Oral Therapies for SARS-CoV-2

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of January 15, 2022

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Objectives

- Summarize the life cycle of SARS-CoV-2 and identify possible targets for drug development.
- Summarize clinical and safety data for molnupiravir and nirmatrelvir/ritonavir (Paxlovid).

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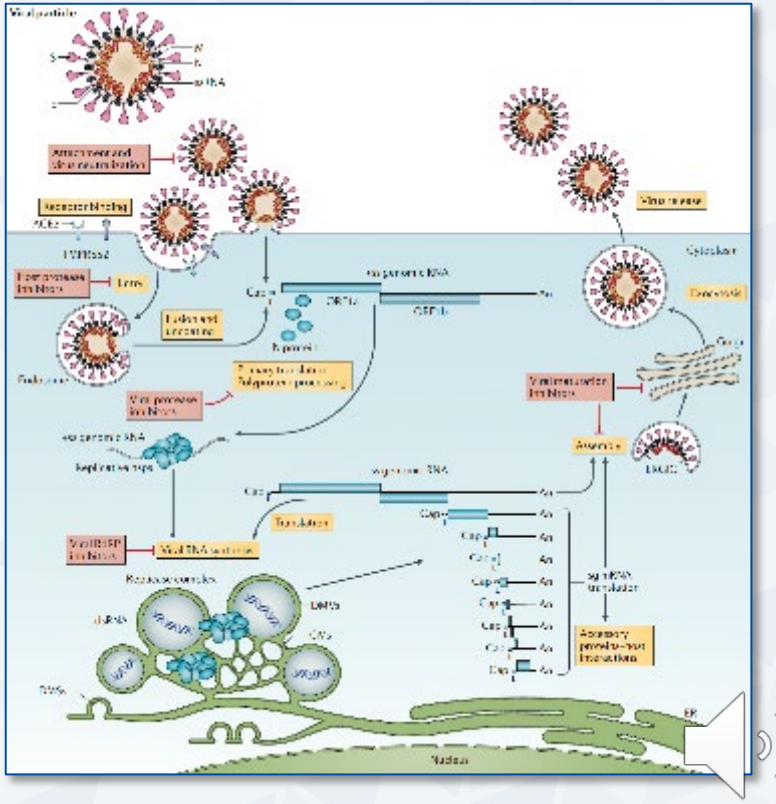
Coronavirus Replication

- SARS-CoV-2 is an enveloped, positive sense, single-stranded RNA virus.
- S proteins on virus surface bind to receptors, host-derived proteases cleave S proteins to permit fusion.
- Following host entry and uncoating, two polyproteins are produced.
  - Cleaved into 16 non-structural proteins by viral proteases.



V'kovski P, et. al., Nature Reviews Micro. 2021

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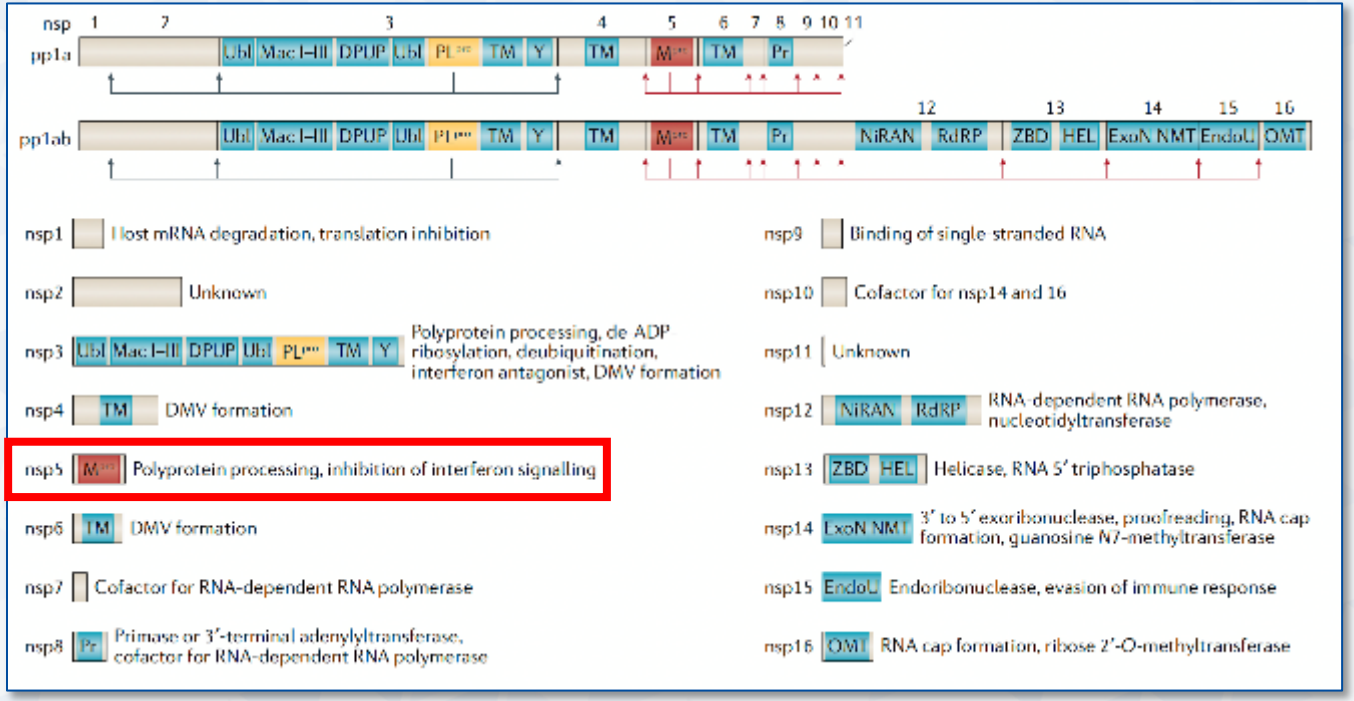
Non-Structural Proteins (NSPs)

