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Reproductive and developmental safety of nirmatrelvir (PF-07321332), an oral SARS-CoV-2 \( M^{\text{pro}} \) inhibitor in animal models

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1. Introduction

The coronavirus disease 2019 (COVID-19) global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over 250 million confirmed COVID-19 cases and over 5 million deaths worldwide as of November 2021, prior to the emergency use authorization (EUA) of PAXLOVID. While vaccines have proven to result in over 250 million confirmed COVID-19 cases and over 5 million deaths worldwide as of November 2021, prior to the emergency use authorization (EUA) of PAXLOVID. While vaccines have proven to...

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and lack of genetic toxicity [1]. The lack of adverse findings in nonclinical species is consistent with the high selectivity of NMV for the intended therapeutic target, which is a virus specific protein not present in mammalian cells [1]. Due to the predominant role of CYP3A4 in the metabolism of NMV, co-administration with ritonavir, a CYP3A4 inhibitor, is being used to enhance pharmacological concentrations of NMV, a clinically proven approach to enhancing pharmacokinetics of protease inhibitors [1,4].

Given that males and females of reproductive age are included in the intended patient population, low risk of effects on fertility and embryofetal development, which includes a lack of genetic toxicity, are desirable for widespread use of PAXLOVID. In addition, favorable developmental toxicity and genetic toxicity profiles are needed to support potential use in pregnant women, which may be of importance given the evidence of higher risk related to COVID-19 during pregnancy [5–15]. Here we report the results of the reproductive and developmental toxicity studies with NMV, the antiviral component of PAXLOVID.

2. Materials and methods

All studies were conducted in compliance with US Food and Drug Administration Good Laboratory Practice (GLP) regulations in a test facility that was accredited by the Association of Assessment and Accreditation of Laboratory Animal Care (AAALAC) with oversight by an Institutional Animal Care and Use Committee (IACUC).

2.1. Test article

For the embryofetal development (EFD) and fertility studies, NMV was manufactured as a 50% spray dried dispersion (SDD; 50% active 2.1. Test article consisting of a suspension of 1% (w/v) Soluplus and 0.5% (w/v) PF-07321332, 50% HPMCAS-MG) and supplied by Pfizer, Inc. (New York, NY, USA) and was formulated for each study in an aqueous vehicle for the embryo, control the MF grade of HPMCAS was used to more closely match the particle size that resulted from the SDD process and was formulated in the same manner as the test article. For each study, NMV concentrations were analyzed and confirmed in dosing formulations.

2.2. Animals and husbandry

Male and female Wistar Han (Crl:WI[Han]) rats (Charles River Laboratories, Inc., Raleigh, NC) and female [Hra:(NZWSPF) New Zealand White rabbits (Envigo Global Services, Inc., Denver, PA) were used in these studies. Animals were group housed, except when pregnant or paired for mating. Rats were provided Certified Irradiated Rodent Diet 2916C (Envigo Teklad Global Diet) available ad libitum. Rabbits were provided 150 g/day of Certified Rabbit Diet 2030C (Envigo Teklad Global Diet). Municipal drinking water purified by reverse osmosis was provided ad libitum. Environmental conditions across studies were set to maintain relative humidity at 30–70% and temperature of 68 °F–79 °F and 61 °F–72 °F for rats and rabbits, respectively. Room lighting was set to provide a 12-h light/dark cycle.

2.3. Study design and test article administration

2.3.1. Fertility and early embryonic development study in rats

Male (9–14 weeks old and 326–397 g at dose initiation) and female (12–14 weeks old and 196–261 g at dose initiation) rats were acclimated and randomly assigned to four groups (n = 20 per group/sex). NMV doses of 0, 60, 200, or 1000 mg/kg/day were orally (gavage) administered to both sexes 14 days prior to mating, throughout the mating phase, and until gestation day (GD) 6 for the females and for a total of 32 doses in the males. NMV was tested up to the limit dose of 1000 mg/kg/day in accordance with ICH guidelines [16]. Control animals were administered the vehicle by the same dosing route and regimen. The dosing volume was 10 mL/kg. Blood samples were taken from male and female rats at 0.5 h after dosing on day 10, and systemic exposure was consistent with previous studies (data not shown).

