Development of Oral Antiviral for COVID-19

Session 7: Future opportunities and research priorities in therapeutics

Ravi Shankar Singh, PhD, FCP
Senior Director, Clinical Pharmacology, CP&B
Pfizer Inc.

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Nirmatrelvir tablets; ritonavir tablets (PAXLOVID™) Approval and Emergency Use Authorization

- PAXLOVID is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.
- PAXLOVID has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death; and
- The emergency use of PAXLOVID is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

EUA, Emergency Use Authorization; FDA, Food and Drug Administration.

1. PAXLOVID [prescribing information]. New York, NY: Pfizer Inc.; May 2023.
2. PAXLOVID™ (nirmatrelvir tablets; ritonavir tablets) Emergency Use Authorization Fact Sheet for Healthcare Providers. Pfizer Inc.

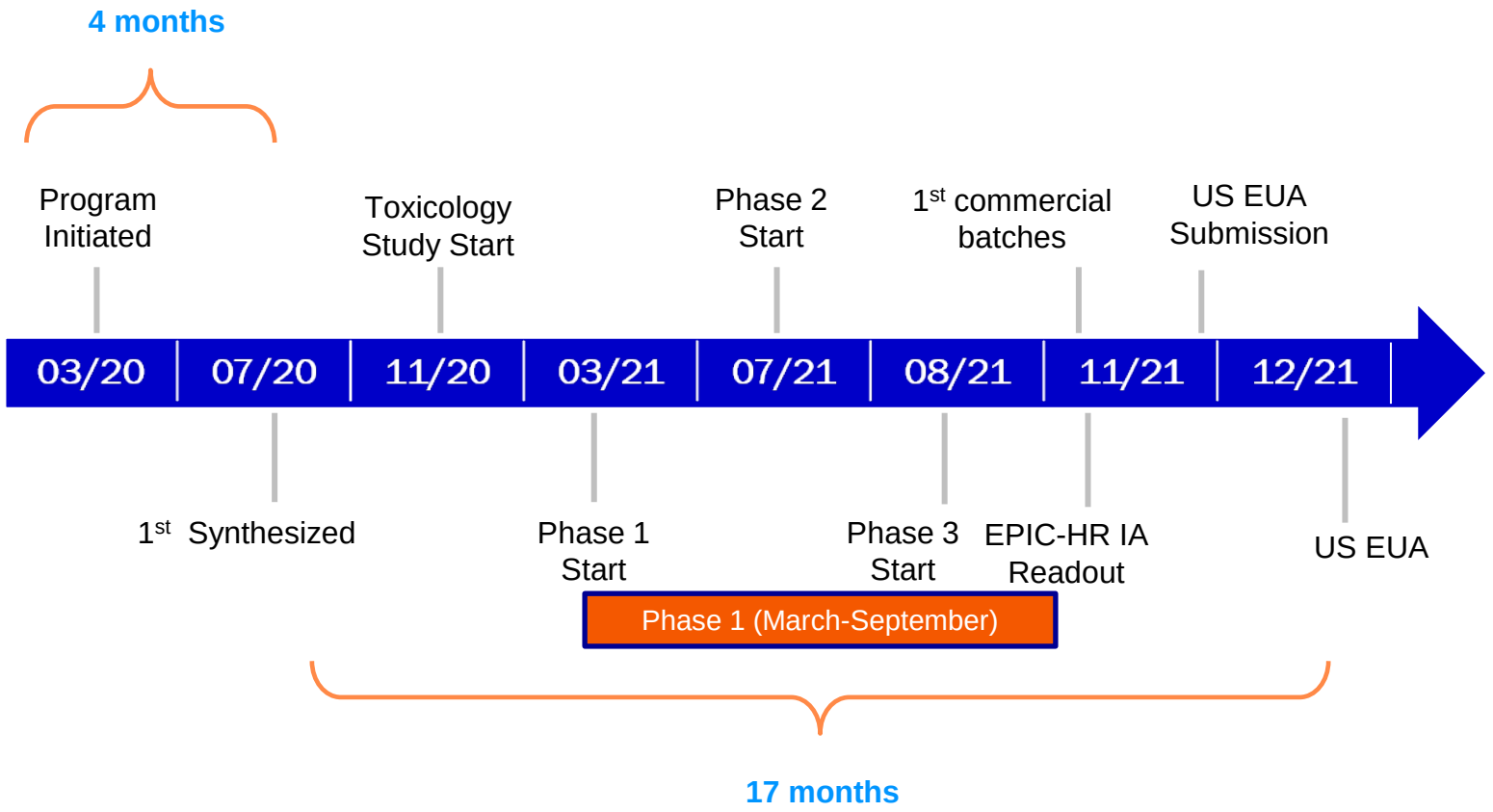
Nirmatrelvir tablets; ritonavir tablets (PAXLOVID™) Boxed Warning

WARNING: SIGNIFICANT DRUG INTERACTIONS WITH PAXLOVID

- **PAXLOVID includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.**
- **Prior to prescribing PAXLOVID: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3A inhibitor like PAXLOVID and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring *[see Drug Interactions (7)].***
- **Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed *[see Warnings and Precautions (5.1), Drug Interactions (7), and Clinical Studies (14)].***

PAXLOVID [prescribing information]. New York, NY: Pfizer Inc.; May 2023.