The protease, M^{pro}, releases the majority of NSPs from the polyproteins and is essential for the viral life cycle. (Attractive drug target)



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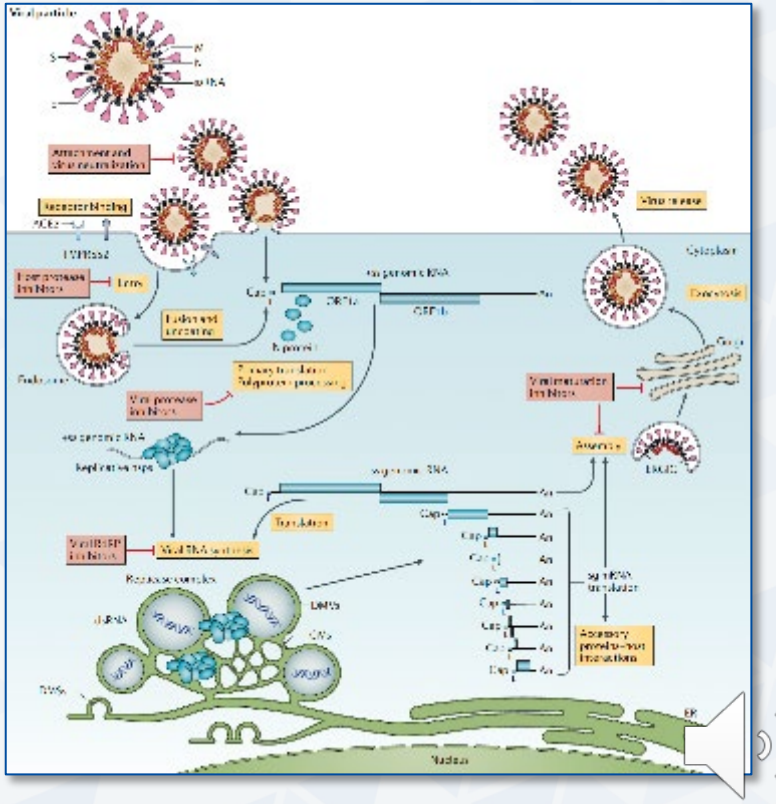
V'kovski P, et. al., Nature Reviews Micro. 2021

Coronavirus Replication

- Viral genomic replication is facilitated by an RNA-dependent RNA polymerase (RdRP) that resides in nsp 12.
  - Target for remdesivir.
- Leads to production of structural proteins.



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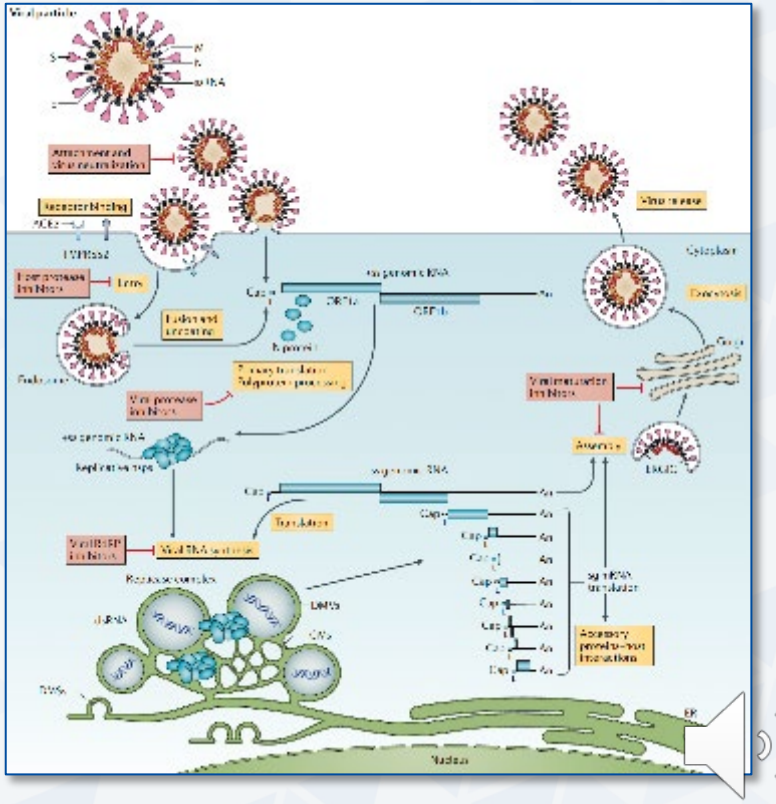
V'kovski P, et. al., Nature Reviews Micro. 2021

Coronavirus Replication

- Structural proteins assemble and assist in budding of new virions.



