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

Name of the Finished Pharmaceutical Product	[CV026 trade name]*
Manufacturer of Prequalified Product	Shanghai Desano Bio-Pharmaceutical Co., Ltd. Block No. 2 1479 Zhangheng Road China (Shanghai) Pilot Free Trade Zone Shanghai 201203, P.R. China
Active Pharmaceutical Ingredient(s) (API)	Nirmatrelvir, ritonavir
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, protease inhibitors, ATC code: J05AE30
Therapeutic indication	[CV026 trade name] is indicated for treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and whose disease is at higher risk for progressing to severe COVID-19

1. Introduction

[CV026 trade name] is indicated for treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and whose disease is at higher risk for progressing to severe COVID-19. The management of COVID-19 should follow the most recent authoritative guidelines, including those issued by WHO

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)

Nirmatrelvir and ritonavir have 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 APIs, used in the manufacture of [CV026 trade name] are of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements

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

Other ingredients

Other ingredients used in the nirmatrelvir core tablet formulation include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and colloidal silicon dioxide, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol, titanium dioxide and iron oxide yellow. Lactose monohydrate is from bovine origin. TSE/BSE compliance declarations were provided for the excipients.

Other ingredients used in the ritonavir core tablet formulation include copovidone, colloidal silicon dioxide, sorbitan monolaurate, dicalcium phosphate anhydrous and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, polyethylene glycol, talc and titanium dioxide. TSE/BSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product is a co-blistered product, consisting of four and two dosage units of nirmatrelvir 150mg film-coated tablets and ritonavir 100mg film-coated tablets, respectively, per aluminium foil on aluminium foil blister card.

Pharmaceutical development and manufacture

The multisource product is a light yellow, oval, film- coated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has ‘D33’ debossed (stamped into) one side and is plain on the other side.

The aim of the formulation development was to obtain a stable, robust, immediate release solid oral dosage form, bioequivalent to the Nirmatrelvir 150mg film-coated tablets of the WHO recommended comparator product, PaxlovidTM (Nirmatrelvir 150mg film-coated tablets and Ritonavir 100mg film-coated tablets; co-pack by Pfizer Labs). The quality target product profile was defined based on literature review and characterization of the comparator product and critical quality attributes were identified. The excipients of the core tablets were selected based on the excipients used in the comparator product and API-excipient compatibility data. Based on the poor solubility, poor flowability and average compressibility of the API, dry granulation by compaction, which was used for the comparator product, was selected as the manufacturing process for the tablets. The manufacturing process was validated and dissolution profile similarity with the comparator tablets was also demonstrated. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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

Ritonavir100mg film-coated tablets

The multisource product is a white to off-white, oval, film- coated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has ‘D32’ debossed (stamped into) one side and is plain on the other side.

The aim of the formulation development was to obtain a stable, robust, immediate release solid oral dosage form, bioequivalent to the Ritonavir 100mg film-coated tablets of the WHO recommended comparator product, PaxlovidTM (Nirmatrelvir 150mg film-coated tablets and Ritonavir 100mg film-coated tablets; co-pack by Pfizer Labs). The quality target product profile was defined based on literature review and characterization of the comparator product and critical quality attributes were identified. The excipients of the core tablets were selected based on the excipients used in the comparator product and API-excipient compatibility data. Hot melt extrusion technology was adopted to obtain the solid dispersion, which is same as for the comparator product indicated in the EMA public assessment report. The manufacturing process was validated and dissolution profile similarity with the comparator tablets was also demonstrated. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has no potential to contain N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitrosamines on selected batches post prequalification.

Specifications

The specifications for nirmatrelvir 150mg film-coated tablets include tests for description, identification of API (IR and HPLC), assay (HPLC), related substances (HPLC), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), water content (KF) and microbial limits. The test procedures have been adequately validated.

