy and safety of oral Molnupiravir as an add on to SoC for treatment of mild COVID-19 patients. Patients who met all the entry criteria were randomized (by IWRS) in 1:1 proportion with 609 patients allocated per arm. Total 1218 eligible participants were randomized in 1:1 ratio in two treatment arms, oral Molnupiravir 800 mg (administered as 4 capsules of 200 mg) every 12 hours (i.e. twice daily) for 5 days + SoC and SoC. The diagram illustrating patient recruitment and treatment allocation is depicted in Figure 1.

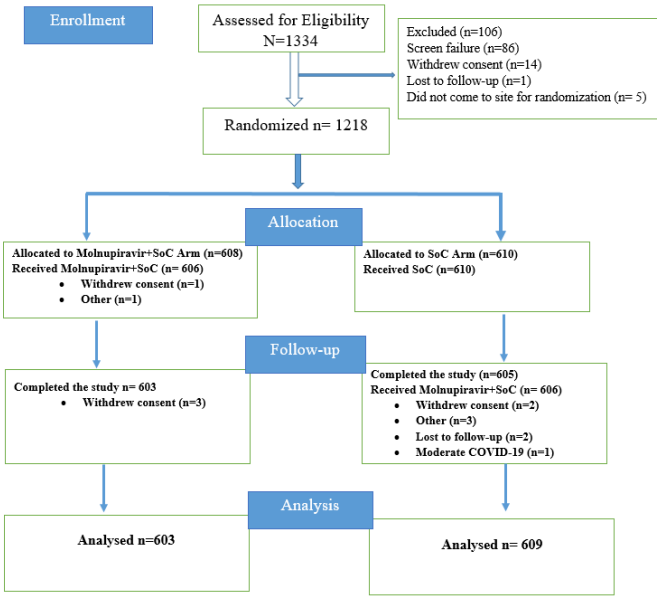

Figure 1: Diagram illustrating patient recruitment and treatment allocation.

Key inclusion criteria at randomization were SARS-CoV-2 infection that had been laboratory-confirmed no more than 5 days earlier (if rapid antigen test had been performed and patient found positive or RT-PCR test results without CT value then RT-PCR was performed prior to randomization), onset of signs or symptoms (fever, cough, sore throat/throat irritation, body ache/headache, malaise/weakness, diarrhoea or gastrointestinal upset, with or

without anorexia/nausea/vomiting, with or without loss of smell and/or taste, no shortness of breath/breathlessness, respiratory rate of less than 24/min, SpO2 ≥ 94% on room air no more than 5 days earlier) as defined by comprehensive guidelines for management of COVID-19 patients Directorate General of Health Services, MoHFW, GOI; 27-May-2021, at least one sign or symptom of Covid-19. Female patients of child bearing age with negative urine pregnancy test prior to study treatment initiation were included in the study. Key exclusion criteria were an anticipated need for hospitalization for Covid-19 within the next 48

hours, dialysis or estimated glomerular filtration rate less than 30 ml per minute per 1.73 m2, pregnancy, unwillingness to use contraception during the intervention period and for at least 4 days after completion of the regimen, severe neutropenia (absolute neutrophil count of <500 per milliliter), platelet count below 100,000 per microliter, and SARS-CoV-2 vaccination. Standard-of-care treatment with antipyretic agents, anti-inflammatory agents, glucocorticoids, or a combination was permitted; use of therapies intended as Covid-19 treatments (including any monoclonal antibodies, remdesivir, and convalescent plasma) was prohibited.

Participants were screened for demographics, physical and vital examination, WHO ordinal score, evaluation of Cycle Threshold (CT) value, RT-PCR (Real-Time Polymerase Chain Reaction) and laboratory investigations.

The present study evaluated the percentage of patients who required hospitalization due to COVID-19 up to Day 14 (primary endpoint), the efficacy of Molnupiravir compared to SoC for the change in clinical improvement on the WHO ordinal scale [18], which were recorded as the percentage of patients who show one point and two point improvement on WHO scale in clinical status, change in SARSCoV-2 viral load, increased rate of SARS-CoV2 RT-PCR negativity and incidence of Treatment-Emergent Adverse Events (TEAEs).

Sample size

The sample size was calculated based on the comparison of percentage of patients who require hospitalization ≥ 24 hours due to COVID-19 up to Day 14 between Molnupiravir + SoC vs SoC only.