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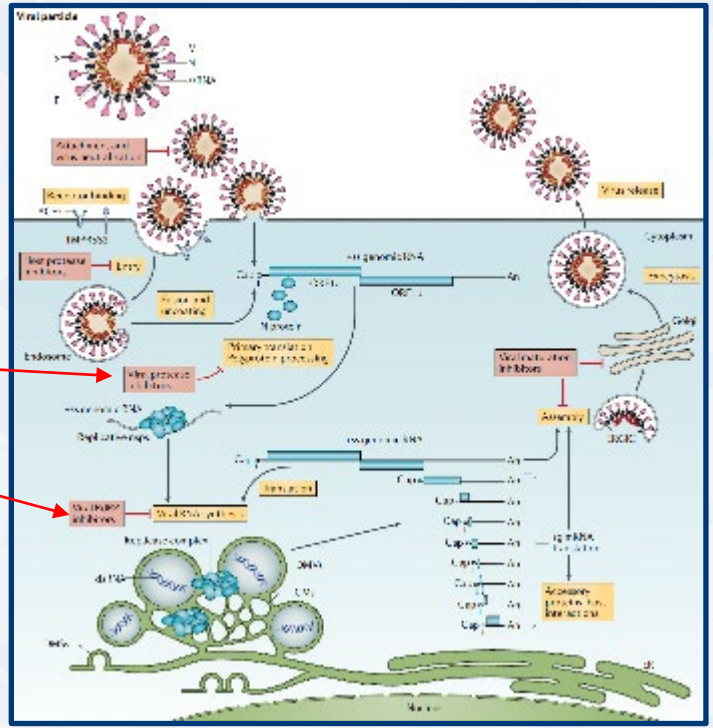
Oral Therapies for SARS-CoV-2

Nirmatrelvir

Molnupiravir



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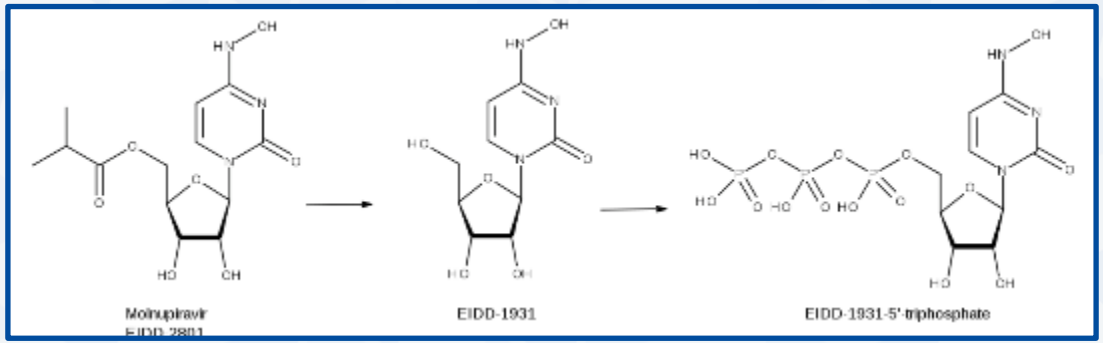
V'kovski P, et. al., Nature Reviews Micro. 2021

Molnupiravir (Lagevrio)

- Ribonucleoside analog
  - Inhibits viral reproduction by promoting widespread mutations in the replication of viral RNA by RNA-dependent RNA polymerase.
    - Molnupiravir is metabolized into a ribonucleoside analog that resembles cytidine (also called EIDD-1931 5’-triphosphate or NHC-TP).



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Kabinger F, et. al., Nature Structural & Molecular Biology volume 28, pages 740–746 (2021)

Molnupiravir

- Pharmacokinetics
  - Following administration of 800mg every 12 hours
    - $AUC_{0\text{-}12hr}$ = 8,260 ng • hr/mL
    - C_{max} = 2,970 ng/mL
    - C_{min} = 31.1 ng/mL
    - Administration of a single 200 mg dose of molnupiravir with a high-fat meal resulted in a 35% reduction in NHC; however, C_{max}, AUC were not significantly affected.
  - Elimination
    - Renal and hepatic elimination are not major routes of elimination.
    - Drug-drug interaction potential is low.
  - The half-life of NHC is approximately 3.3 hours.
    - The fraction of dose excreted as NHC in the urine was ≤3% in healthy participants.

Molnupiravir - Pre-Clinical Safety

- Bone marrow suppression
  - Dogs
    - Reversible, dose-related bone marrow toxicity affecting all haematopoietic cell lines was observed at 0.4 times the human NHC exposure at the recommended human dose.
    - Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe haematological changes after 14 days of treatment
  - Mice
    - Neither bone marrow nor haematological toxicity was observed

Molnupiravir - Pre-Clinical Safety

- Bone ands cartilage
  - Bone and cartilage toxicity, consisting of an increase in the thickness of physeal and epiphyseal growth cartilage with decreases in trabecular bone was observed in the femur and tibia of rapidly growing rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5.4 times the human NHC exposure at the RHD).
  - Not observed in shorter studies.

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Fact Sheet for Healthcare Providers: Emergency Use Authorizat r Molnupiravir

Molnupiravir - Pre-Clinical Safety

- Fetal Development
  - Rats
    - Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure) and decreased fetal body weights and delayed ossification at ≥500 mg/kg/day (2.9 times the human NHC exposure).
    - There were no developmental toxicities at ≤250 mg/kg/day (0.8 times the human NHC exposure at the RHD).
  - Rabbits
    - Developmental toxicity was limited to reduced fetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD) but not at doses ≤400 mg/kg/day (7 times the human NHC exposures at the RHD).