PAXLOVID™ Timeline



EPIC-HR = Evaluation of Protease Inhibition for COVID-19 in High Risk Patients; EUA = Emergency Use Authorization

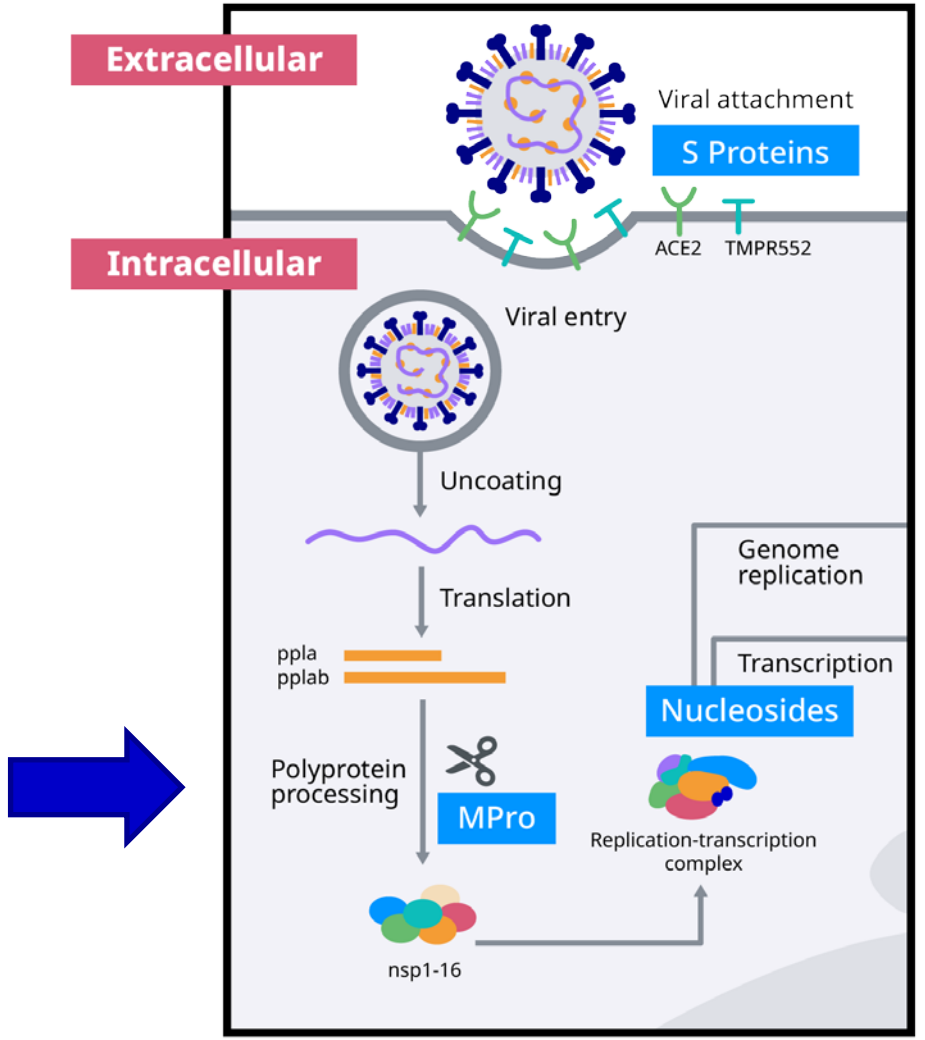
MIDD=Model Informed Drug Development

Enablers:

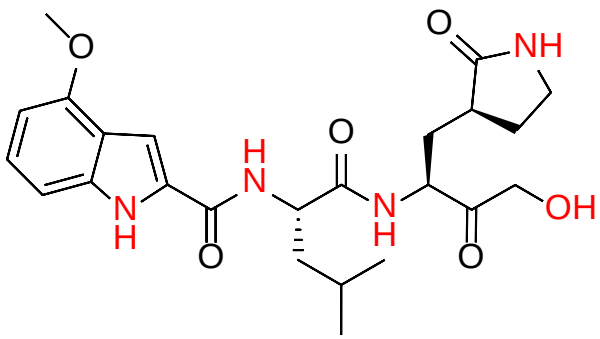
- Excellence in medicine design
- Expedited manufacture of API and drug product
- At-risk investment in commercial batches.
- Rapid internal decision making and regulatory interaction
- Record clinical development speed -- enabled by Phase 1 designs and MIDD analyses