The specifications for ritonavir 100mg film-coated tablets are pharmacopoeial based and include tests for description, identification of API (HPLC and UV), polymorphic form (p-XRD), assay (HPLC), related substances (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), water content (KF) and microbial limits. The test procedures have been adequately validated

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the co-blistered product. The data showed a slight increase for some of the degradation products, though the levels stayed well within agreed limits at the storage conditions for both tablets. The absence (below detection limit) of the crystalline form of the ritonavir API in the ritonavir film-coated tablets was demonstrated by p-XRD up to 6 months at accelerated storage condition and up to 12 months at long-term storage condition. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

Two bioequivalence studies have been performed.

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.

Study title:

A randomized, open label, balanced, two treatment, four period, two sequence, single dose, full replicate, crossover bioequivalence study of Nirmatrelvir 300 mg (2x150 mg film-coated tablets) + Ritonavir 100 mg (1 film-coated tablet) of Shanghai Desano Bio-Pharmaceutical Co., Ltd. with Paxlovid (nirmatrelvir 300mg (2 x150mg) + ritonavir 100mg), of Pfizer Labs, Division of Pfizer Inc. New York, NY10017, in normal, healthy, adult, human subjects under fasting conditions (study no. ARL/22/208).

The objective of the study was to compare the bioavailability of the stated Nirmatrelvir 150 mg tablet (co-packed with Ritonavir 100 mg tablets) manufactured for/by Desano Bio-Pharmaceutical Co., Ltd., China (test drug) with the reference formulation PaxlovidTM 150 mg (co-packed with Ritonavir 100 mg (Pfizer)) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, full replicate, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments twice in a randomized fashion:

Treatment T:	Test – 2 tablets Nirmatrelvir 150 mg + 1 tablet Ritonavir 100 mg (nirmatrelvir 300 mg + ritonavir 100 mg) Batch no. DGE22003
Treatment R:	Reference –Paxlovid^{TM} (2 tablets nirmatrelvir 150 mg + 1 tablet ritonavir 100 mg)

(nirmatrelvir 300 mg + ritonavir 100 mg)
Batch no. GC4759

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for nirmatrelvir and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for nirmatrelvir and about 10 ng/ml for ritonavir.

The study was performed with 44 participants; data generated from a total of 43 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for nirmatrelvir and ritonavir as well as statistical results are summarised in the following tables:

Nirmatrelvir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	2.71 ± 1.09	2.58 ± 1.35	–	–
C_{max} ng/mL)	3777 ± 1191 (3608)	3936 ± 1272 (3727)	96.8	92.2 – 101.7
AUC_{0-t} (ng·h/mL)	38537 ± 13002 (36473)	40781 ± 14364 (38252)	95.3	91.0 – 99.9
AUC_{0-inf} (ng·h/mL)	40443 ± 13354 (38342)	42862 ± 14830 (40213)	95.3	91.0 – 99.9

Ritonavir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.97 ± 0.72	3.67 ± 0.92	–	–
C_{max} ng/mL)	766 ± 445 (670)	897 ± 445 (793)	84.5	78.1 – 91.4
AUC_{0-t} (ng·h/mL)	6739 ± 3847 (6010)	7802 ± 3468 (7117)	84.4	79.0 – 90.2
AUC_{0-inf} (ng·h/mL)	6977 ± 3898 (6270)	8060 ± 3521 (7382)	84.9	79.7 – 90.4

The results of the study show that preset acceptance limits of 80 -125 % are met for both AUC and Cmax values regarding nirmatrelvir. For ritonavir, the preset acceptance limits of 80 -125 % are not met for both AUC and Cmax values (widening was not allowed, as the intraCV was below 30%). Accordingly, the test Nirmatrelvir 150 mg tablet co-packed with Ritonavir 100 mg meets not the

criteria for bioequivalence with regard to the rate and extent of absorption and is therefore not bioequivalent to the reference PaxlovidTM (Pfizer) co-packed with Ritonavir 100 mg.

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.

Study title:

A randomized, open label, balanced, two treatment, four period, two sequence, single dose, full replicate, crossover bioequivalence study of Nirmatrelvir 300 mg (2 x 150 mg film-coated tablets) + Ritonavir 100 mg (1 film-coated tablet) of Shanghai Desano Bio-Pharmaceutical Co., Ltd. with Paxlovid (nirmatrelvir 300 mg (2 x 150 mg) + ritonavir 100 mg), of Pfizer Labs, Division of Pfizer Inc. New York, NY10017, in normal, healthy, adult, human subjects under fasting conditions (study no. ACE-CT-037B-fast).