Molnupiravir

- Preclinical studies reveal broad-spectrum antiviral activity against coronaviruses, including SARS-CoV-2 with a high barrier to resistance.
  - A theoretical concern is that molnupiravir could generate mutations in the coronavirus genome could lead to the emergence of a new variant of concern.

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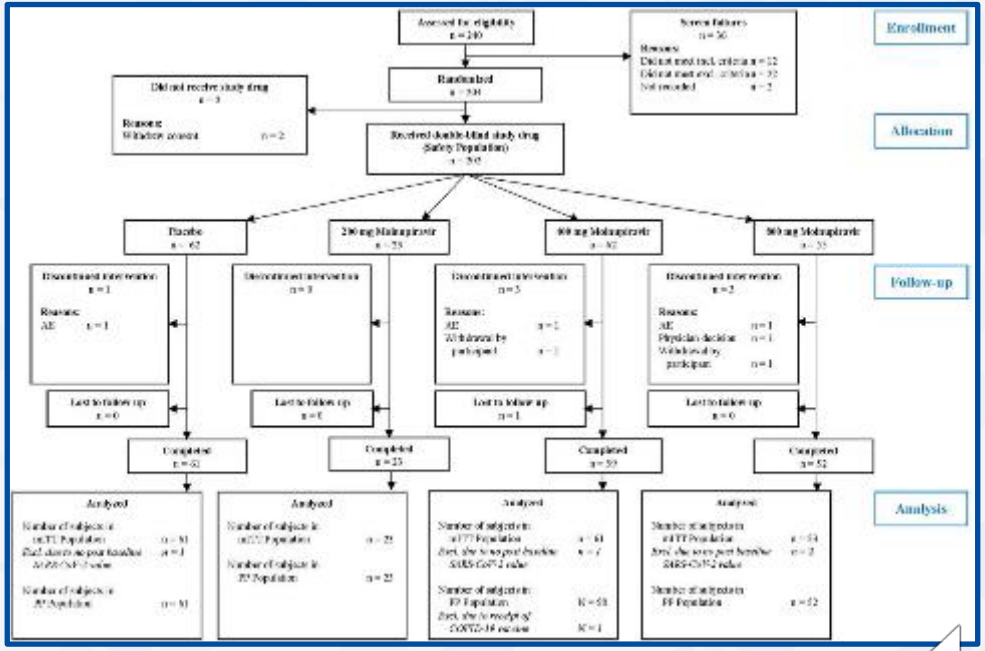
Molnupiravir – Clinical Trials

- Phase 2a, double-blind, placebo-controlled, randomized, multicenter trial designed to evaluate the safety, tolerability, and antiviral activity of molnupiravir dosed twice-daily for 5 days in the treatment of patients with mild to moderate COVID-19.



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Fischer W, et. al, doi: https://doi.org/10.1101/2021.06.17.21258639

Molnupiravir – Clinical Trials

- Adults aged ≥18 years were eligible if they tested positive for SARS-CoV-2 infection within 96 hours and had symptoms of COVID-19 within 7 days of treatment initiation.
- Antiviral activity, safety, and tolerability were assessed for 28 days following study treatment initiation.
  - Nasopharyngeal swabs were collected on Days 1 (baseline), 3, 5, 7, 14, and 28 for measurement of antiviral activity.
  - Safety was assessed on Days 1, 3, 5, 7, 14, and 28 and adverse events were monitored throughout.

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Fischer W, et. al, doi: https://doi.org/10.1101/2021.06.17.21258639

Molnupiravir – Clinical Trials

- Participants were randomized 1:1 to 200 mg molnupiravir or matching placebo or 3:1 to molnupiravir (400 or 800 mg) or placebo.
  - Doses were administered orally twice-daily for 5 days and dose escalations occurred following review of safety and virology data from this and other studies of molnupiravir.

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Molnupiravir – Clinical Trials

- Endpoints:
  - The primary antiviral efficacy outcome was time to viral RNA clearance defined as the first timepoint where viral RNA was achieved and was below the limit of quantitation (<1,018 copies/mL).
  - Secondary antiviral efficacy outcomes were time to infectious virus elimination and median viral RNA change from baseline on Days 3, 5, and 7.

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Demographics

	200 mg Molnupiravir N = 23	400 mg Molnupiravir N = 62	800 mg Molnupiravir N = 55	Placebo N = 62
Age, median (range), years	32.0 (19 - 65)	42.5 (19 - 82)	42.0 (18 - 68)	39.0 (19 - 71)
Age ≥65 years, n (%)	1 (4.3)	3 (4.8)	4 (7.3)	3 (4.8)
Sex, female, n (%)	11 (47.8)	32 (51.6)	27 (49.1)	34 (54.8)
Race, n (%)				
Asian	3 (13.0)	3 (4.8)	3 (5.5)	2 (3.2)
Black or African American	1 (4.3)	2 (3.2)	1 (1.8)	2 (3.2)
White	17 (73.9)	56 (90.3)	49 (89.1)	54 (87.1)
Other	2 (8.7)	0	2 (3.6)	1 (1.6)
Multiple	0	1 (1.6)	0	3 (4.8)
Ethnicity, Hispanic or Latino, n (%)	7 (30.4)	23 (37.1)	33 (60.0)	23 (37.1)
BMI, median, kg/m^2	25.40	26.90	27.10	27.00
BMI ≥30 kg/m^2, n (%)	7 (30.4)	19 (30.6)	15 (27.3)	18 (29.0)
Baseline viral load, mean (SD), $\log_{10}$ copies/mL	6.69 (1.888)	6.38 (1.837)	5.80 (1.823)	6.11 (1.794)