Protease Inhibition and Anti-Viral Activity

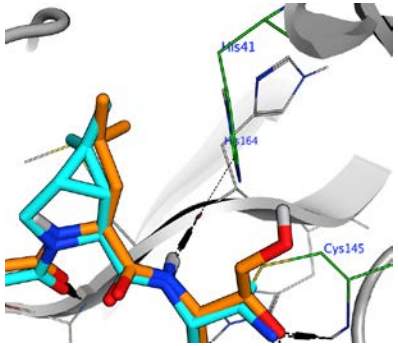
- January-March 2020: COVID-19 global spread
- Pfizer had worked protease inhibitors pre-clinically for SARS (a coronavirus) in 2003
- Similarities in the structures of the SARS and SARS-CoV-2 viral proteases offered an opportunity to leverage our earlier work in our efforts to develop a SARS-CoV-2 therapeutic

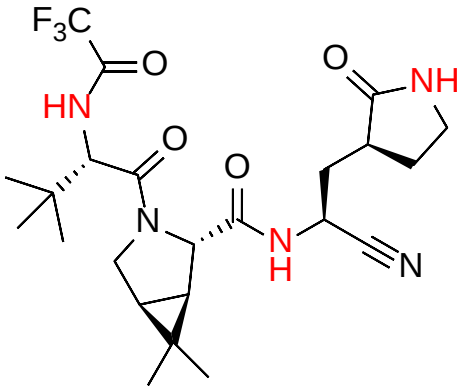


Designing Molecules to Treat COVID-19



PF-00835231* (dosed IV)





Nirmatrelvir (dosed orally)

- The blue arrows represent about 600 different molecules we designed, made and tested
- There were thousands of options, so by design, we had to predict the best ones to make
- Needed to inhibit the viral protease, be orally bioavailable and most importantly, safe

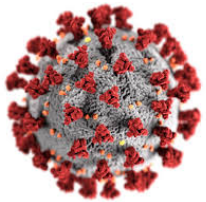
**Lufotrelvir – a prodrug of PF-00835231 was administered IV*