Considering expected proportions of patients who require hospitalization in SoC group as 12.0% and in Molnupiravir + SoC group as 6% (assumed 50% less from SoC), the estimated sample size of 477 patients with PCR Confirmed COVID-19 in each arm provided 90% power at 5% two sided level of significance to compare the rate of hospitalization. Overall, 1218 patients were planned to be enrolled in the study including more than 20% drop outs. These patients were randomly allocated in two arms in1:1 ratio.

Statistical Analysis

All patients who were randomized in the study and received at least one dose of study treatment and had evaluable assessment of primary endpoint constituted full analysis set. Per-Protocol set included all patients who received study treatment with evaluable assessment for primary efficacy endpoint and had no major protocol deviations impacting efficacy outcome. Patients who were randomized in the study and received at least one dose of study treatment formed the safety analysis set.

Percentage of participants who required hospitalization due to COVID-19 up to Day 14 was assessed using Chi-square test. 95% CI (confidence interval) for the proportions in each treatment group were calculated by using Clopper-Pearson method. Also, 95% CI for the proportion difference were evaluated by using Miettinen-Nurminen method.

Proportion of patients with clinical improvement at the end of treatment, Day 10, Day 14 and time to clinical improvement from randomization was computed by Kaplan-Meier methods. The comparison between two groups was done through log-rank test. For mortality rate at Day 14, comparison was done by using Chi-square test. The proportion of patients with RT-PCR negative and patients with at least one TEAE/ discontinued the study was compared between treatment and placebo arm by using Chi-square test/ Fisher's exact

test. Paired t-test was used to compare the change in SARS-CoV-2 viral load from baseline to end of treatment. Analysis of covariance (ANCOVA) model was used to test mean difference between the two treatments in change from baseline.

Results

Patient Disposition and Demography

Of the 1218 (100%) randomized patients, 608 patients received Molnupiravir 800mg (IP) + SoC and rest 610 received SoC alone. Two patients of the randomized population (1218) were excluded from safety population as they did not receive a single dose of the study product (one patient hospitalized after randomization and the other one withdrew consent). Demography details of the enrolled patients is summarized in Table 1. Of the 1216 patients (safety analysis set), 710 (58.4%) patients were male and remaining 506 (41.6%) were females. All the patients were of Asian ethnicity. Overall Mean ± SD age, weight (Kg), height and BMI (Kg/m2) of patients was recorded to be 38.9 ± 11.29 years, 65.0 ± 9.28 kg, 163.4 ± 7.19 cm and 24.3 ± 3.18, respectively. Of the 1216 patients, 108 had at least one high risk factor (obesity, diabetes, or hypertension) of developing severe illness. The overall demographics were similar between the two treatment groups.

Table 1: Summary of Patient Demography-Safety Analysis Set

Parameter	Statistic/Category, n (%) [1]	Molnupiravir 800 mg + SOC (N=606)	SOC (N=610)	Overall (N=1216)
Age (Years)				
	Mean± SD	38.4±11.36	39.3±11.21	38.9±11.29
Age Group				
	18-30	172 (28.4%)	154 (25.2%)	326 (26.8%)
	31-40	176 (29.0%)	176 (28.9%)	352 (28.9%)
	41-50	147 (24.3%)	155 (25.4%)	302 (24.8%)
	51-60	111 (18.3%)	125 (20.5%)	236 (19.4%)
Gender				
	Male	343 (56.6%)	367 (60.2%)	710 (58.4%)
	Female	263 (43.4%)	243 (39.8%)	506 (41.6%)
Height (cm)				
	Mean±SD	163.1±7.07	163.7±7.30	163.4±7.19
Weight (kgs)				
	Mean±SD	64.9±8.96	65.1±9.60	65.0±9.28
BMI (Kg/m2)				
	Mean±SD	24.4±3.20	24.3±3.17	24.3±3.18

[1] Percentage were calculated using respective column header count as denominator.

Efficacy and safety

Of the 1218 patients randomized, this report presents efficacy data from 1212 patients (included in Full Analysis Set) and safety data from 1216 patients. One (1) patient in SoC group was hospitalized due to COVID-19 up to Day 14 and 2 patients in SoC group required hospitalization due to COVID-19 up to Day 28. None of the patients from IP+SoC group required hospitalization at any point of time during the study.