The objective of the study was to compare the bioavailability of the stated Nirmatrelvir 150 mg tablet (co-packed with Ritonavir 100 mg tablets) manufactured for/by Desano Bio-Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Paxlovid^{TM} 150 mg (co-packed with Ritonavir 100 mg (Pfizer)) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, full replicate, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments twice in a randomized fashion:

Treatment T: Test – 2 tablets Nirmatrelvir 150 mg + 1 tablet Ritonavir 100 mg (nirmatrelvir 300 mg + ritonavir 100 mg)
Batch no. DGE22003

Treatment R: Reference – 2 tablets Paxlovid^{TM} 150 mg + 1 tablet Ritonavir 100 mg (nirmatrelvir 300 mg + ritonavir 100 mg)
Batch no. GC4759

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for nirmatrelvir and ritonavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for nirmatrelvir and about 10 ng/ml for ritonavir.

The study was performed with 32 participants; data generated from a total of 32 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for nirmatrelvir and ritonavir as well as statistical results are summarised in the following tables:

Nirmatrelvir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	2.59 ± 1.05	2.41 ± 1.06	–	–
C_{max} ng/mL)	3159 ± 835 (3056)	3155 ± 693 (3076)	99.3	94.1 – 104.9
AUC_{0-t} (ng·h/mL)	26719 ± 6139 (26064)	27055 ± 5887 (26391)	98.8	94.6 – 103.1
AUC_{0-inf} (ng·h/mL)	28482 ± 6527 (27774)	28709 ± 6015 (28077)	98.9	94.7 – 103.3

Ritonavir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.41 ± 0.82	3.11 ± 1.18	–	–
C_{max} ng/mL)	693 ± 366 (606)	746 ± 324 (678)	89.5	81.0 – 98.9
AUC_{0-t} (ng·h/mL)	4908 ± 2209 (4427)	5314 ± 1918 (4965)	89.2	82.8 – 96.7
AUC_{0-inf} (ng·h/mL)	5099 ± 2215 (4636)	5502 ± 1957 (5149)	90.0	83.2 – 97.4

The results of the study show that preset acceptance limits of 80 -125 % are met for both AUC and C_{max} values regarding nirmatrelvir and ritonavir. Accordingly, the test Nirmatrelvir 150 mg tablet co-packed with Ritonavir 100 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Paxlovid™ (Pfizer) co-packed with Ritonavir 100 mg.

After confirming absence of a statistically significant study-by-formulation interaction, pooled analysis of the two bioequivalence studies showed that preset acceptance limits of 80 -125 % are met for both AUC and C_{max} values regarding nirmatrelvir and ritonavir. Accordingly, it can be concluded that the test Nirmatrelvir 150 mg tablet co-packed with Ritonavir 100 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Paxlovid™ (Pfizer) co-packed with Ritonavir 100 mg.

4. Summary of product safety and efficacy

[CV026 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, [CV026 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Paxlovid™ (nirmatrelvir tablets 150 mg; ritonavir tablets 100 mg) (co-packaged) of Pfizer Labs for which benefits have been proven in terms of clinical efficacy. The clinical safety of [CV026 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 [CV026 trade name] is used in accordance with the SmPC.

Bioequivalence

[CV026 trade name] has been shown to be bioequivalent with Paxlovid™ (nirmatrelvir tablets 150 mg; ritonavir tablets 100 mg) (co-packaged) of Pfizer Labs.

Efficacy and Safety

Regarding clinical efficacy and safety, [CV026 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 [CV026 trade name] was acceptable for the following indication: 'treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and whose disease is at higher risk for progressing to severe COVID-19', and would allow inclusion of [CV026 trade name], manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd., Block No. 2, 1479 Zhangheng Road, China (Shanghai) Pilot Free Trade Zone Shanghai 201203, P.R. China in the list of prequalified medicinal products.