Multiparameter Design Optimization Based on Big Data

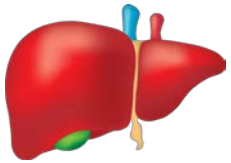
Virus Related

Potency

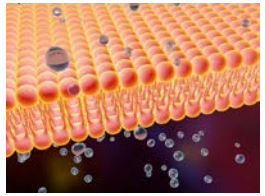
Antiviral



Oral Bioavailability Related

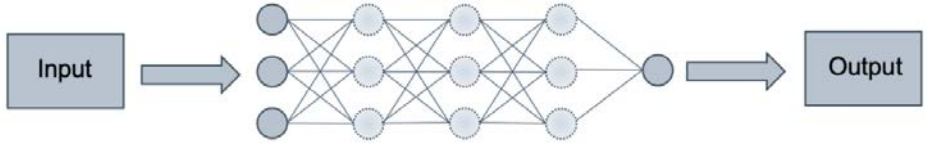


Metabolism

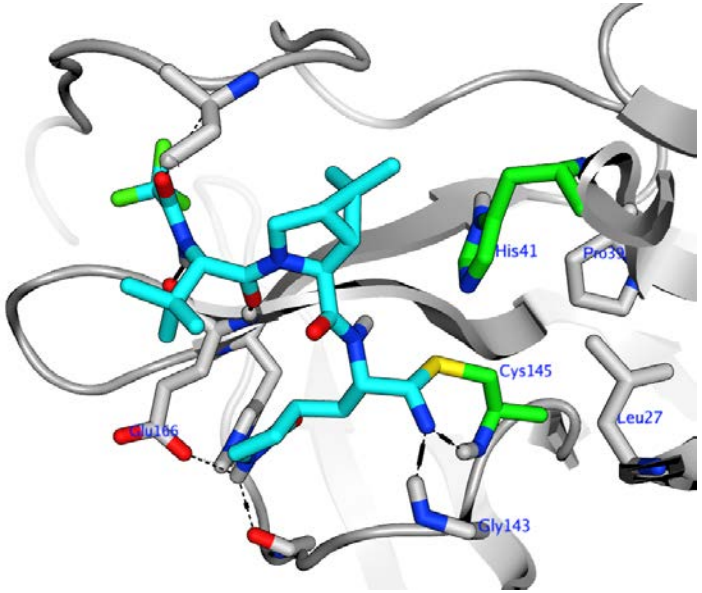


Permeability

Machine Learnings Tools



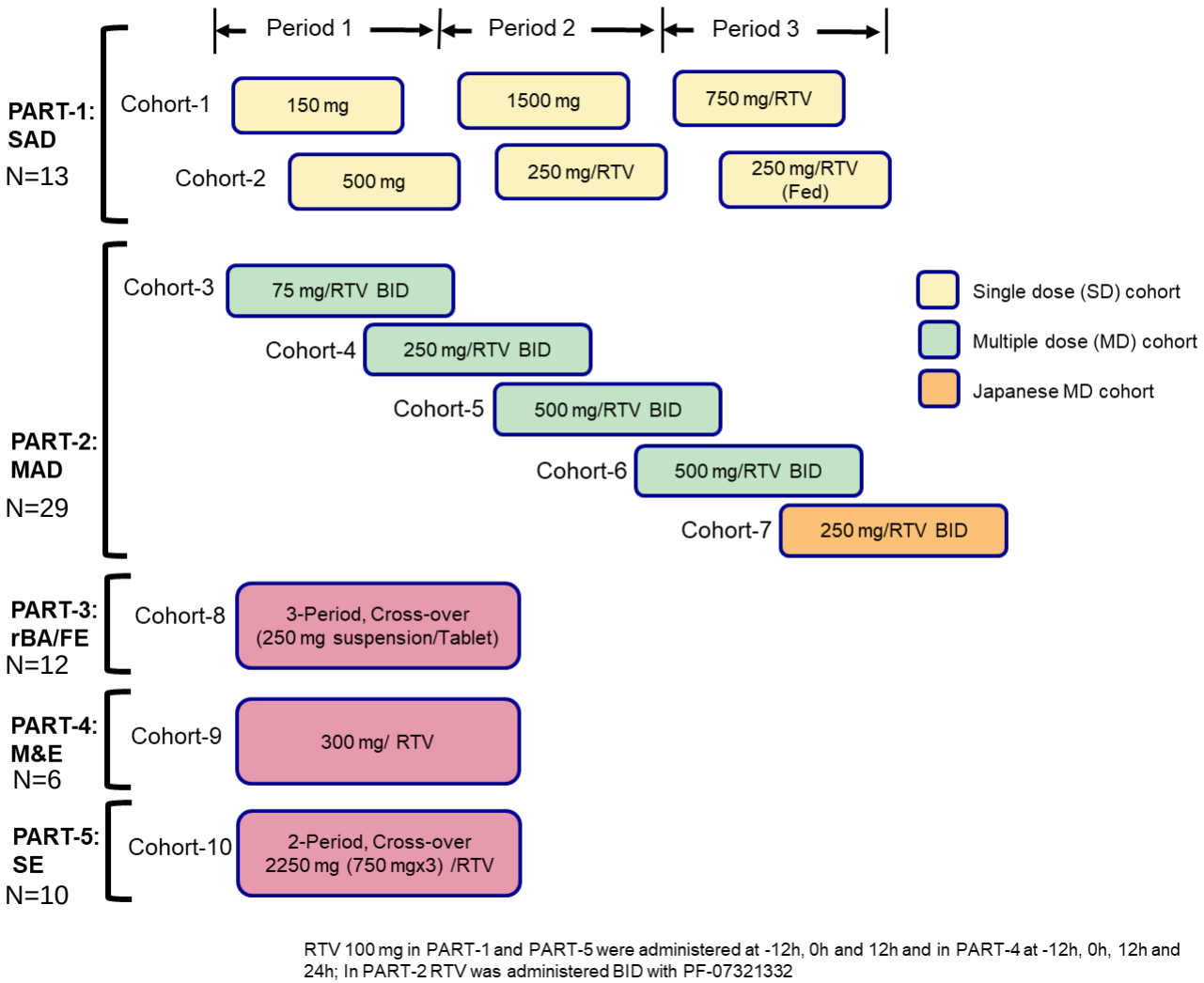
Structural Biology



We have huge data sets where we have built Machine Learning-enhanced AI Design tools

Pfizer

Innovative FIH Study Design to Accelerate and Inform Pivotal Trial



RTV 100 mg in PART-1 and PART-5 were administered at -12h, 0h and 12h and in PART-4 at -12h, 0h, 12h and 24h; In PART-2 RTV was administered BID with PF-07321332