At Day 5, 401 (66.5%) in IP + SoC group and 305 (50.1%) patients in SoC group showed at least one-point improvement in ordinal score from baseline which was statistically significant difference between the groups [p= <.0001(C)]. Also, at Day 10, significant difference between both the groups was observed where 582 (96.5%) patients in IP + SoC group showed at least one-point improvement in ordinal score from baseline as compared to 407 (67.2%) patients in SoC group [p= <.0001(C)]. At Day 14, significant difference in improvement in ordinal score from baseline was not observed between both the groups [p=0.5951]. Summary of at least one-point and two-point improvement in ordinal score at Day 5, Day 10 and Day 14 for Full Analysis Set (N=1212) is given in Table 2.

Table 2: Clinical Improvement in one point and two point based on WHO ordinal score.

Day/ Parameters	Molnupiravir + SoC (N=603)	SoC (N=609)	Estimated difference (95% CI)*	P-Value
Day 5				
Subject with at least two-point improvement	337 (55.9%)	234 (38.4%)	17.46 (11.88:22.94)	P=<.0001
Subject with at least one-point improvement	401 (66.5%)	305 (50.1%)	16.42 (10.90:21.84)	P=<.0001
Day 10				
Subject with at least two-point improvement	551 (91.4%)	370 (61.1%)	30.32 (25.82:34.79)	P<0.0001
Subject with at least one-point improvement	582 (96.5%)	407 (67.2%)	29.36 (25.39:33.43)	P<0.0001
Day 14				
Subject with at least two-point improvement	581 (96.4%)	579 (95.7%)	0.65 (-1.61:2.94)	P=0.5636
Subject with at least one-point improvement	597 (99.0%)	597 (98.7%)	0.33 (-0.99:1.71)	P=0.5951

*95% C.I. for difference in proportion was calculated using Mietinen-Nurminen Method

The median Kaplan-Meier time to clinical improvement based on at least one-point improvement in 11-Point ordinal scale by WHO was 5 days in the IP + SoC group as compared to 6 days for SoC group (Figure 2a). In efficacy analysis, the median Kaplan-Meier time to clinical improvement based on at least two-point improvement in 11-Point ordinal scale by WHO was 5 days in the Molnupiravir + SoC arm as compared to 10 days for SoC arm (Figure 2b).

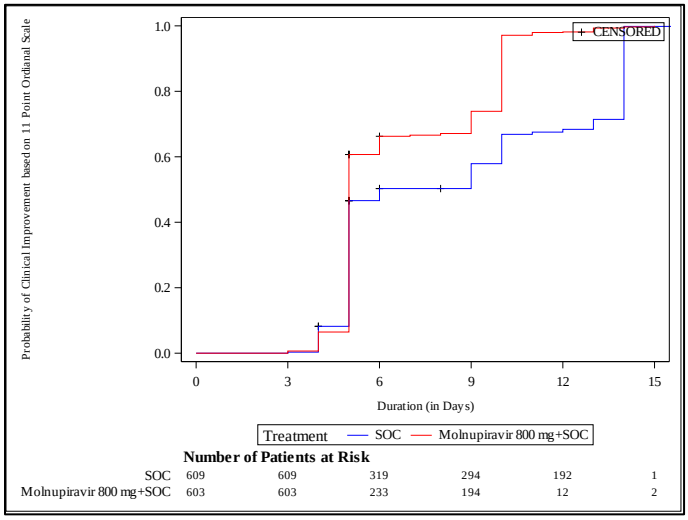

Figure 2 (a): Time to achieve at least one-point improvement in 11-Point ordinal scale by WHO up to Day 14- Full Analysis Set (N=1212)

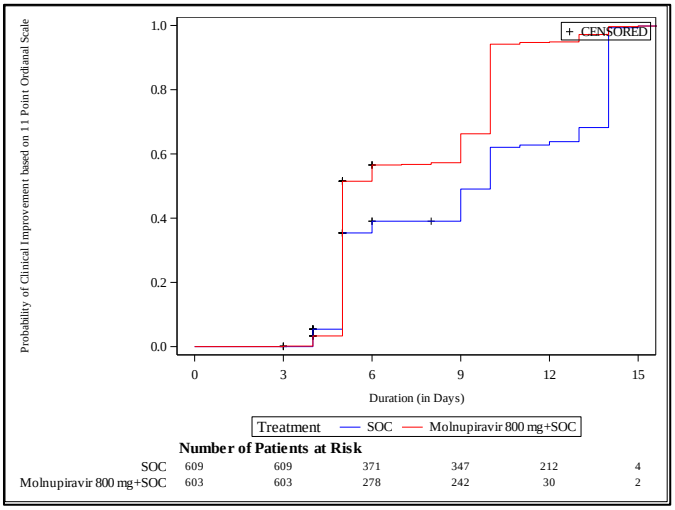

Figure 2 (b): Time to achieve at least two-point improvement in 11-Point ordinal scale by WHO up to Day 14- Full Analysis Set (N=1212)