2.3.2. Embryo-fetal development studies in rats and rabbits

A total of 80 presumed pregnant rats (8–11 weeks old and 192–253 g at dose initiation) and 80 presumed pregnant rabbits (4–6 months old and 2.8–3.6 kg at dose initiation) were acclimated and randomly assigned to dose groups (n = 20 per group). Rats and rabbits were administered 0, 100, 300, or 1000 mg/kg/day NMV by oral gavage once daily from GD 6 through 17 and GD 7 through 19, respectively. NMV was tested up to the limit dose of 1000 mg/kg/day in accordance with ICH guidelines [16]. Control animals were administered the vehicle by the same dosing route and regimen. The dose volume for both species was 10 mL/kg. Blood samples were taken from maternal animals (n = 5 per group) at 0 (predose), 0.5, 1, 2, and 4 h after the GD 17 and GD 19 dose in rats and rabbits, respectively, to determine NMV systemic concentrations.

2.3.3. Observations and measurements

Clinical signs, body weight, and food consumption were monitored throughout all studies.

The study design, toxicokinetic analysis, and statistical analysis used for the fertility and rat and rabbit EFD studies have been previously described [17,18]. Briefly, in the fertility study estrous cycling was monitored in the female rats 14 days prior to dose initiation, during dosing, and continuing until positive evidence of mating was observed (sperm present in smear of vaginal contents or presence of copulatory plug). The day on which evidence of mating was found was designated as GD 0. Females were euthanized on GD 14 by gas anesthesia (isoflurane) followed by exsanguination, and underwent a macroscopic evaluation of the abdominal, thoracic, and pelvic viscera. The ovaries and uterine contents were examined for number and distribution of corpora lutea, implantation sites, placentae, and viable and nonviable embryos. Apparently non-gravid uteri were stained with 10% ammonium sulfide to visualize potential implantation sites [19]. Male rats were euthanized after 32 days of dose administration, and also underwent macroscopic evaluation of the abdominal, thoracic, and pelvic viscera. The testes, epididymides, and accessory sex organs (prostate gland and seminal vesicles) were examined and retained for possible microscopic evaluation.

In the EFD studies, maternal rats and rabbits were euthanized on GD 21 and GD 29, respectively, via gas anesthesia (isoflurane) followed by exsanguination (rats) or intravenous injection of a barbiturate followed by exsanguination (rabbits). Following euthanasia, maternal animals underwent macroscopic examination of the abdominal, thoracic, and pelvic viscera, and examination of ovarian and uterine contents (number and distribution of corpora lutea, implantation sites, placenta [size, color, or shape], live and dead fetuses, and early and late resorptions). Fetuses were removed from the uterus, weighed individually, and examined for sex and external abnormalities. All fetal rats and rabbits were examined for visceral abnormalities using a modification of the microdissection technique of Staples [20] and following evisceration, cleared, and stained with alizarin red S [21], they were examined for skeletal abnormalities.

3. Results

3.1. Fertility and early embryonic development

NMV was well-tolerated, with no evidence of systemic toxicity in both males and females as demonstrated by lack of NMV-related clinical signs, food consumption or body weights (Table 1). Lower food consumption observed during the premating phase for the males at 1000 mg/kg/day was not considered NMV-related due to the low magnitude, lack of consistency, and there was no overall impact on body weight.
providing further evidence for lack of effects on male and female fertility number of corpora lutea, implantation sites, and embryo viability, mating, fecundity, and fertility indices ( Table 1 ). In addition, there were percentage of post-implantation loss across all dose groups, including shown) as well as lack of effects on maternal body weight gain, body weight, or food consumption at any dose ( Table 2 ). There were also no NMV-related effects on embryo-fetal viability, based on similar per percentage of post-implantation loss across all dose groups, including shown) as well as lack of effects on maternal body weight gain, body weight, or food consumption at any dose ( Table 2 ). There were also no NMV-related effects on embryo-fetal viability, based on similar per

There were no NMV-related effects on male or female fertility, as evidenced by lack of effects on estrous cyclicity, precoital interval, and mating, fecundity, and fertility indices (Table 1). In addition, there were no NMV-related effects on uterine examination endpoints such as the number of corpora lutea, implantation sites, and embryo viability, providing further evidence for lack of effects on male and female fertility as well as early embryonic development and a no observed adverse effect level (NOAEL) of 1000 mg/kg/day (the highest dose tested).