	200 mg Molnupiravir N = 23	400 mg Molnupiravir N = 62	800 mg Molnupiravir N = 55	Placebo N = 62
Baseline viral load, median (range), $\log_{10}$ copies/mL	7.25 (3.0 – 9.5)	6.72 (3.0 – 9.9)	6.12 (3.0 – 9.4)	6.40 (3.0 – 9.3)
Days from symptom onset, median (range), n	4.00 (1.8 – 7.0)	4.85 (2.3 – 7.1)	4.00 (1.4 – 7.1)	4.55 (1.5 – 7.5)
At least 1 risk factor for severe disease, n (%)	15 (65.2)	37 (59.7)	33 (60.0)	37 (59.7)
SARS-CoV-2 antibody positive on Day 1, n/N* (%)	3/20 (15.0)	15/59 (25.4)	18/51 (35.3)	18/55 (32.7)

Abbreviation: BMI = body mass index; Ig = immunoglobulin; n = numbers of participants; SD = standard deviation.

* N = number of participants with an antibody assay

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Fischer W, et. al, doi: https://doi.org/10.1101/2021.06.17.21258639

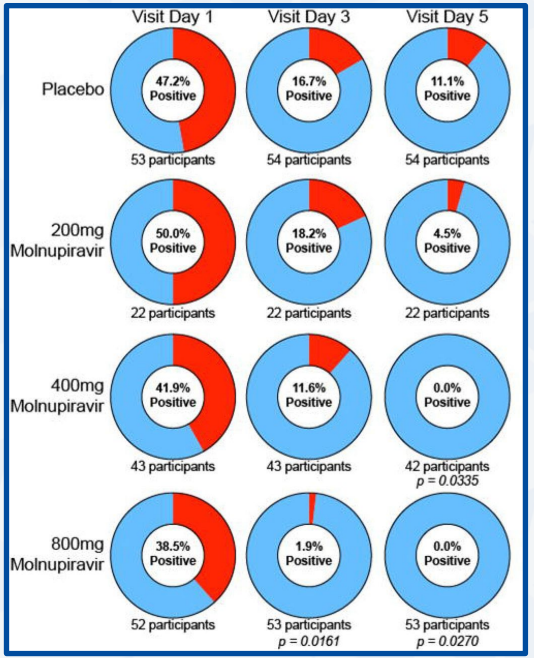
Results – Time to Viral Clearance

Percentage of Participants Positive for Infectious SARS-CoV-2 Virus

	200 mg Molnupiravir	400 mg Molnupiravir	800 mg Molnupiravir	Placebo
Day 1, n/N (%)	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	25/53 (47.2)
Day 3, n/N (%)	4/22 (18.2)	5/43 (11.6)	1/53 (1.9)	9/54 (16.7)
Fisher's exact p-value	>0.99	0.57	0.016	
Dose response p-value				0.010
Day 5, n/N (%)	1/22 (4.5)	0/42 (0.0)	0/52 (0.0)	6/54 (11.1)
Fisher's exact p-value	0.67	0.03	0.03	
Dose response p-value				0.003

Time to SARS-CoV-2 Viral RNA Negativity

	200 mg Molnupiravir	400 mg Molnupiravir	800 mg Molnupiravir	Placebo
Participants with Response, n/N (%)	21/23 (91.3)	48/61 (78.7)	49/53 (92.5)	49/61 (80.3)
Median time to response (95% CI), days	22.0 (15.0, 28.0)	27.0 (15.0, 28.0)	14.0 (13.0, 14.0)	15.0 (15.0, 27.0)
Log-rank p-value	0.56	0.73	0.013	



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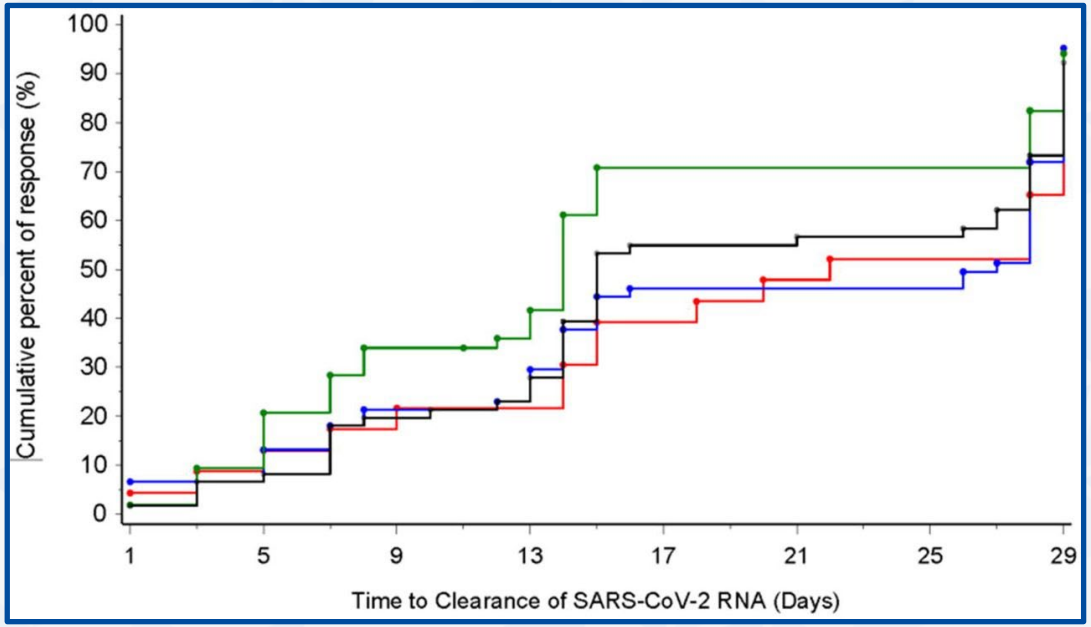
Results – Time to Viral Clearance