The Mean ± SD change (Day 5- Day 1) in SARS-CoV-2 viral load (CT value) was found to be 10.2 ± 10.97 in IP+SoC group as compared to 5.8 ± 10.74 in SoC group [p=<0.0001]. The Mean ± SD change (Day 10- Day 1) in SARS-CoV-2 viral load (CT value) was found to be 15.9 ± 7.59 in IP+SoC group as compared to 10.5 ± 6.54 in SoC group [p=<0.0001] (Table 3).

Table 3: Cumulative Change in SARS-CoV-2 viral load (CT value) from baseline to each visit.

CT Value /Day	Statistic	Molnupiravir800mg+SOC(N=603)	SOC (N=609)	Overall(N=1212)
Change (Day 5-Day1)				
	n	573	571	1144
	Mean	10.2	5.8	8.0
	SD	10.97	10.74	11.07
	Median	11.0	6.0	9.0
	Range (Min: Max)	-34.0:34.0	-32.0:27.0	-34.0:34.0
	p-value*	<.0001(W)	<.0001(W)	<.0001(W)
Change (Day 10-Day1)				
	n	577	573	1150
	Mean	10.2	5.8	8.0
	SD	10.96	10.75	11.06
	Median	11.0	6.0	9.0
	Range (Min: Max)	-34.0:34.0	-32.0:27.0	-34.0:34.0
	p-value*	<.0001(W)	<.0001(W)	<.0001(W)

*p value was calculated by using either paired ‘t’ test (T) or Wilcoxon test (W) depending upon normality of the data.

At Day 5, 10 and 14, 397 (66.8%), 196 (87.9%) and 41 (77.4%) patients, respectively, were found negative for RT-PCR Test result in IP+SoC group whereas in SoC group, 294 (49.0%), 105 (32.6%) and 224 (94.9%) patients, respectively, had negative RT-PCR test result. The p-value was <.0001(C), <.0001(C), 0.0002(F) at Day 5, 10 and 14, respectively (Table 4.)

Table 4: SARS-CoV RT-PCR negative test results

SARS-CoV-2 Negativity, Statistics, n (%) [1]	Molnupiravir 800 mg+SOC (N=603)	SOC (N=609)
Day 5		
RT-PCR Test Result (Available N)	594	600
Proportion of subjects with negative test result	66.84	49.00
95% CI for the proportion [2]	(62.89:70.61)	(44.93:53.08)
p-value [3]	<.0001(C)	
Day 10		
RT-PCR Test Result (Available N)	223	322
Proportion of subjects with negative test result	87.89	32.61
95% CI for the proportion [2]	(82.87:91.87)	(27.51:38.03)
p-value [3]	<.0001(C)	
Day 14		
RT-PCR Test Result (Available N)	53	236
Proportion of subjects with negative test result	77.36	94.92
95% CI for the proportion [2]	(63.79:87.72)	(91.29:97.35)
p-value [3]	0.0002(F)	

[1] Percentages were calculated using 'Available N' group count of those who got the test done, at each visit as denominator. [2] 95% CI for the proportion was calculated using Clopper-Pearson Method. [3] p-value for comparison of proportion between Molnupiravir +SOC and SOC was calculated by Chi square test (C)/Fisher's Exact test (F).

A total of 49 adverse events (AEs) were reported in 37 (3.0%) participants. Out of which 19 AEs in 17 (2.8%) participants in SoC arm and 30 AEs in 20 (3.3%) participants in Molnupiravir+SoC arm. Two Serious Adverse Events (Renal calculi and Covid 19 Pneumonia) were reported in SoC arm during the study which required in patient hospitalization. However, participants were recovered completely. The severity of AEs reported in Molnupiravir+SoC arm and SoC arm were mild and moderate in intensity. The relationship of the AEs reported in 27 AEs in 17 (2.8%) participants in Molnupiravir+SoC arm was unrelated/Not related followed by AEs in 2 (0.3%) participants (Gastritis and Nausea) was possible and AE in 1 (0.2%) participant was unlikely. In SoC arm, AEs in 11 (2.7%) participants were observed to be unrelated/Not related followed by AE in 1 (0.2%) participant as unlikely. No SAE and deaths were observed in Molnupiravir+SoC arm as compared to SoC.