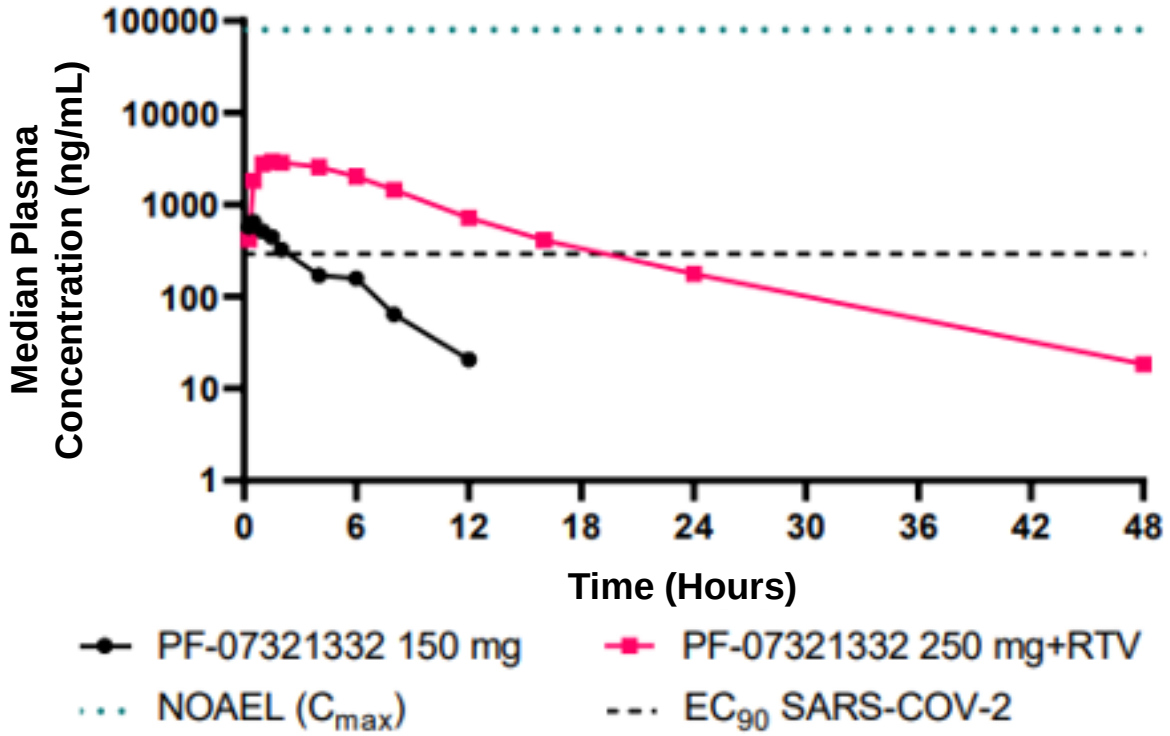
- Goals of Phase 1 development:
  - Safety, tolerability & PK + formulation
  - Dose and regimen selection to unequivocally test the mechanism
  - Keep the protocol flexible to answer critical questions needed for Phase 2/3
- Designed to gain operational efficiency
- Prospective provision to include ritonavir
- Adapted in real time to emerging data to inform & accelerate development
- Protocol and Statistical Analysis Plan available on Clinicaltrials.gov

Singh et al. *Clin Pharmacol Ther.* 2022; 112(1): 101-111. doi: 10.1002/cpt.2603.

Pfizer

Ritonavir as a PK Enhancer

- Ritonavir slows nirmatrelvir CYP3A4 metabolism and increases its half-life from 2.0 to 6.9 hours
- Available as generic and widely used PK enhancer for HIV & HCV protease inhibitors
- Ritonavir (100 mg BID) does not have antiviral activity against SARS-CoV-2
- Ritonavir has a well-characterized safety (and DDI) profile
- No overlapping toxicities with nirmatrelvir

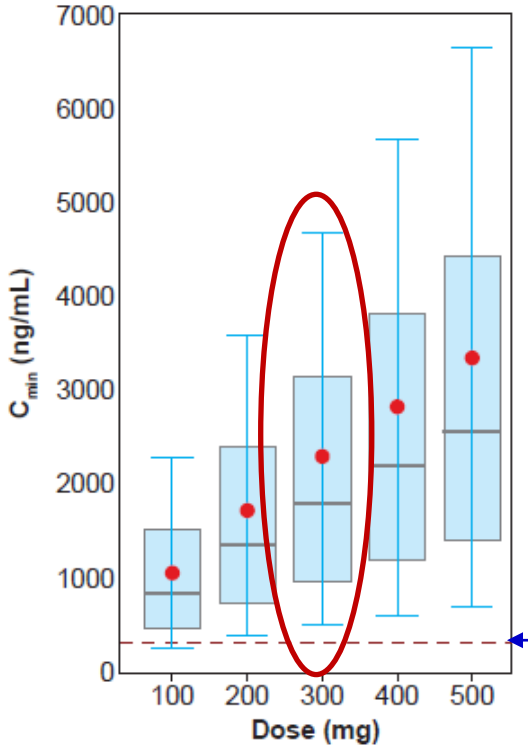


Singh et al. *Clin Pharmacol Ther.* 2022; 112(1): 101-111. doi: 10.1002/cpt.2603.

Dose selection: Population PK simulations

- Preliminary PopPK from emerging Ph1 data
- Exposure simulated for Phase 2/3 sample size & variability
- Simulations at 300 mg BID showed that >90% participants would achieve the target unbound C_{min} above EC_{90}

Distribution of simulated C_{min} at steady-state (Day 5) with different doses (BID) enhanced with ritonavir



