

Evaluation of publication bias for 12 clinical trials of molnupiravir to treat SARS-CoV-2 infection in 13,694 patients

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Abstract

Introduction:

During the COVID-19 pandemic, Merck Sharp and Dohme (MSD) acquired the global licensing rights for molnupiravir. MSD allowed Indian manufacturers to produce the drug under voluntary license. Indian companies conducted local clinical trials to evaluate the efficacy and safety of molnupiravir.

Methods

Searches of the Clinical Trials Registry-India (CTRI) were conducted to find registered trials of molnupiravir in India. Subsequent investigations were performed to assess which clinical trials had been presented or published.

Results

According to the CTRI, 12 randomised trials of molnupiravir were conducted in India, in 13,694 patients, starting in late May 2021. By July 2022, none of the 12 trials has been published, one was presented at a medical conference, and two were announced in press releases suggesting failure of treatment. Results from three trials were shared with the World Health Organisation. One of these three trials had many unexplained results, with effects of treatment significantly different from the MSD MOVE-OUT trial in a similar population.

Discussion

The lack of results runs counter to established practices and leaves a situation where approximately 90% of the global data on molnupiravir has not been published in any form. Access to patient-level databases is required to investigate risks of bias or medical fraud.

Introduction

The COVID-19 pandemic spurred the rapid development and clinical evaluation of novel antiviral therapeutics. In March 2020, Sheahan *et al.*, published a preprint on the *in vitro* efficacy of molnupiravir against SARS-CoV-2 (1). In May 2020, Ridgeback Biotherapeutics partnered with Merck Sharp and Dohme (MSD) to develop and commercialise the drug globally (2).

MSD initiated two Phase II/III trials, one focused on hospitalised patients (MOVE-IN, n = 304) and the second on non-hospitalised patients (MOVE-OUT, n = 1433). In April 2021, the MOVE-IN trial was terminated after an interim analysis showed no clinical benefits and trends for higher death rates on molnupiravir (3). The Phase 2 stage of the MOVE-OUT trial was first analysed in April 2021, with a recommendation to expand recruitment to a larger trial. The larger trial was stopped in October 2021 after an interim analysis of approximately 762 of the 1433 patients showed a 50% reduction in the risk of hospitalisation (4). When final results were published, there was an overall 30% reduction in hospitalisation (5), which was not statistically significant in a key sensitivity analysis. Several questions have been raised about the reliability of this clinical trial (6).

Relying on the initial interim analysis in October 2021, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) approved the use of molnupiravir in limited circumstances. Molnupiravir is approved in the US, but only as an option for patients not eligible to receive other antiviral drugs (7).

In April 2021, MSD signed non-exclusive voluntary licensing agreements with multiple Indian generic drug manufacturers (8). Soon afterwards, several Indian companies (see Table 1), presented their proposed molnupiravir trial protocols to the COVID-19 subject expert committee (SEC) at the Indian Central Drugs Standard Control Organisation (CDSCO) (9). Following initial proposals, the CDSCO SEC requested the companies to revise their protocols, with standardised primary objectives, endpoints, and sample sizes. Revised trial protocols for molnupiravir were considered by the CDSCO and deliberated upon on the 6th and 7th of May 2021 (10). The CDSCO generated a set of common objectives and endpoints after the meeting. The primary outcome for all trials of outpatients with mild SARS-CoV-2 infection was the "rate of hospitalisation from randomisation up to Day 14". For trials of moderate stage patients, the endpoint was the "proportion of patients with clinical improvement" at day 14. The CDSCO recommended that the firms commence trials in both patient groups and mandated a minimum sample size of 1218 for trials in mild patients and 1282 in moderately ill patients. For moderate patients, the CDSCO recommended trials should take the form of a Phase II/III trial split into two distinct steps. The companies were to start with a preliminary study on 100 patients and then present this data to the CDSCO before continuing onto the larger trial. On the 28th of December, it was widely reported that the Drugs Controller General of India (DCGI) had granted emergency use authorisation (EUA), allowing the companies to manufacture and market the drug for patients at high risk of disease progression (11). The SEC had highlighted molnupiravir's approval in the United Kingdom to support its approval in India. Other Indian health authorities were uncertain regarding the molnupiravir data, with Balram Bhargava, the head of the Indian Council of Medical Research (ICMR), outlining multiple reasons for scepticism (12) and noting "major safety concerns" (13).