Discussion

On December 23, 2021, the US-FDA approved EUA to Molnupiravir (from Ridgeback/Merck) for non-

hospitalised adult patients with mild-to-moderate COVID-19. It is the first oral antiviral medication to be recommended by the WHO in the treatment guidelines for COVID-19 therapy. Based on the most comprehensive data from six randomised controlled studies involving 4796 participants, the WHO recommended this medication.[19] On November 4, 2021, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) approved Molnupiravir based on an interim analysis of the MOVe-OUT study. Additionally, on December 28, 2021, the Central Drugs Standard Control Organization (CDSCO), India, approved Molnupiravir a restricted use authorization (RUA). [20]

The trial cohort in the current study was typical of real-world patients with Covid-19-related mild illness. In order to focus on individuals who are most likely to require antiviral treatment and to enable a rapid evaluation of the therapeutic efficacy of Molnupiravir, only patients who had not had a Covid-19 vaccination were eligible for the current clinical trial. Additionally, 108 patients (n=108) had one or more high risk factors (obesity, diabetes, or hypertension) for severe illness due to Covid-19.

When compared to the SOC arm alone, the results shown that a considerably higher number of patients in the Molnupiravir + SoC arm had improved clinically by Day 5. Thus, the efficacy data revealed that clinical improvement was quicker in the group administered with Molnupiravir along with standard of care. However, as expected with course of mild COVID-19, majority of patients in both arm had significant clinical improvement in 14 days.

In this study, the findings suggested that higher proportion of patients reported RT-PCR negativity who received Molnupiravir in addition to SoC versus to those who received SoC alone. Higher CT values in IP+SoC group depicts greater viral load reduction in Molnupiravir arm.

Results of the present study indicated clinically significant improvement in WHO ordinal score (two and one point) of time to clinical improvement, reduction in SARS CoV-2 viral load and rate of SARS CoV-2 RT-PCR negativity in Molnupiravir+SoC arm which was comparable with the findings of MOVe-OUT clinical trial (Phase 2-3).[21] The MOVe-OUT was a large multicentre Phase 3 clinical trial conducted in 1433 mild COVID-19 patients who were at high risk for progression to severe disease. The incidence of hospitalization was lower in the Molnupiravir-treated group, and on average it was 8% from the published reports. From the phase I and II trials, it was reported that Molnupiravir (800 mg) was safe and well tolerated with no serious adverse events.[22-25]

Participants with atleast one adverse event were similar in both groups (3.4% in Molnupiravir+SoC and 2.9% in SoC). No severe/serious adverse events were deemed to be related to drug regime. Two SAEs were reported in SoC group which required hospitalisation, participants were recovered completely. No additional safety concerns were reported with use of Molnupiravir + SoC in high risk population. Commonly reported adverse events of Molnupiravir were headache, dizziness and GI symptoms. Overall, the present study safety and efficacy data are consistent with that of other published studies of Molnupiravir in COVID-19 patients.

The present study has some limitations namely, (i) it has been conducted in unvaccinated patients, and (ii) less number of high risk patients.

During the pandemic, when many drugs failed to show response against COVID-19, it is the first report of a

randomised controlled clinical trial from India on Molnupiravir representing comprehensive results on safety and efficacy in mild COVID-19.

Conclusion

Oral Molnupiravir when initiated within 5 days of onset of signs and symptoms in mild COVID-19 patients was found to be effective and well tolerated without any safety concerns.

Acknowledgement

We would like to acknowledge the efforts from Consortium of Companies which has led to the success of this clinical study. This consortium is one of its kind in India. This comprises of Dr Reddy's Ltd, Cipla Ltd, Emcure Pharmaceuticals, Mylan Pharma Ltd, Sun Pharmaceutical Ltd, and Torrent Pharma Ltd. Editorial assistance was provided by Mariya Bohra, Mawrah Arshad both from Dr. Reddy's Ltd. We thank all the participants, site staff and Ethics Committees for their contribution in the study. Exclusive partner for the study were JSS Medical Research Asia Pacific, Translational Health Science and Technology Institute (THSTI), and Metropolis Labs for providing their services.

Funding

Dr. Reddy's Laboratories and consortium of companies including, Cipla Ltd, Emcure Pharmaceuticals, Mylan Pharma Ltd, Sun Pharmaceutical Ltd and Torrent Pharmaceuticals Ltd.