### Table 1

| Dose (mg/kg/day) | 0     | 60    | 200   | 1000  |
|------------------|-------|-------|-------|-------|
| Number of females/males | 20/20 | 20/20 | 20/20 | 20/20 |
| Male Terminal Body | 408.9 ± 409.9 | 411.6 ± 408.9 | 23.1 | 22.7 | 22.2 | 19.7 |
| Female Terminal Body | 273.6 ± 277.0 | 272.0 ± 277.8 | 15.8 | 24.1 | 21.3 | 14.1 |
| Preimplantation Day 1–14 | 22.4 ± 1.3 | 22.0 ± 1.1 | 23.0 ± 1.2 | 20.9 ± 0.9 |
| Mating Day 15–19 | 18.4 ± 2.2 | 19.3 ± 2.8 | 18.0 ± 3.1 | 18.3 ± 3.2 |
| Female Food Consumption (g/day) | 58.4 ± 57.3 | 56.7 ± 55.8 | 55.0 ± 54.1 | 53.3 ± 52.4 |
| Maternal Body Weight (g) | 304.5 ± 298.3 | 303.6 ± 310.6 | 13.5 | 13.5 | 13.5 | 13.5 |
| Weight (GD 21) | 20.1 ± 8.3 | 14.5 ± 14.8 |
| Live Fetus/Offspring | 320.4 ± 313.4 | 322.3 ± 309.5 |
| Consumption (g/day) | 42.3 ± 32.0 | 20.8 ± 43.1 |
| Uterine Examination Data | | | | |
| Corpora lutea | 12.1 ± 11.4 | 11.5 ± 11.5 | 11.5 ± 11.9 |
| Implantation sites | 11.2 ± 9.9 | 9.3 ± 9.7 | 9.7 ± 10.3 |
| Postimplantation loss (%) | 1.7 ± 1.5 | 2.4 ± 2.6 | (8.9–11.5) |
| Pelvic asphyxia | 10.4 ± 11.1 | 19.9 ± 21.0 | (5.8–18.9) |
| Live fetuses/litter | 10.2 ± 9.2 | 8.7 ± 9.9 | (7.3–9.6) |
| Sex ratio (% male) | 50.5 ± 49.3 | 48.9 ± 50.9 | 48.3 |
| Fetal weight (g)/Litter | 5.2 ± 5.3 | 5.5 ± 5.4 | 5.1–5.4 |

### Table 2

| Dose (mg/kg) | 0     | 100   | 300   | 1000  |
|--------------|-------|-------|-------|-------|
| Number of Pregnant Dams | 18    | 17    | 20    | 19    |
| Maternal Body Weight (g) | 298.3 ± 293.6 | 303.6 ± 310.6 | 13.5 | 13.5 | 13.5 | 13.5 |
| Weight (GD 21) | 16.3 ± 15.7 | 17.7 ± 18.1 | (21.0–22.5) |
| Live Fetus/Offspring | 320.4 ± 313.4 | 322.3 ± 309.5 |
| Consumption (g/day) | 42.3 ± 32.0 | 20.8 ± 43.1 |
| Uterine Examination Data | | | | |
| Corpora lutea | 12.1 ± 11.4 | 11.5 ± 11.5 | 11.5 ± 11.9 |
| Implantation sites | 11.2 ± 9.9 | 9.3 ± 9.7 | 9.7 ± 10.3 |
| Postimplantation loss (%) | 1.7 ± 1.5 | 2.4 ± 2.6 | (8.9–11.5) |
| Pelvic asphyxia | 10.4 ± 11.1 | 19.9 ± 21.0 | (5.8–18.9) |
| Live fetuses/litter | 10.2 ± 9.2 | 8.7 ± 9.9 | (7.3–9.6) |
| Sex ratio (% male) | 50.5 ± 49.3 | 48.9 ± 50.9 | 48.3 |
| Fetal weight (g)/Litter | 5.2 ± 5.3 | 5.5 ± 5.4 | 5.1–5.4 |

(g) = grams; GD = Gestation Day.

| Historical Control Dataa |
|--------------------------|
| Control Datab |
| Body weight | | | | |
| Maternal Body Weight (g) | | | | |
| Weight (GD 21) | | | | |
| Live Fetus/Offspring | | | | |
| Consumption (g/day) | | | | |
| Uterine Examination Data | | | | |
| Corpora lutea | | | | |
| Implantation sites | | | | |
| Postimplantation loss (%) | | | | |
| Pelvic asphyxia | | | | |
| Live fetuses/litter | | | | |
| Sex ratio (% male) | | | | |
| Fetal weight (g)/Litter | | | | |

There were no NMV-related maternal mortality or clinical signs at any dose (data not shown). In the 1000 mg/kg/day group, mean maternal body weight gains and food consumption were slightly lower than control, with effects on maternal body weight gain and food consumption at ≤300 mg/kg/day (Table 4). There were no NMV-related effects on embryo-fetal viability. Lower fetal body weights (91% of controls) were observed in all dose groups, and no effects on fetal external, visceral, or skeletal morphological development (Supplemental Table 1). All fetal visceral and skeletal findings that were observed in the study were considered to be incidental and unrelated to NMV because the findings were not dose-dependent, limited to single incidences within a dose group, and/or occurred at an incidence within the normal range of historical control. Based on the lack of adverse effects in this study, the NOAEL was 1000 mg/kg/day (the highest dose tested). Toxico kinetic analysis revealed that NMV exposure increased with increasing dose on GD 17 (Table 3).