Table 1

A list of the 12 Indian molnupiravir trials. A lack of transparency pervades the Indian molnupiravir trial registrations and their results. Many trial details have not been updated for months, and key details such as trial completion dates and trial outcomes are almost totally absent, as are final enrolment numbers for several trials. Data drawn from the Clinical Trials Registry- India (CTRI). * This was a joint trial with four other companies led by Dr Reddy's. ** Indicates information was obtained from press reporting rather than the CTRI.

Company	CTRI Number	Target population	Stated Sample Size	Date Registered	Completion date	Data Published in Paper/Preprint	Data Published in Press Release/Media/Other	Data Provided to WHO
Aurobindo Pharma	CTRI/2021/07/034588	Mild COVID-19 18-60	1220	05/07/2021	18/08/2021	No	No	Yes
Aurobindo Pharma	CTRI/2021/08/035424	Moderate COVID-19 18-60	100	04/08/2021	Terminated early**	No	Termination details only	Unknown
BDR Pharmaceuticals Internationals	CTRI/2021/06/034130	Mild COVID-19 18-60	1218	10/06/2021	Unknown	No	No	Unknown
BDR Pharmaceuticals Internationals	CTRI/2021/06/034220	Moderate COVID-19 18-60	1282	14/06/2021	Unknown	No	No	Unknown
Dr. Reddy's Laboratories*	CTRI/2021/06/033938	Mild COVID-19 18-60	1218	01/06/2021	Unknown	No	No	Yes
Hetero Drugs	CTRI/2021/05/033739	Mild COVID-19 18-60	1218	21/05/2022	05/08/2021	No	Interim press release and conference abstract	Yes (appears limited)
Hetero Drugs	CTRI/2021/05/033736	Moderate COVID-19 18-60	1282	21/05/2022	Unknown	No	No	Unknown
MSN Laboratories	CTRI/2021/05/033904	Mild COVID-19 18-60	1218	31/05/2021	04/11/2021	No	No	Unknown
MSN Laboratories	CTRI/2021/05/033864	Moderate COVID-19 18-60	1282	28/05/2021	Terminated early**	No	Termination details only	Unknown
Natco Pharma	CTRI/2021/05/033693	Mild COVID-19 18-60	1218	20/05/2021	Unknown	No	No	Unknown
Optimus Pharma	CTRI/2021/06/033992	Mild COVID-19 18-60	1218	04/06/2021	Unknown	No	Limited press releases	Unknown
Strides Pharma Science	CTRI/2021/06/034015	Mild COVID-19 18-60	1220	05/06/2021	Unknown	No	No	Unknown

The aim of this analysis was to evaluate the efficacy and safety of molnupiravir in Indian trials, given the large scale of the research programme undertaken by the Indian companies.

Methods

A search was conducted on the Clinical Trials Registry- India (CTRI) platform using the search terms molnupiravir, MK-4482, EIDD-2801, and Lagevrio. Details were then extracted from the trial registrations and evaluated for relevance. Additionally, searches of PubMed, Google Scholar, arXiv, bioRxiv, medRxiv, Research Square, trial sponsor's websites, and press sources were performed using the same search terms to detect publications and identify additional information about the trials. All contacts listed on the trial registrations were also contacted for updates. For the Hetero trial in patients with mild COVID-19, each trial site principal investigator was also contacted individually in February 2022. The results from the World Health Organization guidelines on molnupiravir were also evaluated, as they referred to the results from several Indian trials.

Results

The search on CTRI presented 12 trials listed in Table 1 (14–25).

While most companies conducted or contracted out individual trials, five of them ran a joint trial led by Dr Reddy's Laboratories (26). Several companies have been slow to update their CTRI records, making it unclear if their trials are complete or still taking place. We did not receive any response from emails to trial contacts requesting additional details. As of 25th July 2022, none of the 12 trials have published results in any journal or preprint repository. Nonetheless, indications of results have been made public for several of the trials in different ways. Additionally, some data is non-public but has been provided to the WHO by companies including Hetero and Aurobindo Pharma. This data has been added to the living meta-analysis of COVID-19 treatments hosted by the BMJ, which serves to advise the WHO, and has access to WHO data (27).

Clinical trials from Hetero

The Hetero trial in patients with mild COVID-19 began enrolment on 25th May 2021 and reported interim results based on 741 patients in a press conference just six weeks and three days later, on 9th July 2021, (28). As patients were followed up for at least 14 days for the data presented in the interim analysis, the latest a patient could have been recruited was the 25th of June. By contrast, recruitment for the Phase III portion of the MSD MOVE-OUT trial was started on 6th May 2021 and produced results from the main interim analysis of 762 patients on the 1st of October 2021, four months and 25 days later.

