Abstract: #03159

Ensitrelvir for the Prevention of COVID-19 Among Household Contacts: Key Subgroup Analyses of SCORPIO-PEP Phase 3 Study

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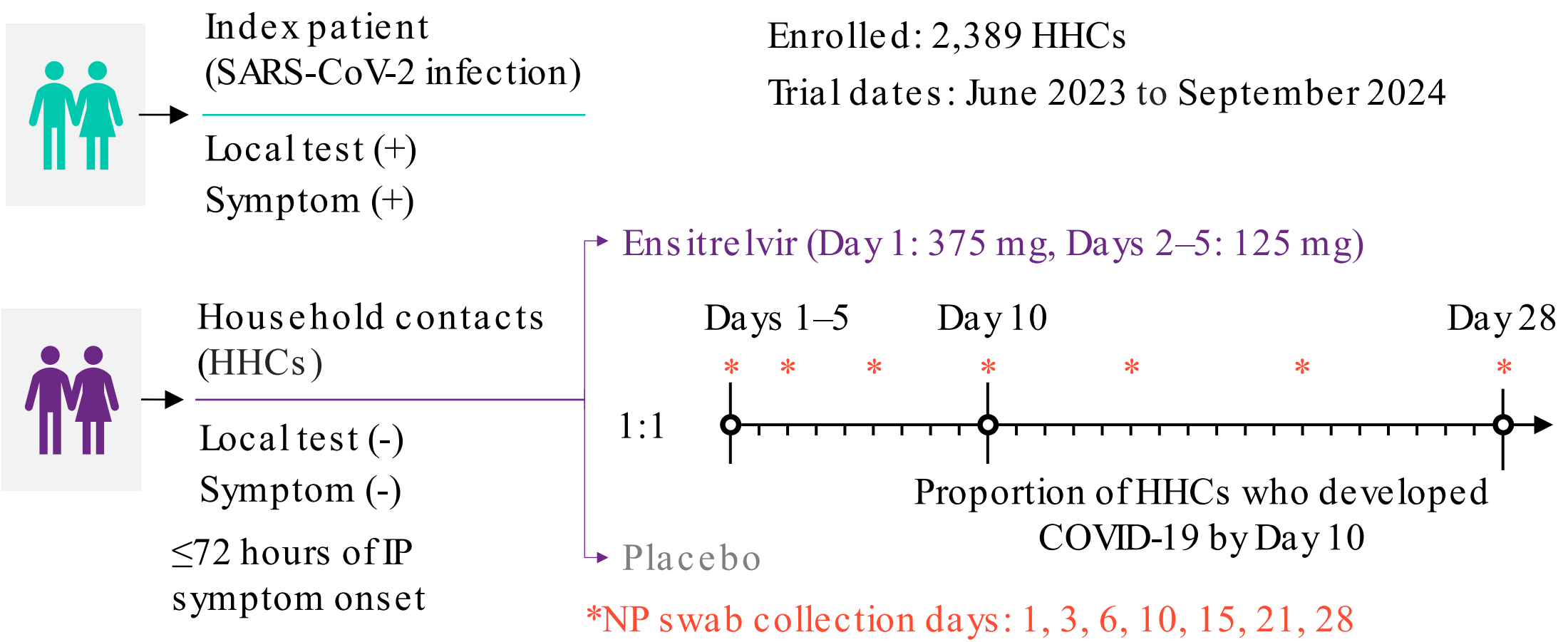
Introduction

- Households are major sites for SARS-CoV-2 transmission, with secondary attack rates ranging from 18.9% to 42.7%[1,2]
- There is an unmet need for an antiviral effective post-exposure prophylaxis, particularly in high-risk household contacts[3,4]
- Ensitrelvir, an oral SARS-CoV-2 3C-like protease inhibitor, is approved in Japan for the treatment of mild-to-moderate COVID-19[5-7]
- The SCORPIO-PEP Phase 3 (NCT05047601) trial evaluated the post-exposure prophylaxis efficacy of ensitrelvir in household contacts of index patients with confirmed COVID-19

1. Madewell ZJ, et al. JAMA Netw Open 2021;4:e2122240; 2. Madewell ZJ, et al. JAMA Netw Open 2022;5:e229317; 3. Alpizar SA, et al. J Infect 2023;87:392-402; 4. Cox RM, et al. Nat Commun 2023;14:4731; 5. Kawashima S, et al. Biochem Biophys Res Commun 2023;645:132-136; 6. Kuroda T, et al. J Antimicrob Chemother 2023;78:946-952; 7. Nobori H, et al. Antiviral Res 2024;224:105852.
COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Study Design

Double-blind, randomised, placebo-controlled Phase 3 study



Enrolled: 2,389 HHCs

Trial dates: June 2023 to September 2024

HHC, household contact; IP, index patient; NP, nasopharyngeal.