- 200 mg molnupiravir
- 400 mg molnupiravir
- 800 mg molnupiravir (median 14 days)
- placebo (median 27 days)

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Fischer W, et. al, doi: https://doi.org/10.1101/2021.06.17.21258639

Results – Mechanism Validation

- Genotypic changes in the RNA-dependent RNA polymerase (RdRp) occurred at a higher rate among participants who received molnupiravir compared to placebo.
  - On average, 10.9 and 5.7 nucleotide changes in the RdRp were observed following treatment with molnupiravir and placebo, respectively ($p = 0.02$) supporting viral error catastrophe as the mechanism of action.

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Fischer W, et. al, doi: https://doi.org/10.1101/2021.06.17.21258639

Results – Safety and Tolerability

- The incidence of treatment-associated adverse events was lowest in the molnupiravir 800 mg group. The only adverse events reported by more than 4 participants were headache, insomnia, and increased alanine aminotransferase.

Number (%) of participants experiencing an event	Molnupiravir 200 mg N = 23	Molnupiravir 400 mg N = 62	Molnupiravir 800 mg N = 55	Placebo N = 62
Any adverse event	11 (47.8)	20 (32.3)	11 (20.0)	18 (29.0)
Adverse events reported by >5% subjects in any group				
Dizziness	2 (8.7)	1 (1.6)	0	0
Insomnia	2 (8.7)	1 (1.6)	1 (1.8)	4 (6.5)
Any adverse event grade 3 or higher	1 (4.3)	2 (3.2)	4 (7.3)	5 (8.1)
Any adverse event leading to discontinuation from study drug	0	1 (1.6)	1 (1.8)	1 (1.6)
Any serious adverse event	0	2 (3.2)	1 (1.8)	1 (1.6)
Any adverse event leading to death	0	0	0	1 (1.6)*

Abbreviation: n = number of participants.

* The subject had an adverse event of hypoxia that led to death. This occurred 31 days after discontinuation from the study following completion of study assessments and was not recorded in the study database but was recorded in the safety database.

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Fischer W, et. al, doi: https://doi.org/10.1101/2021.06.17.21258639

Conclusions

- Molnupiravir was well tolerated and produced significant:
  - Reduction in infectious virus isolation
  - Reduction in time to elimination of SARS-CoV-2 RNA
  - Increase in proportion of participants that cleared SARS-CoV-2 RNA
  - Reduction in SARS-CoV-2 viral RNA from baseline compared to placebo in outpatients with COVID-19.

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MOVe-OUT Trial

- Phase 3 (MOVe-OUT) Trial
  - Phase 3, randomized, placebo-controlled, double-blind, multi-site study of non-hospitalized adult patients with laboratory-confirmed mild to moderate COVID-19, at least one risk factor associated with poor disease outcomes, and symptom onset within five days prior to randomization.
  - The primary efficacy objective of MOVe-OUT was to evaluate the efficacy of molnupiravir compared to placebo as assessed by the ***percentage of participants who are hospitalized and/or die*** from the time of randomization through Day 29.

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Bernal AJ, et. al, DOI: 10.1056/NEJMoa2116044

MOVe-OUT Trial

- Eligibility criteria required that all patients had laboratory-confirmed mild-to-moderate COVID-19, with symptom onset within 5 days of study randomization.
  - All patients were required to have at least one risk factor associated with poor disease outcome at study entry.

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Bernal AJ, et. al, DOI: 10.1056/NEJMoa2116044

MOVe-OUT Trial – Interim Analysis

- A planned interim analysis evaluated data from 775 patients who were initially enrolled prior to Aug. 5, 2021.
  - At the time of the decision to stop recruitment based on the compelling interim efficacy results, the trial was approaching full recruitment of the Phase 3 sample size of 1,550 patients, with more than 90% of the intended sample size already enrolled.

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https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antivi-
molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-5 rcent-
compared-to-placebo-for-patients-with-mild-or-moderat/

MOVe-OUT Trial – Interim Analysis

Molnupiravir reduced the risk of hospitalization or death by about 50%.

Risk of death was 100% lower with molnupiravir.

