This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

# SCIENTIFIC DISCUSSION

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|---|---|
| **Name of the Finished Pharmaceutical Product** | [CV009 trade name][*] |
| **Manufacturer of Prequalified Product** | Dr. Reddy's Laboratories Ltd<br>Formulation Tech Ops – II<br>Survey No. 42p, 43, 44p, 45p, 46p, 53, 54 & 83<br>Bachupally Village<br>Qutubullapur Mandal<br>Ranga Reddy District<br>Telangana<br>India. |
| **Active Pharmaceutical Ingredient(s) (API)** | Molnupiravir |
| **Pharmaco-therapeutic group (ATC Code)** | Nucleosides and nucleotides excluding reverse transcriptase inhibitors (J05AB18) |
| **Therapeutic indication** | [CV009 trade name] is indicated for treating mild or moderate COVID-19 in adults who do not require supplemental oxygen but who are at risk of their disease becoming severe. |

## 1. Introduction

[CV009 trade name] is indicated for treating mild or moderate COVID-19 in adults who do not require supplemental oxygen but who are at risk of their disease becoming severe.

Treatment with [CV009 trade name] should be started as soon as possible after diagnosing COVID-19 and within 5 days of the onset of COVID-19 symptoms.

## 2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

### Active pharmaceutical Ingredient (API)

Molnupiravir has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [CV009 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

(APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

**Other ingredients**

Other ingredients used in the capsule fill formulation include microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate. The capsule shell contains hypromellose carrageenan, potassium acetate and titanium dioxide. None of the excipients used in the manufacture of the capsules are of human or animal origin. TSE/BSE free certificates from the suppliers have been provided with regard to the excipients.

## Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

[CV009 trade name] is presented as size '0' hard cellulose capsules with white opaque cap and white opaque body without imprinting.They contain white to off-white granular powder. The capsules are packaged in Alu-Alu blister cards.

The development of the final composition of the capsules has been described. The objective was to develop an immediate release solid oral dosage form, bioequivalent to the WHO recommended comparator product, Lagevrio® (molnupiravir) 200mg capsules (Merck Sharp & Dohme). With reference to the technical package from MSD, the comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. Cellulose capsule shell composed of hypromellose was selected for encapsulation of the lubricated blend. It is widely used in oral dosage forms, generally considered non-irritant and non-toxic upon oral administration. The excipients were selected based on the excipients used in the comparator product and API-excipient compatibility data. Based on literature information, characterisation of the API and the API-excipient compatibility study, a wet granulation process was selected for the manufacture of the granules. The rationale for selection of the wet granulation process is to obtain granules with uniform distribution of the API, with improved flow properties to aid the capsule filling process. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

*Specifications*

The finished product specifications include tests for description, identification of the API (UV and HPLC), uniformity of dosage units (by weight variation), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), water content (KF) and microbial limits. The test methods have been satisfactorily validated.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. No significant change was observed and all parameters were well within the agreed limits at both storage conditions, with only a slight increase of the total degradation products. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are regarded acceptable.

## Conclusion

The quality part of the dossier is accepted.

## 3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Molnupiravir capsules 200 mg of (Test-T) of Dr. Reddy's Laboratories Limited, India comparing with Lagevrio® (Molnupiravir) 200 mg hard capsules of Merck Sharp & Dohme B.V, Netherlands in normal, healthy, adult, human subjects under fasting conditions (study no. 21-150).
The objective of the study was to compare the bioavailability of the stated molnupiravir 200 mg capsule manufactured by/for Dr. Reddy's Laboratories Limited, India (test drug) with the reference formulation Lagevrio® (MSD) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

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|---|---|
| Treatment T: | Test – 1 capsule Molnupiravir 200 mg (molnupiravir 200 mg) Batch no. B2200426 |
| Treatment R: | Reference – 1 capsule Lagevrio® 200 mg (molnupiravir 200 mg) Batch no. U038659 |

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 17 samples within 12 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, $C_{max,}$ and $t_{max}$ for bioequivalence evaluation. Drug concentrations for the active metabolite N4-hydroxycytidine were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/mL for N4-hydroxycytidine.
The study was performed with 40 participants. Data generated from a total of 39 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for N4-hydroxycytidine as well as statistical results are summarised in the following table:

**N4-hydroxycytidine**

| Pharmacokinetic Parameter | Test formulation (T) arithmetic mean ± SD (*) | Reference (R) arithmetic mean ± SD (*) | log-transformed parameters | |
|---|---|---|---|---|
| | | | Ratio T/R (%) | Conventional 90% CI (ANOVAlog) |
| $t_{max}$ (h) | 1.26 ± 0.47 | 1.15 ± 0.31 | - | - |
| $C_{max}$ (ng/mL) | 1369 ± 368 (1324) | 1405 ± 343 (1365) | 96.9 | 91.1 – 103.0 |
| $AUC_{0-t}$ (ng.h/mL) | 2789 ± 513 (2740) | 2687 ± 573 (2625) | 104.2 | 100.0 – 108.6 |
| $AUC_{0-inf}$ (ng.h/mL) | 2803 ± 513 (2754) | 2699 ± 572 (2643) | 104.2 | 100.1 – 108.5 |

*geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and $C_{max}$ values regarding N4-hydroxycytidine. Accordingly, the test Molnupiravir 200 mg capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Lagevrio® (MSD).

## 4. Summary of product safety and efficacy

[CV009 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [CV009 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Lagevrio® (MSD) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [CV009 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

## 5. Benefit risk assessment and overall conclusion

### Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [CV009 trade name] is used in accordance with the SmPC.

### Bioequivalence

[CV009 trade name] has been shown to be bioequivalent with Lagevrio® (MSD).

### Efficacy and Safety

Regarding clinical efficacy and safety, [CV009 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.**}**

### Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [CV00 trade name] was acceptable for the following indication: 'for treating mild or moderate COVID-19 in adults who do not require supplemental oxygen but who are at risk of their disease becoming severe", and would allow inclusion of [CV trade name], manufactured at Dr. Reddy's Laboratories Ltd, Formulation Tech Ops – II, Survey No. 42p, 43, 44p, 45p, 46p, 53, 54 & 83, Bachupally Village, Qutubullapur Mandal, Ranga Reddy District, Telangana, India, in the list of prequalified medicinal products.