### 3.3. Rabbit embryo-fetal development

There was no NMV-related maternal mortality or clinical signs at any dose (data not shown). In the 1000 mg/kg/day group, mean maternal body weight gains and food consumption were slightly lower than control, with effects on maternal body weight gain and food consumption at ≤300 mg/kg/day (Table 4). There were no NMV-related effects on embryo-fetal viability. Lower fetal body weights (91% of controls) were observed in all dose groups, and no effects on fetal external, visceral, or skeletal morphological development (Supplemental Table 2). All fetal findings that were observed in the study were considered to be incidental and unrelated to NMV because the findings were not dose-dependent, limited to single incidences within a dose group, and/or

### 3.2. Rat embryo-fetal development

There was no NMV-related maternal toxicity, as demonstrated by lack of NMV-related maternal mortality or clinical signs (data not shown) as well as lack of effects on maternal body weight gain, body weight, or food consumption at any dose (Table 2). There were also no NMV-related effects on embryo-fetal viability, based on similar percentage of post-implantation loss across all dose groups, including control (Table 2). While the number of live fetuses is slightly lower in the
however, the NOAEL for developmental toxicity was 300 mg/kg/day. There was no effect on fetal viability or morphological development, (Table 3).

- occurred at an incidence within the normal range of historical control.

NMV did not cause malformations or lower embryo-fetal survival when administered to pregnant rats and rabbits. The only finding was a slight reduction in rabbit fetal body weights in the presence of lower maternal gestational body weight gain. The lower fetal body weight is consistent with delayed development and occurred following exposure throughout the period of organogenesis (GD 7–19 in rabbits that corresponds with first trimester gestation in humans) which represents 43% (13 days of dosing out of 30-day gestation period) of the total gestational period in rabbits. In comparison, the intended 5-day course of PAXLOVID treatment represents < 2% (5 days of treatment for 280 days of gestation) of the human gestational period. Additionally, the reduction in rabbit fetal weights occurred at 10-fold the highest anticipated exposure in humans (Table 3) and therefore the lower rabbit fetal weight is not considered a meaningful human risk. There were no effects on male or female fertility or pre-implantation embryonic development. Taken together, the studies presented here indicate that NMV has a favorable reproductive safety profile based on the lack of clinically meaningful effects on embryo-fetal development and male or female fertility in animals along with a lack of findings in a battery of genetic toxicology tests [1].

In addition, the intended therapeutic target of NMV further supports the favorable reproductive risk assessment. NMV inhibits SARS-CoV-2 3CL \(^{\text{Mpro}}\), a virus specific enzyme that is not present in mammalian cells and therefore would not be expected to interfere with pathways involved in mammalian development. Furthermore, NMV demonstrated a favorable off-target selectivity profile [1], further supporting the favorable reproductive risk assessment.