Hetero subsequently provided final results based on 1218 patients in a conference abstract in February 2022 (29). As with the MOVE-OUT trial, the interim data from the Hetero study showed evidence of a strong benefit for molnupiravir, while the data from patients enrolled after the interim analysis showed no statistically significant benefit for molnupiravir. In the interim data, the 14-day hospitalisation rate was 1.89% (7/370) in the molnupiravir group versus 6.2% (23/371) in the standard care group.

In comparison, among patients recruited after the interim data deadline, 0.8% (2/238) of participants in the molnupiravir arm versus 1.3% (3/239) in the standard of care arm were hospitalised.

Table 2 highlights some of the key comparisons between the MOVE-OUT and Hetero data. There are unexplained differences in outcomes between the trials. For example, there were no patients with any adverse events in the Hetero trial: this would be almost unprecedented in clinical trials. The Hetero trial showed statistically significant benefits of molnupiravir for viral clearance and clinical recovery, both of which were not seen for the MOVE-OUT trial.

Table 2

A comparison of the MOVE-OUT and Hetero molnupiravir trials. Key comparisons between the two trials, including various clinical outcomes, are listed. Phase 1 hospitalisations are those that were analysed in the interim analyses of both companies, while phase 2 hospitalisations are all subsequent/additional hospitalisations.

Comparisons/Outcomes	MOVE-OUT Molnupiravir vs Placebo	Hetero Molnupiravir vs Standard of Care
Trial sites	173	15
Total sample size	1433	1218
Time to report interim results	4 months, 25 days (762 patients)	6 weeks, 3 days (741 patients)
Serious adverse events	7% vs 10%	0% vs 0%
Discontinuation for adverse events	1.4% vs 2.9%	0% vs 0%
Viral clearance Day 5	13% vs 6% (n.s.)	77% vs 29% (p < 0.001)
WHO 2-point improvement Day 10	5.9% vs 4.8% (n.s.)	95.6% vs 74.3% (p < 0.001)
Hospitalisations phase 1	7.3% vs 14.1% (p = 0.001)	1.9% vs 6.2% (p = 0.0027)
Hospitalisations phase 2	6.2% vs 4.4% (p = n.s.)	0.8% vs 1.3% (p = n.s.)
Hospitalisations overall	6.8% vs. 9.7% (p = 0.06)	1.5% vs 4.3% (p < 0.01)

It appears that Hetero provided the WHO only basic summary data as the BMJ meta-analysis supplementary data files report no records of mean patient age or 'percentage male' for the Hetero trial (30). However, these details were both present in the Hetero February 2022 conference presentation (29).

Clinical trials from other Indian companies

Dr Reddy's Laboratories appears to have provided the BMJ/WHO with more detailed data on 736 patients (30). It is unclear if this represents interim data; as per the CDSCO requirements, they were due to enrol 1218 patients (20). Aurobindo Pharma also appears to have provided the WHO with data on a trial of 1220 patients. It is uncertain which trial this was as the CTRI number referred to by BMJ is the same as the Aurobindo trial in patients with moderate COVID-19, which reportedly terminated early in October 2021 due to negative results and claims to have only recruited 100 patients on the CTRI (31). No additional information is available on this trial or one by MSN Laboratories on moderately ill COVID-19 patients, which was also terminated early due to negative results (31). The trial number provided by BMJ was likely a data entry error as there is a second Aurobindo trial in mild COVID-19 patients that recruited 1220 patients. The BMJ meta-analysis flags the three Indian trials as being "probably at high risk of bias" regarding deviations from the intended intervention, however, provides no trial-level breakdown of results.

Natco Pharma has not released any public data but informed investors their investments in COVID-19 therapeutics “has been a disaster” (32, 33). Another company, Optimus Pharma, have made slight mentions of their results on several occasions during their trial (34–37), ending with a claim in December 2021 that “the trial is consistent with 30–35% improvement within the first five days of the administration” (38). Despite sharing data on four occasions, Optimus only once provided details on the hospitalisation outcome, revealing in an email to the authors of an October 2021 review of molnupiravir data that one patient in the molnupiravir group was hospitalised versus three in the standard care group (35). The outcome most frequently reported by Optimus was PCR negativity. Data from their public statements are summarised in Table 3.

Table 3
A summary of the RT-PCR negativity data derived from public statements about the Optimus Pharma trial. Partial figures on the percentage of study participants who were RT-PCR negative at day 5 and 10 were provided by Optimus Pharma at various points in 2022. Mol = molnupiravir, SoC = standard of care, NR = no record.