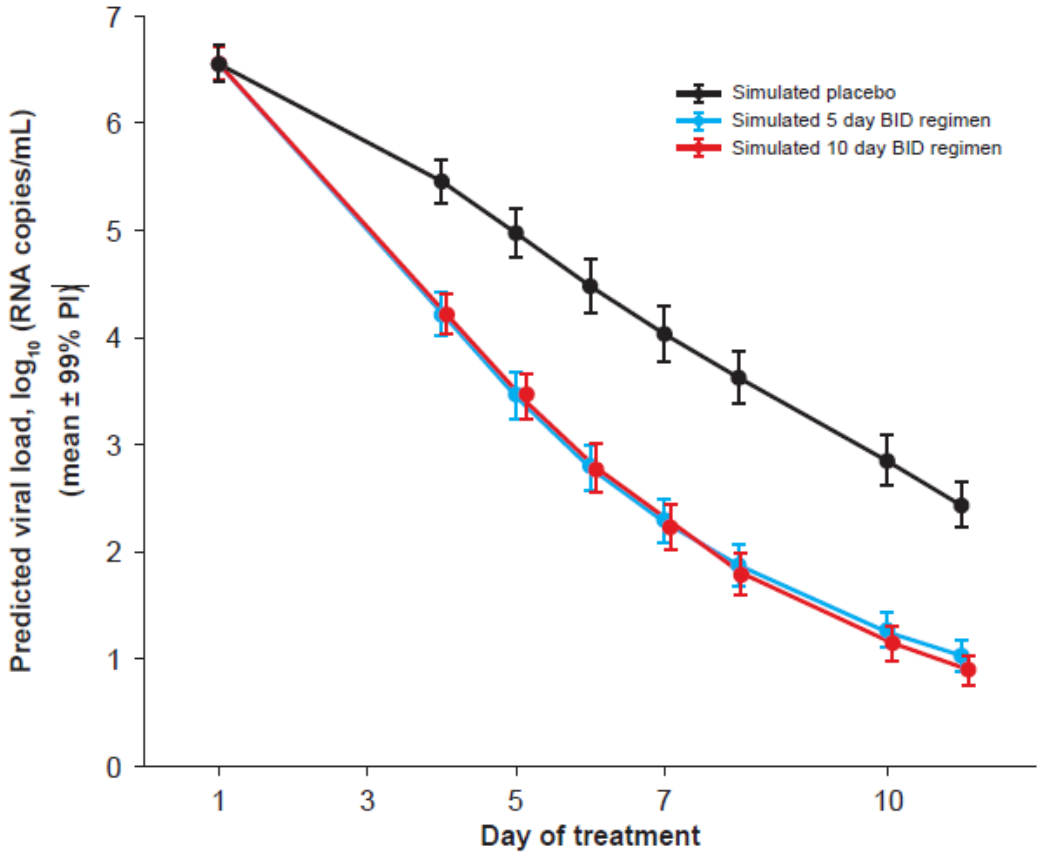
Red dots indicate the means, grey lines indicate the medians, boxes are 25th and 75th percentiles, error bars show 10th and 90th percentiles.
BID, twice daily; C_{min}, minimum concentration; EC_{90}, concentration at which 90% inhibition of viral replication is observed; PK, pharmacokinetic; RNA ribonucleic acid.

Singh RSP, et al. C*lin Pharmacol Ther. 2022 Jul;112(1):101-111. doi: 10.1002/cpt.2603.*

Dosing duration selection: Quantitative System Pharmacology (QSP) model simulations

- QSP Predicted robust antiviral activity
- QSP model simulations of a virtual population treated with nirmatrelvir; ritonavir 300/100 mg BID predicted that five days of treatment is needed for robust viral reduction* in patients with symptomatic COVID-19
  - No meaningful additional benefit predicted with longer dosing

Simulation of a virtual population (n=502) to predict viral load efficacy for nirmatrelvir/ritonavir 300/100 mg BID in symptomatic COVID-19 patients

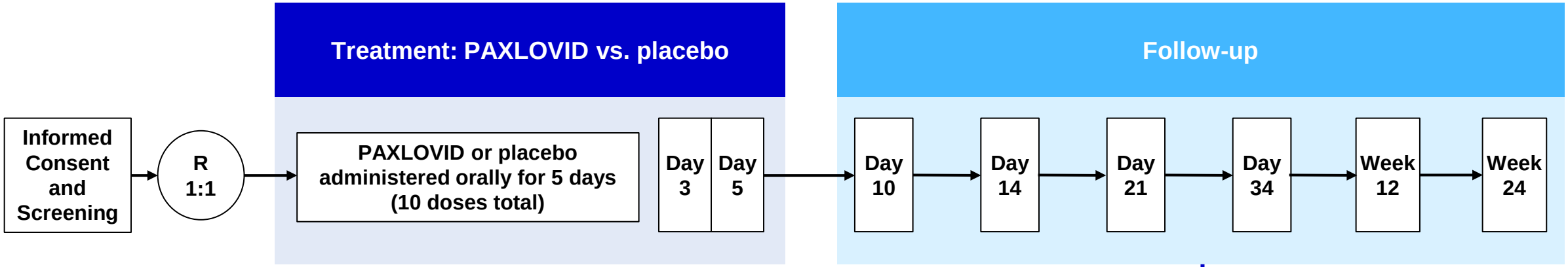


*Based on clinical trials of monoclonal antibodies.
BID, twice daily; QSP, quantitative systems pharmacology; RNA ribonucleic acid.