Study Populations and Endpoint

mITT population

All randomised HHCs with central laboratory–confirmed SARS-CoV-2 negativity by RT-PCR at baseline*

ITT population

All randomised HHCs including those with central laboratory–confirmed RT-PCR positivity at baseline

Primary endpoint

Proportion of HHCs with COVID-19 development (central laboratory–confirmed RT-PCR positivity of SARS-CoV-2 and ≥1 of the 14 COVID-19 symptoms lasting ≥48 hours)**

*Participants with local test (-) and central (+) were excluded from the mITT population.
**Or worsening (increase in symptom score from baseline) in the case of pre-existing COVID-19–like symptoms for ≥48 hours.
ITT, intention-to-treat; mITT, modified ITT; RT-PCR, reverse transcriptase-polymerase chain reaction.

Participant Disposition

Screened: n=2,524

↓

ITT population (randomised): n=2,387
(ensitrelvir: n=1,194 [100%];
placebo: n=1,193 [100%])

↓

mITT population: n=2,041
(ensitrelvir: n=1,030 [86.3%];
placebo: n=1,011 [84.7%])

→ Excluded from mITT: n=346 (reason*)

1. Not given PEP after randomisation: n=10
2. Local test not available at baseline: n=4
3. Central laboratory–positive PCR: n=237 or missing PCR at baseline: n=3
4. IP negative PCR (central laboratory) or missing PCR at baseline: n=92

*If participants had multiple reasons for exclusion, they were counted in one category with a priority order of 1, 2, 3 and 4.

Household Contact Characteristics (mITT)

Characteristic	Ensitrelvir (N=1,030)	Placebo (N=1,011)
Age—yr, mean (SD)	41.8 (17.0)	43.0 (16.1)
≥65, n (%)	99 (9.6)	90 (8.9)
Female, n (%)	584 (56.7)	627 (62.0)
BMI—kg/m^2, mean (SD)	26.4 (5.7)	26.6 (5.3)
Hispanic or Latino, n (%)	620 (60.2)	623 (61.6)
Race, n (%)		
White	632 (61.4)	615 (60.8)
Black or African American	51 (5.0)	56 (5.5)
Asian	325 (31.6)	321 (31.8)
American Indian or Alaska Native	2 (0.2)	4 (0.4)
Other	20 (1.9)	15 (1.5)

BMI, body mass index; SD, standard deviation.

Household Contact Characteristics (mITT) (Contd.)

Characteristic	Ensitrelvir (N=1,030)	Placebo (N=1,011)
Hours from symptom onset in the index patient to enrolment of household contacts, n (%)		
<48	732 (71.1)	720 (71.2)
Geographic region, n (%)		
US	692 (67.2)	683 (67.6)
Japan	266 (25.8)	270 (26.7)
Vietnam	59 (5.7)	49 (4.8)
Argentina	7 (0.7)	4 (0.4)
South Africa	6 (0.6)	5 (0.5)
Risk status, n (%)		
High risk for severe COVID-19*	382 (37.1)	374 (37.0)
Positive baseline serology, n (%)**		
S-antibody	1018 (99.4)	1004 (99.7)

[a]Number of participants with each non-missing serology data was used as the denominator (ensitrelvir: n=1,024; placebo: 1,007).
*Key representative high-risk factors: BMI ≥30 kg/m^2, smoking (current or former), age (≥65 years), heart disease, diabetes (type 1 or type 2); high risk is ≥1 risk factor listed.
**Number of participants with non-missing serology data was used as the denominator.
US, United States.

