

Perspective

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Ensitrelvir postexposure prophylaxis for COVID−19: Translating trial efficacy into clinical practice

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Despite vaccination and widespread acquired immunity, COVID-19 continues to impose a substantial global burden, driven by waning immunity and the emergence of new variants. Households are key sites for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with secondary attack rates of up to 32% to 48% among household contacts during the omicron era[1]. Despite this well-documented transmission burden, no oral antiviral had previously demonstrated significant efficacy as postexposure prophylaxis in exposed household contacts, leaving a critical gap in clinical management[2,3].

The SCORPIO-PEP trial by Hayden *et al*.[1] provides the most compelling evidence to date that ensitrelvir, an oral inhibitor of the SARS-CoV-2 3C-like protease, can meaningfully prevent symptomatic COVID-19 when administered as postexposure prophylaxis in household contacts. With an absolute risk reduction of 6.1 percentage points (from 9.0% with placebo to 2.9% with ensitrelvir), corresponding to a relative risk reduction of 67% (risk ratio 0.33; 95% *CI* 0.22-0.49), and a manageable safety profile, this trial establishes a new therapeutic option for clinicians managing exposed household contacts. The evidence now supports a shift from asking if ensitrelvir works to asking when and for whom it should be prescribed.

The trial's overall efficacy figure is substantially shaped by the Japanese cohort, where the placebo attack rate was 23.0%, which is nearly sixfold higher than the 3.7% observed in United States participants[1]. The number needed to treat (NNT) differs by more than an order of magnitude across these regions (Table 1). These are not abstract statistical differences; they reflect profoundly different clinical calculus. A clinician counselling a household contact in a high-transmission setting faces a very different risk-benefit equation than one in a low-background-transmission outpatient practice. Importantly, clinicians should note that the US subgroup risk ratio of 0.60 (95% *CI* 0.32-1.12) did not reach statistical significance, reflecting the low attack rate in that context and the limited precision of subgroup estimates. The overall trial result is predominantly driven by the Japanese cohort. Guideline bodies and clinicians in low-transmission settings should interpret the US subgroup data with appropriate caution, while acknowledging that the point estimate consistently favours treatment across all regions.

Table 1. Region-specific absolute benefit estimates derived from the SCORPIO-PEP subgroup analysis.

Region	Ensitrelvir attack rate	Placebo attack rate	ARR	RRR	NNT
Japan	4.1%	23.0%	18.9%	82%	5
United States	2.2%	3.7%	1.5%	40%*	67*
Overall (mITT)	2.9%	9.0%	6.1%	67%	16

ARR=absolute risk reduction; RRR=relative risk reduction; NNT=number needed to treat; mITT=modified intention-to-treat population. *US subgroup *RR*=0.60 (95% *CI* 0.32-1.12); confidence interval crosses 1.0 and should be interpreted with caution.

Nasopharyngeal viral loads among Japanese index patients were on average 1.68 $\log_{10}$ copies/mL higher than in US participants[1], and antiviral treatment of the index patient was initiated in 38% of Japanese cases *versus* approximately 6% in the United States. Critically, unmeasured household-level variables such as dwelling size, masking adherence, and social distancing were not captured. Clinicians should appreciate that local transmission ecology, not just individual patient biology, is a key determinant of prophylaxis value. Future postexposure prophylaxis trials should standardise collection of these household-level cofactors.

Several trial features are directly relevant to prescribing decisions. First, the treatment window is unforgiving: ensitrelvir must be initiated within 72 hours of symptom onset in the index patient, and 71.1% of contacts in this trial were enrolled within 48 hours[1]. The subgroup enrolled at 48-72 hours showed a non-significant risk ratio of 0.69 (95% *CI* 0.33-1.42), suggesting that the majority of benefit may be concentrated in those treated within 48 hours; clinicians must therefore have systems to identify and evaluate household

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contacts as rapidly as possible. Second, among high-risk contacts (37% of the cohort), the placebo attack rate was 9.9% *versus* 2.4% with ensitrelvir, corresponding to an NNT of approximately 13, which is clinically meaningful in virtually any healthcare setting[1]. These patients, including older adults, persons with obesity, and those with other protocol-defined risk factors for severe illness (such as cardiovascular disease, diabetes, chronic lung disease, and immunocompromised conditions), should be prioritised. Third, ensitrelvir is a moderately strong cytochrome P450 3A inhibitor. Co-prescription with drugs metabolised by CYP3A warrants careful review, a consideration particularly salient for the polypharmacy patients most likely to be offered prophylaxis. The transient high-density lipoprotein decline (median 27% by day 6, normalising by day 15) was reversible and not associated with clinical events; routine monitoring is therefore not required[1].

Prior postexposure prophylaxis trials of nirmatrelvir-ritonavir[2] and molnupiravir[3] failed to demonstrate significant protection. SCORPIO-PEP's superior result likely reflects a narrower enrollment window (≤72 *vs*. 96-120 hours after index patient symptom onset), a more accurate illness definition (symptom duration ≥48 *vs*. ≥24 hours), and a shorter primary endpoint window (day 10 *vs*. day 14)[1]. A pharmacokinetic advantage may also contribute: ensitrelvir's prolonged plasma half-life maintains concentrations above the nonclinical target through day 10 despite only 5 days of dosing[1], potentially providing effective prophylactic activity well beyond the administration period.

Amino acid substitutions in the 3C-like protease emerged in 1.9% of treated contacts in the modified intention-to-treat population[1]. Importantly, no secondary transmission of substitution-bearing variants from ensitrelvir-treated index patients to placebo-treated household contacts was documented[1]. The Japan Institute for Health Security has not reported such amino acid substitutions in clinical specimens even with the widespread use of the drug in Japan since November 2022[1]. These findings are reassuring for near-term prescribing, although the authors note that further studies are needed to monitor this potential risk[1].

The recommended ensitrelvir regimen is 375 mg on Day 1, followed by 125 mg once daily on Days 2-5, totaling seven tablets per treatment course[4]. At 7 090 Japanese yen (JPY) per 125-mg tablet, the total cost is 49 630 Japanese yen (JPY) (approximately 310 US dollars) per 5-day course[5]. This cost may limit access in many low- and middle-income countries, highlighting the need for government reimbursement, subsidy programs, or negotiated pricing mechanisms to improve affordability and ensure equitable access to treatment.

In conclusion, SCORPIO-PEP establishes ensitrelvir as the first antiviral with proven efficacy for COVID-19 postexposure prophylaxis in household contacts. The clinical imperative is to deploy this evidence thoughtfully: prioritising early identification of high-risk contacts, ideally within 48 hours while respecting the narrow 72-hour treatment window, screening for potential drug-drug interactions (particularly those related to CYP3A inhibition), and calibrating recommendations to local transmission intensity. In low-transmission settings such as the United States, the subgroup data do not independently support a statistically significant benefit, and prescribing decisions should be individualized accordingly. Guideline bodies may now consider revisiting postexposure prophylaxis recommendations, ideally stratifying by baseline transmission risk.

Conflict of interest statement

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Author's contributions

The author contributed to the conception, drafting, critical revision, and final approval of the manuscript.

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