Singh RSP, et al. C*lin Pharmacol Ther. 2022 Jul;112(1):101-111. doi: 10.1002/cpt.2603.*

Study Design
Pivotal Study C4671005 (EPIC-HR)

Phase 2/3 safety and efficacy study in unvaccinated, symptomatic adult participants with confirmed COVID-19 who have at least 1 risk factor[a] for developing severe COVID-19 illness



- Final Approved Protocol (Original): 18 June 2021
- First Subject Dose: 16 July 2021
- Provision to terminate early for futility or exceptional efficacy

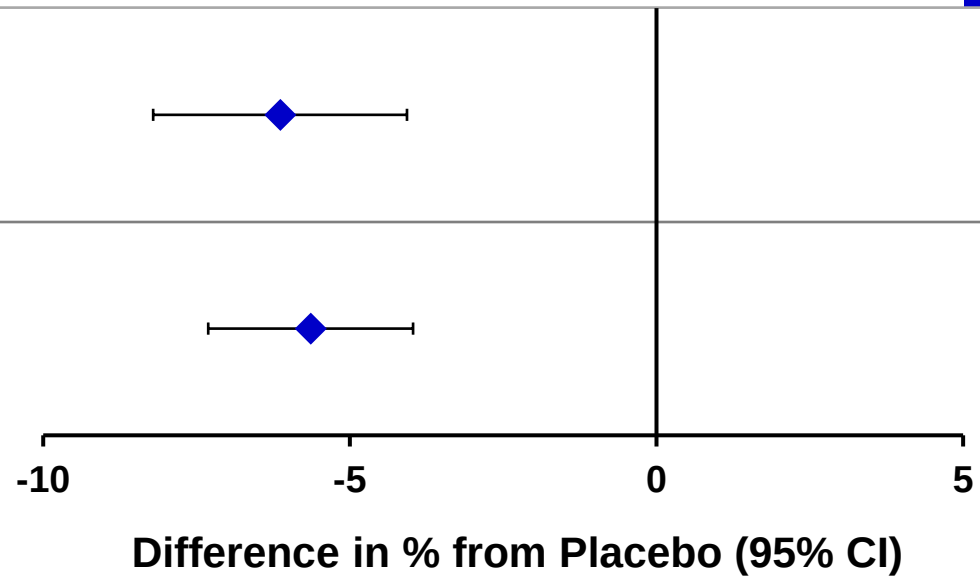
Day 28 Primary Endpoint
Proportion of participants with COVID-19 related hospitalization or All-cause Death through Day 28

a. Risk Factors Include: Age ≥60, BMI >25, Medical History terms of Cancer, Cigarette Smoker, Cardiovascular Disorder, Chronic kidney Disease, Chronic Lung Disease, Diabetes Mellitus, Device Dependence, HIV Infection, Hypertension, Immunosuppression, Neurodevelopmental Disorder and Sickle Cell Disease

Significant Reduction in COVID-19 Related Hospitalization or All-cause Death when Treatment is Initiated within 3 or 5 Days of Symptom Onset

EPIC-HR

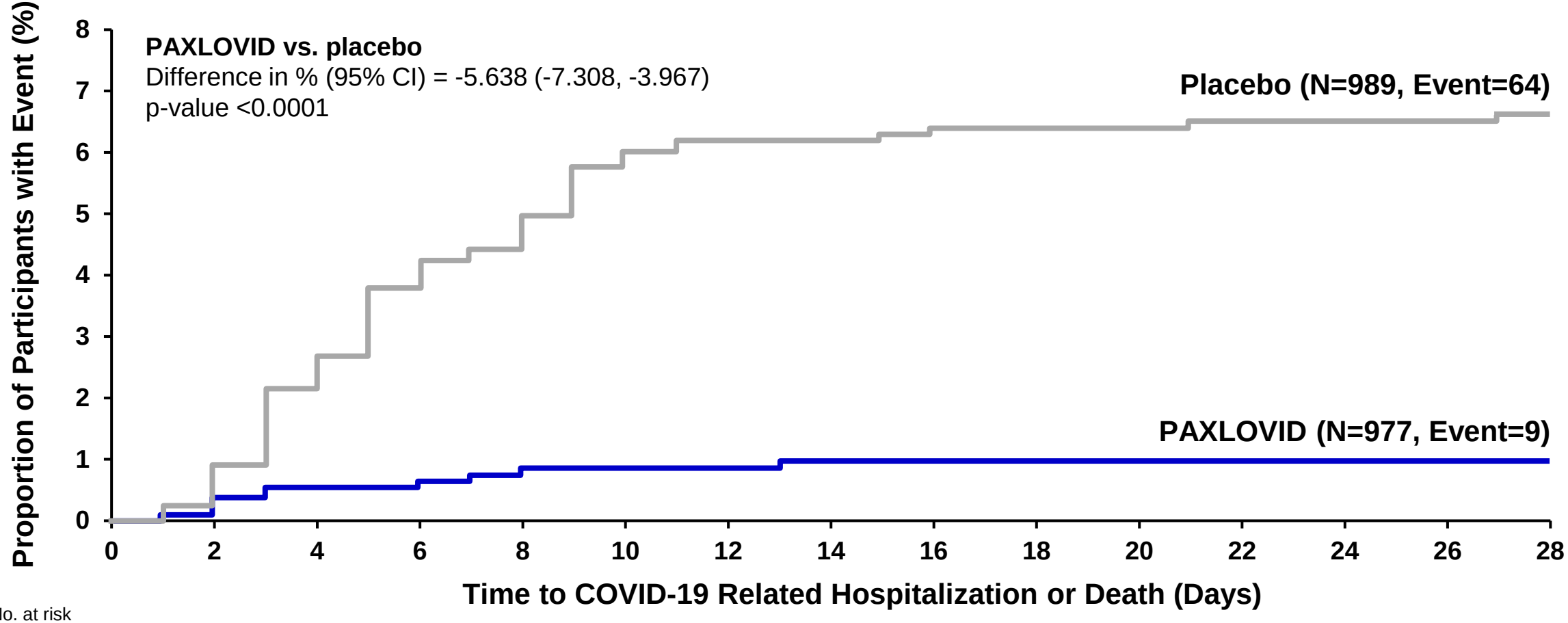
	PAXLOVID n/N (%)	Placebo n/N (%)	p-value
Primary Analysis (mITT)	5/671 (0.752)	44/647 (6.888)	<0.0001
Secondary Analysis (mITT1)	9/977 (0.933)	64/989 (6.571)	<0.0001