	July 2021		October A 2021		October B 2021		December 2021	
	PCR Negativity		PCR Negativity		PCR Negativity		PCR Negativity	
Treatment	Mol	SoC	Mol	SoC	Mol	SoC	Mol	SoC
Day 5	78%	48%	77%	52%	78%	48%	71%	52%
Day 10	0%	NR	99.5%	69.5%	91.5%	43%	97.3%	84%

Discussion

Altogether, data from 13,694 Indian trial participants has not been formally published, with data from 11,258 of these not being *publicly* available, not even in summary form e.g., in press releases. There is also a lack of transparency about what level of access the Indian drug regulator and the WHO have to the data. The companies themselves appear to be the only ones with complete access. The CDSCO is likely to be the best informed, having seen presentations of the data for all the trials (39). Meanwhile, the WHO appears to have access to only limited summary data from 3 of the 12 trials. The full extent of the information organisations such as the CDSCO and WHO have used to make national and international guidelines is unclear.

The Hetero trial’s interim analysis presents somewhat of a puzzling case. It is hard to understand how the Indian trial could have recruited, followed up and analysed a similar number of patients to the MSD trial in a far shorter period. Enrolling, treating, and assessing 741 patients across 15 sites in a few weeks and then immediately analysing and publishing this data is an unusual achievement – even for COVID-19 trials with accelerated timelines. Hetero’s timeline looks even more out of place in comparison to the interim analysis of the MSD run MOVE-OUT trial, which took almost five months to produce their interim analysis compared to just over six weeks for Hetero, as Table 2 demonstrates. This disparity is difficult to comprehend, especially when accounting for the reality that MSD’s annual revenue is 40–50 times greater than that of Hetero (40, 41). It is also troubling that both trials exhibit the same trend of very positive interim results followed by negative outcomes in post-interim analysis data. Concerningly, Hetero, has also been involved in numerous scandals over the past decade ranging from poor manufacturing practices (42–44), pollution breaches (45, 46), being accused of corruption and intimidation (45), and suspect accounting practices (47).

The Optimus Pharma data also raises questions for several reasons. Firstly, the trial was reported to have been completed in October 2021 in a press release containing very limited results (36) though this was not reported to the CTRI (see Table 1). Then, in December 2021, a new statement containing different results was released (37). While this may be because the October figures were based on interim results, this was not made clear in the press release. More generally, while PCR negativity in the molnupiravir arm varies somewhat, it fluctuates widely in the Standard of Care (SoC) arm. Of more concern is the fact that the PCR negativity reported by Optimus Pharma in the second set of figures they released in October 2021 is nearly identical to that reported by Hetero (29, 36). Neither of these results is consistent with the MOVE-OUT data (see Table 2).

Globally, the largest molnupiravir trial is the UK Panoramic trial coordinated by Oxford University, which has recruited over 20,000 patients to either molnupiravir or standard of care since December 2021 (48). This is over double the initial planned sample size of 10,600 (49), but no explanation is available for such a large increase in sample size.

While the results from Panoramic are due imminently, they have not been published at the time of writing. Adding the number of patients from Panoramic to the unpublished Indian data leaves data for at least 31,258 molnupiravir patients unpublished (or 33,694 when including the Hetero and Optimus Pharma patients whose data was only partially released). Therefore, almost 90% of the global data on patient outcomes following treatment with molnupiravir are currently unavailable. Even when the Panoramic trial reports results, that will still leave at least a third of the global molnupiravir data unpublished. Previously, when it emerged that 60% of the patient data related to Tamiflu had not been published (50), this was viewed as a scandal; so far, there has been no similar level of concern regarding the molnupiravir data. Whether the Indian molnupiravir data is unreleased due to neglect or because of commercial considerations as occurred when GlaxoSmithKline concealed data regarding the lack of efficacy of the antidepressant paroxetine in patients under 18 (51) cannot be determined. Patient-level data would help answer many of the unanswered questions swirling around the molnupiravir trials; however, even summary data is largely absent, as discussed. The inherent danger of making decisions without access to all the relevant information is heightened, given the concerns about molnupiravir’s genotoxicity and potential risk to pregnant patients (52). Given the scale of the missing data, the MHRA’s decision to grant EUA for the drug seems premature, as others have previously argued (53).

Unfortunately, the problem of a lack of data transparency is not isolated to one country. While the USA has required trial sponsors to publish trial data within one year of study completion, these rules do not apply globally. Even in the US, compliance is poor, with only 41% of sponsors meeting this requirement (54). It

is approaching 12 months since most of the 12 Indian trials concluded. While it is concerning that data from so many patients is missing, the circumstances are worsened because there is currently nothing to prevent the same situation from reoccurring with another drug.

Declarations

The authors declare no conflicts of interest.

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