The lack of genotoxicity and off-target activity for NMV is an important consideration for the pregnancy risk assessment of antiviral compounds. Similar to NMV, remdesivir, a viral RNA-dependent RNA polymerase inhibitor approved for treatment of hospitalized COVID-19 patients, demonstrated no adverse effects on embryo-fetal development in rats or rabbits up the highest dose tested, 20 mg/kg/day [22]. In contrast, molnupiravir, an antiviral oral treatment that is authorized in the UK, resulted in severe manifestations of developmental toxicity (malformations and embryo-fetal lethality) as well as lower fetal body weight and developmental variations at the highest dose of molnupiravir in rats, 1000 mg/kg/day, with lower fetal body weights and delayed ossification observed in the presence of decreased maternal body weight gain at 500 mg/kg/day and no developmental toxicity at 250 mg/kg/day [23]. Developmental toxicity of molnupiravir in rabbits was limited to lower fetal body weights in the presence of slight maternal toxicity (lower food consumption, body weight gain, and abnormal fetal output) at 750 mg/kg/day with no developmental toxicity observed at 400 mg/kg/day [23]. Molnupiravir is a nucleoside analog that induces lethal mutagenesis after it is metabolized into a ribonucleoside analog that resembles cytidine, which is then incorporated into newly made RNA in place of cytidine. Continued replication of RNA containing deleterious mutations results in an accumulation of errors in the viral genome leading to inhibition of replication, an effect known as viral error catastrophe [23]. Other antiviral compounds that work by targeting incorporation into viral RNA include ribavirin (RBV) and favipiravir (FAV). Both of these compounds have shown to be teratogenic in multiple species. RBV has been shown to be embryocidal and/or teratogenic in rats, rabbits, and guinea pigs [24–26] and FAV for which teratogenesis has been reported in monkeys, mice, rats, and rabbits [27]. There is a concern that the mutagenic mechanism that results in antiviral activity of these compounds could theoretically result in incorporation and subsequent mutagenesis of the host DNA [28,29]. Consistent with the mechanism of action, molnupiravir and its active metabolite were positive in the in vitro bacterial reverse mutation assay (Ames assay) and a mammalian cell hypoxanthine phosphoribosyltransferase (HPRT) gene mutation assay; however it was reported to be negative in the Big Blue® (cII Locus) transgenic rodent mutagenesis.
NMV is being administered in combination with ritonavir as a pharmacokinetic enhancer. Inhibition of CYP3A with ritonavir increases the bioavailability of NMV by inhibiting its metabolism, thereby increasing the duration of therapeutic levels. While no longer widely used as a sole antiviral agent, several antiviral regimens use ritonavir to reduce metabolism and prolong exposure, and as such there is a body of human literature on the use of ritonavir in a broad patient population that includes pediatrics, males and females of reproductive age, and pregnant women. Specifically in regards to use during pregnancy, in 3453 live births following exposure to ritonavir-containing regimens in the first-trimester there was no difference in the rate of overall birth defects for ritonavir (2.35 %) compared with the background birth defect rate of 2.72 % in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) [31]. The number of first trimester exposures to ritonavir is sufficient to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genital-urinary system; no such increases have been observed [31]. In nonclinical studies with ritonavir, no evidence of fetal malformations was observed in rat and rabbit EFD studies at doses of 15, 35, and 75 mg/kg and 25, 50, and 110 mg/kg/day, respectively. Developmental toxicity associated with ritonavir administration in EFD studies in rats and/or rabbits (higher resorptions, lower fetal body weight, ossification delays, and increased skeletal variations) occurred only at the highest dose evaluated in each species, which were also maternally toxic doses. Most of these findings typically represent a developmental delay and are often associated with exposure throughout the entire period of organogenesis rather than to a specific sensitive window of gestation. Extending the treatment period through the end of gestation and through lactation (pre-and postnatal development study [PPND]) in rats did not appear to exacerbate these findings.

In addition to the findings mentioned above, cryptorchidism was reported in the mid (35 mg/kg/day) and high (75 mg/kg/day) ritonavir doses in the rat EFD study; however, there is limited biologic plausibility of identifying cryptorchidism in a rat EFD study as testicular descent does not occur until after weaning [32]. In addition, there were no reports of cryptorchidism in postnatal developing rats in the rat PPND study in which maternal rats are dosed from GD 6 through parturition and continuing out to postpartum day 20 and offspring are allowed to develop until adulthood. Mature male offspring in the PPND study showed normal reproductive function, supporting the lack of effects of ritonavir on the developing male reproductive system. Ritonavir was also evaluated in combination with paritaprevir in embryo fetal toxicity studies in rats and mice. There were no effects on embryo-fetal development in either species at the highest combination dose, which contained 45 mg/kg/day and 30 mg/kg/day ritonavir in rats and mice, respectively [33], further indicating that the observation of cryptorchidism was spurious.

Women who are pregnant are at increased risk for severe illness with COVID-19 and pregnant women with COVID-19 are more likely to have premature birth and might be at increased risk for pregnancy complications or loss, highlighting the need for antiviral therapies and the importance of reproductive safety of these potential therapies [5–15]. The potential risks and benefits of PAXLOVID use during pregnancy should be discussed with the patient and her physician. However, a published review noted lack of meaningful clinical effects on embryo-fetal development and pregnancy outcomes [23,29,30]. Therefore, it seems unlikely that mutagenesis is the mechanism responsible for the embryo-fetal toxicity observed in animals with molnupiravir.

Declaration of Competing Interest
The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data
Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reprotox.2022.01.006.

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