	Molnupiravir (N=385), n (%)	Placebo (N=377), n (%)	Risk difference*, (95% CI)	p-value
All-cause hospitalization or death through Day 29 (mITT)	**28 (7.3%)**	**53 (14.1%)**	**6.8, (-11.3, -2.4)**	**0.0012**
Hospitalisation	28 (7.3%)	52 (13.8%)		
Death	0 (0%)	8 (2.1%)		
Unknown	0 (0%)	1 (0.3%)		

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Bernal AJ, et. al, DOI: 10.1056/NEJMoa2116044

MOVe-OUT Trial – Final Analysis

Relative risk reduction of 30% (relative risk 0.70; 95% CI: 0.49, 0.99).

Risk of death was 89% lower with molnupiravir.

	Molnupiravir (N=709), n (%)	Placebo (N=699), n (%)	Risk difference*, (95% CI)	p-value
All-cause hospitalization or death through Day 29 (mITT)	**48 (6.8%)**	**68 (9.7%)**	**3.0%, (0.1, 5.9)**	**0.0218**
Hospitalisation	28 (7.3%)	52 (13.8%)		
Death	1 (0.14%)	9 (1.3%)		
Unknown	0 (0%)	1 (0.3%)		

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Bernal AJ, et. al, DOI: 10.1056/NEJMoa2116044

MOVe-OUT Trial

- Safety and Tolerability
  - The incidence of any adverse event was comparable in the molnupiravir and placebo groups (30% and 33%, respectively).
    - Incidence of drug-related adverse events was also comparable (8% and 8.4%, respectively).
    - Fewer subjects discontinued study therapy due to an adverse event in the molnupiravir group (1.4%) compared to the placebo group (2.9%).
    - Most common adverse events were diarrhea, nausea, and dizziness

Bernal AJ, et. al, DOI: 10.1056/NEJMoa2116044

Molnupiravir

- Was reviewed and narrowly was granted EUA on November 30.
  - Approved in the UK on November 4
    - Dose 800 mg (4 x 200mg capsules) every 12 hours for 5 days
    - Not authorized for individuals <18 years
    - Not recommended during pregnancy or breast feeding

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Fact Sheet for Healthcare Providers: Emergency Use Authorizat r Molnupiravir

Molnupiravir – Eligibility for Use

- Intended use: Treatment of mild-to-moderate COVID-19 in adults with a positive result of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.
  - Patient eligibility:
    - Adult (> 18 years of age)
    - Not pregnant or breastfeeding
    - Positive test for SARS-CoV-2
    - Possess at least one risk factor for developing severe illness

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Fact Sheet for Healthcare Providers: Emergency Use Authorizat r Molnupiravir

Risk Factors for Developing Severe Illness

Conditions with Strong Evidence	Conditions with Moderate Evidence	Conditions with Limited Evidence
☐ Age ☐ Cancer ☐ Cerebrovascular disease ☐ Chronic kidney disease ☐ Chronic lung diseases limited to: o Interstitial lung disease o Pulmonary embolism o Pulmonary hypertension o Bronchopulmonary dysplasia o Bronchiectasis o COPD (chronic obstructive pulmonary disease) ☐ Chronic liver diseases limited to: o Cirrhosis o Non-alcoholic fatty liver disease o Alcoholic liver disease o Autoimmune hepatitis ☐ Diabetes mellitus, type 1 and type 2 ☐ Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies) ☐ Mental health disorders limited to: o Mood disorders, including depression o Schizophrenia spectrum disorders ☐ Obesity (BMI ≥30 kg/m^2) ☐ Smoking, current and former ☐ Tuberculosis	☐ Children with certain underlying conditions ☐ Down syndrome ☐ HIV (human immunodeficiency virus) ☐ Neurologic conditions, including dementia ☐ Overweight (BMI ≥25 kg/m^2, but <30 kg/m^2) ☐ Sickle cell disease ☐ Solid organ or blood stem cell transplantation ☐ Substance use disorders ☐ Use of corticosteroids or other immunosuppressive medications	☐ Cystic fibrosis ☐ Thalassemia ☐ Asthma ☐ Hypertension, possibly ☐ Immune deficiencies (except people with moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments)

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https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Molnupiravir – Eligibility for Use

- Not authorized for:
  - Use in patients who are less than 18 years of age.
  - Initiation of treatment in patients hospitalized due to COVID-19.
    - Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
  - Use for longer than 5 consecutive days.
  - Pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

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Molnupiravir - Adverse Events

System organ class	Adverse Reaction	Frequency Category
Nervous system disorders	Dizziness and headache	Common
Gastrointestinal disorders	Diarrhea and nauesa; vomiting	Common; uncommon
Skin and subcutaneous tissue disorders	Rash and urticaria	Uncommon

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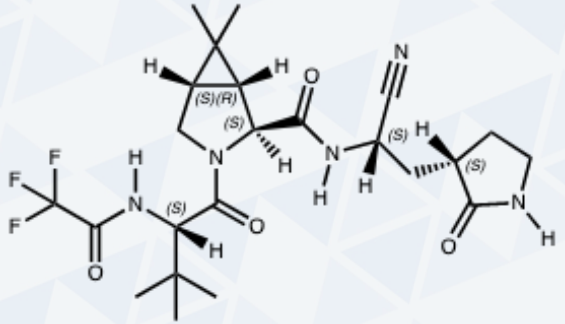
Fact Sheet for Healthcare Providers: Emergency Use Authorizat r Molnupiravir

Paxlovid

- Pfizer
- Paxlovid is a combination of nirmatrelvir and ritonavir.
  - Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication.
  - Medications are co-packaged



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Paxlovid

- Pharmacokinetics
  - Following administration of a single dose nirmatrelvir 300 mg and ritonavir 100 mg
    - AUC = 23.01 μg • hr/mL
    - C_{max} =2.21 μg/mL
  - Elimination
    - When co-administered with ritonavir, the primary route of elimination becomes renal.
      - Dose reduction may be necessary for individuals with renal impairment.
    - Nirmatrelvir, co-packaged with ritonavir, is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A.
      - Induction of CYP3A may result in decreased plasma concentrations of nirmatrelvir and ritonavir
    - Nirmatrelvir is a substrate and inhibitor of P-glycoprotein
  - The half-life is approximately 6 hours.