References

1. WHO (2022) WHO Coronavirus (COVID-19) dashboard [Internet]. Available from: https://covid19.who.int/
2. Covid 19 Treatment Guideline [Internet]. Available from https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
3. Imran M, Kumar Arora M, Asdaq SM, Khan SA, Alaqel SI, Alshammari MK, Alshehri MM, Alshrari AS, Mateq Ali A, Al-Shammeri AM, Alhazmi BD. Discovery, development, and patent trends on Molnupiravir: A prospective oral treatment for COVID-19. Molecules. 2021 Jan;26(19):5795.
4. Ma X, Liang M, Ding M, Liu W, Ma H, Zhou X, Ren H. Extracorporeal Membrane Oxygenation (ECMO) in Critically Ill Patients with Coronavirus Disease 2019 (COVID-19) Pneumonia and Acute Respiratory Distress Syndrome (ARDS). Med Sci Monit. 2020 Aug 6;26: e925364.
5. NIH (2022) COVID-19 treatment guidelines. Clinical Spectrum of SARS-CoV-2 Infection [Internet] (updated 2022 Aug 8). Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
6. Kabinger, F., Stiller, C., Schmitzová, J. et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol 28, 740–746 (2021).
7. Toots M, Yoon JJ, Hart M, Natchus MG, Painter GR, Plemper RK. Quantitative efficacy paradigms of the influenza clinical drug candidate EIDD-2801 in the ferret model. Translational Research. 2020 Apr 1;218:16-28.
8. Fischer W, Eron JJ Jr., Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. June 17, 2021 (https://www.medrxiv.org/content/10.1101/2021.06.17 .21258639v1). preprint.
9. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad spectrum oral antiviral agent with activity against SARS-CoV-2.

Antimicrob Agents Chemother 2021;65(5):e02428-20.

10. Khoo SH, Fitzgerald R, Fletcher T, et al. Optimal dose and safety of molnu piravir in patients with early SARS-CoV-2: a phase I, open-label, dose-escalating, randomized controlled study. J Antimi crob Chemother 2021;76:3286-95.
11. Chawla A, Cao Y, Stone J, et al. Model based dose selection for the phase 3 evaluation of molnupiravir (MOV) in the treatment of COVID-19 in adults. In: Proceedings and abstracts of the 31st Annual Meeting of the European Congress of Clinical Microbiology and Infectious Dis eases, July 9–12, 2021. Basel, Switzerland: European Society of Clinical Microbiology and Infectious Diseases, 2021.
12. Mali, K.R., Eerike, M., Raj, G.M. et al. Efficacy and safety of Molnupiravir in COVID-19 patients: a systematic review. Ir J Med Sci (2022).
13. Rosenberg ES, Holtgrave DR, Dora bawila V, et al. New COVID-19 cases and hospitalizations among adults, by vaccination status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep 2021; 70:1306-11.
14. Tenforde MW, Self WH, Naioti EA, et al. Sustained effectiveness of Pfizer BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults — United States, March– July 2021. MMWR Morb Mortal Wkly Rep 2021; 70:1156-62.
15. Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA vac cines against COVID-19-associated hospitalization — five veterans affairs medical centers, United States, February 1–August 6, 2021. MMWR Morb Mortal Wkly Rep 2021; 70:1294-9.
16. Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. Viruses 2021;13:628.
17. Painter GR, Natchus MG, Cohen O, Holman W, Painter WP. Developing a direct acting, orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19. Current opinion in virology. 2021 Oct 1;50:17-22.
18. WHO (2022) WHO updates its treatment guidelines to include Molnupiravir.Available from: https://www.who.int/news/item/ 03-03-2022-molnupiravir
19. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. New England journal of medicine. 2021 Feb 11;384(6):497-511.
20. Singh AK, Singh A, Singh R, Misra A (2002) An updated practical guideline on use of molnupiravir and comparison with agents having emergency use authorization for treatment of COVID-19. Diabetes Metab Syndr 16(2):102396.
21. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. New England Journal of Medicine. 2022 Feb 10;386(6):509-20.
22. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob Agents Chemother 2021 Mar 1;65(5). e02428-20.

23. Khoo SH, Fitzgerald R, Fletcher T, et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomized controlled study [Online ahead of print] J Antimicrob Chemother 2021 Aug 27.
24. Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. Preprint medRxiv 2021 Jun 17.
25. The safety of molnupiravir (EIDD-2801) and its effect on viral shedding of SARS-CoV-2 (END-COVID) - full text view - ClinicalTrials.gov (Last accessed on October 20, 2022).