Kaplan-Meier Method; difference of the estimated proportions, 95% CI and p-value based upon normal approximation
mITT=modified intent-to treat, mITT1=modified intent-to-treat 1

Between Group Differences in Events of COVID-19 Hospitalization and All-cause Death Evident Beginning at Day 3

EPIC-HR, mITT1

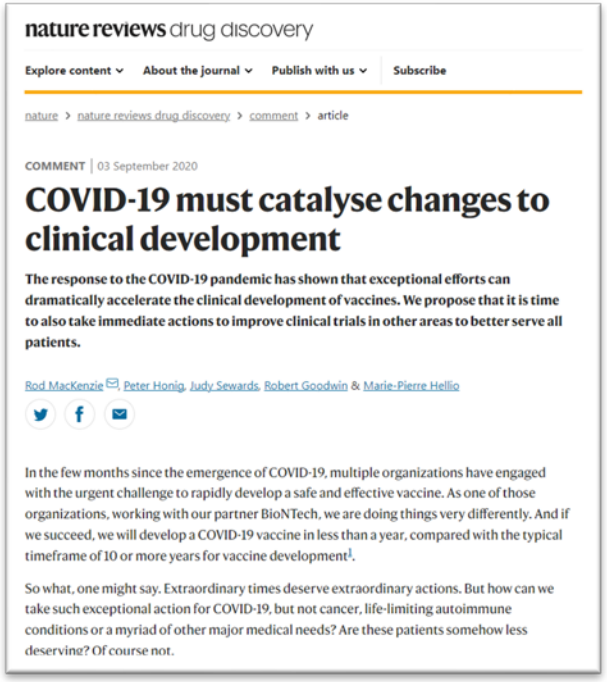


No. at risk

PAXLOVID	977	977	972	966	960	952	952	949	946	943	943	942	941	941	940	939	937	937	936	935	933	933	932	932	932	932	932	932	932
Placebo	989	989	985	975	959	947	935	929	922	917	908	906	904	904	904	902	900	899	898	897	896	896	893	893	893	893	893	893	892

Kaplan-Meier Method; difference of the proportions, 95% CI and p-value based upon normal approximation
mITT1=modified intent-to-treat 1

Learnings for Future Drug Development



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COMMENT | 03 September 2020

COVID-19 must catalyse changes to clinical development

The response to the COVID-19 pandemic has shown that exceptional efforts can dramatically accelerate the clinical development of vaccines. We propose that it is time to also take immediate actions to improve clinical trials in other areas to better serve all patients.

Rod MacKenzie, Peter Honig, Judy Sewards, Robert Goodwin & Marie-Pierre Hellio

In the few months since the emergence of COVID-19, multiple organizations have engaged with the urgent challenge to rapidly develop a safe and effective vaccine. As one of those organizations, working with our partner BioNTech, we are doing things very differently. And if we succeed, we will develop a COVID-19 vaccine in less than a year, compared with the typical timeframe of 10 or more years for vaccine development[1].

So what, one might say. Extraordinary times deserve extraordinary actions. But how can we take such exceptional action for COVID-19, but not cancer, life-limiting autoimmune conditions or a myriad of other major medical needs? Are these patients somehow less deserving? Of course not.

- How do we apply our COVID learnings to all of development to **bring speed, efficiency and innovation** in all clinical development?
  - **Be bold** and expand adoption of parallel processing at risk
  - **Share** prior and emerging clinical development knowledge to enable acceleration
  - **Increase collaboration, flexibility, mutual recognition and reliance**
  - **Streamlined and timely interactions** between sponsors and regulators to enable rapid decision-making
  - **Embrace digital** tools to enhance access, speed, quality, and the patient experience

Source: MacKenzie, Rod; Honig, Peter; Sewards, Judy; Goodwin Robert; Hellio, Marie-Pierre, *COVID-19 must catalyse changes to clinical development*, Nature Reviews, Drug Discovery, Vol 19, October 2020

Thank You