Paxlovid

- Phase 2/3 Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial was a randomized, double-blind study of non-hospitalized adult patients with COVID-19, who were at high risk of progressing to severe illness.
  - Trial was initiated in July 2021.
  - The primary analysis of the interim data set evaluated data from 1,219 adults who were enrolled by September 29, 2021.
  - Dose was two 150 mg tablets of PF-07321332 with one 100 mg tablet of ritonavir, given twice daily for 5 days.

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https://clinicaltrials.gov/ct2/show/NCT04960202
https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results

EPIC-HR – Results

- Final analysis (n= 2,246) showed an 89% reduction in risk of COVID-19-related hospitalization or death compared to placebo in patients treated within 3 days of symptom onset (primary endpoint) and 88% in patients treated within 5 days of symptom onset (secondary endpoint).
  - 0.7% of patients who received Paxlovid were hospitalized through Day 28 following randomization), compared to 6.3% of patients who received placebo and were hospitalized or died (RR -5.62, $p<0.0001$).
    - Relative risk reduction was 94% in patients ≥65 years.
      - 1.1% of patients who received Paxlovid were hospitalized through Day 28 (1/94 hospitalized with no deaths), compared to 16.3% of patients who received placebo (16/98 hospitalized with 6 deaths)
  - In the overall study population through Day 28, no deaths were reported in patients who received Paxlovid as compared to 12 (1.1%) deaths in patients who received placebo.

EPIC-HR – Results

- SARS-CoV-2 viral load at baseline and Day 5 have been evaluated for 499 patients.
  - Paxlovid reduced viral load by approximately 10-fold, or 0.93 log10 copies/mL, relative to placebo.

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EPIC-HR – Results

- Treatment-emergent adverse events were comparable between Paxlovid (23%) and placebo (24%), most of which were mild in intensity.
  - Fewer serious adverse events (1.6% vs. 6.6%) and discontinuation of study drug due to adverse events (2.1% vs. 4.2%) were observed in patients dosed with Paxlovid compared to placebo, respectively.

Paxlovid

- Phase 2/3 Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR) trial was a randomized, double-blind study which included unvaccinated adults who were at standard risk (i.e., low risk of hospitalization or death) as well as vaccinated adults who had one or more risk factors for progressing to severe illness.
- Endpoints:
  - Primary endpoint was self-reported, sustained alleviation of all symptoms for four consecutive days.
  - Secondary endpoints reduction in hospitalization and death.

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EPIC-SR – Interim Results

- Analysis at 80% of enrolled patients
  - ***No difference in the primary endpoint*** (self-reported, sustained alleviation of all symptoms for four consecutive days).
  - For the secondary endpoint, 0.7% of those who received Paxlovid were hospitalized following randomization (3/428 hospitalized with no deaths), compared to 2.4% of patients who received placebo and were hospitalized or died (10/426 hospitalized with no deaths); p=0.051.
  - Additionally, there was approximately a ***10-fold, or 1 log10 copies/mL, decrease in viral load compared to placebo***, consistent with results from the Phase 2/3 EPIC-HR study.

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Paxlovid

- Paxlovid was reviewed and EUA granted on December 22, 2021.
- Intended use: Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
- Patient eligibility:
    - Adult and pediatrics (12 years of age and older weighing at least 40 kg)
    - Positive test for SARS-CoV-2
    - Initiate treatment within 5 days of symptom onset
    - Possess at least one risk factor for developing severe illness
- The Institute for Safe Medication Practices (ISMP) warning regarding renal impairment
    - Patients with moderate renal impairment, pharmacists should remove one of the nirmatrelvir tablets for both the morning and evening doses from each blister card before being dispensed. The empty blisters on all five cards should be covered with manufacturer-supplied stickers.
    - Patients with severe renal impairment should not receive the drug.

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https://www.ismp.org/alerts/medication-safety-issues-newly-authorized-paxlovid

Paxlovid – Eligibility for Use

- Not authorized for:
  - Initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
  - Use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
  - Use for longer than 5 consecutive days.

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Fact Sheet for Healthcare Providers: Emergency Use Authorizat r Molnupiravir

Summary

- Molnupiravir and Paxlovid have received EUA for treatment of SARS-CoV-2 infections.
  - Paxlovid appears to be the more promising agent, but has a high risk of drug-drug interactions
- EUA were granted for treatment of infected outpatients at high-risk for progression to severe illness.
- Owing to language in the EUA, pharmacists are not able to prescribe these medications in spite of being granted authority under the PREP Act.
  - Require a CPA or other mechanism for pharmacy-based test and treat.

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