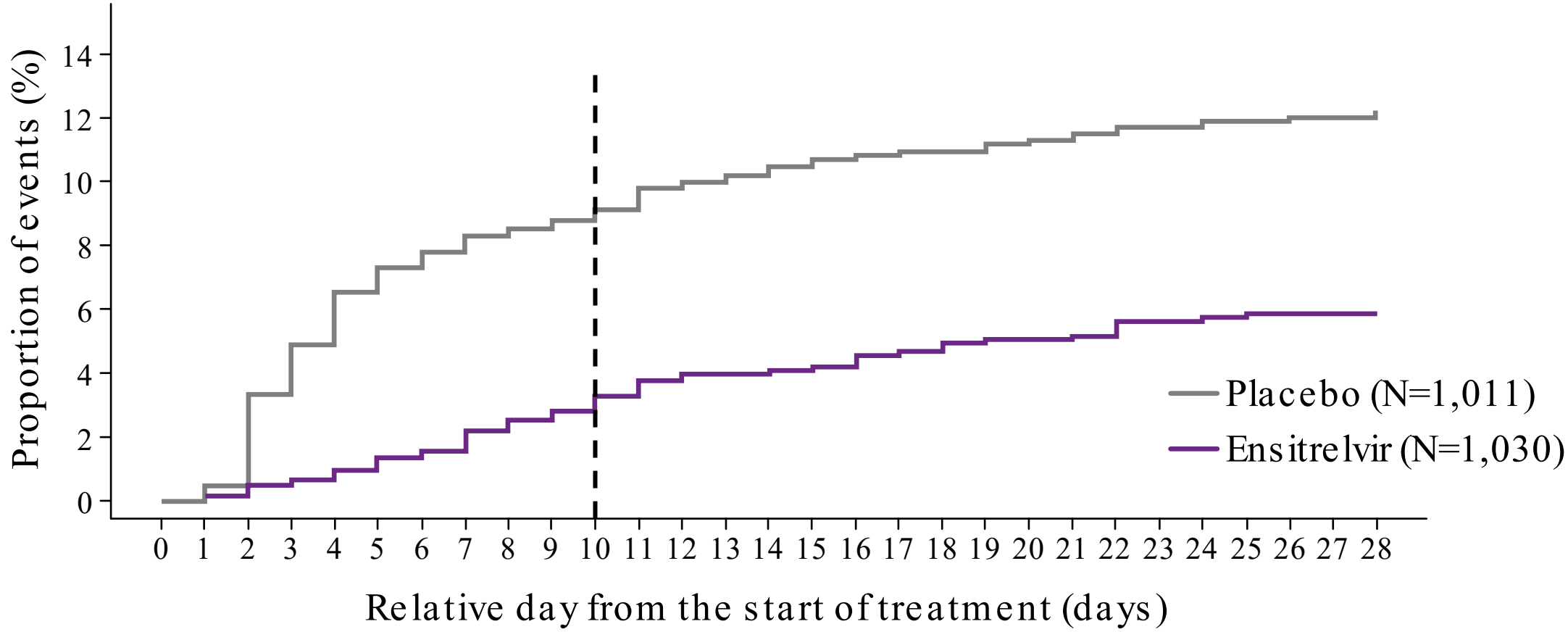
Primary Analysis: Proportion of HHCs with COVID-19 Development Through Day 10 (mITT)

	Ensitrelvir (N=1,030)	Placebo (N=1,011)
COVID-19 development, n (%)	30 (2.9)	91 (9.0)
[95% CI]*	[1.97, 4.13]	[7.31, 10.94]
Risk ratio**	0.33	
[95% CI]***	[0.22, 0.49]	
P-value****	<0.0001	

In participants with central negative tests at baseline, ensitrelvir demonstrated a statistically significant reduction in the risk of COVID-19 vs placebo (2.9% vs 9.0%)

COVID-19 development was defined as a central laboratory–confirmed positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
*CI for the proportion of participants with symptomatic COVID-19 using the Clopper-Pearson method.
**Risk ratio based on the GEE Poisson regression model with covariates of time from symptom onset in the index patient to enrolment (<48 hours/≥48 hours) and the pooled geographic regions (North America/Japan/RoW).
***CI calculated from the GEE Poisson regression model.
****P-value for the log coefficient of treatment effect = 0 in the GEE Poisson regression model.
CI, confidence interval; GEE, generalised estimating equation; RoW, rest of the world.

Primary Endpoint: HHCs with COVID-19 Development Through Day 28 (mITT)



Participants who were randomised but did not receive treatment were excluded from this analysis.

Household Contacts with or without High Risk Factor (mITT)

	Ensitrelvir (N=1,030)	Placebo (N=1,011)
HHCs WITH high risk factor, n	382	374
COVID-19 development, n (%)	9 (2.4)	37 (9.9)
Risk ratio*	0.24	
[95% CI]	[0.12, 0.49]	
HHCs WITHOUT high risk factor, n	648	637
COVID-19 development, n (%)	21 (3.2)	54 (8.5)
Risk ratio*	0.39	
[95% CI]	[0.24, 0.62]	

- More frequent risk factors were BMI ≥30 kg/m^2, smoking (current or former), age (≥65 years), heart disease, diabetes (type 1 or type 2)

COVID-19 development was defined as a CLC positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
*Risk ratio and its 95% CI was calculated using the GEE Poisson regression model.

Time from Initial Symptom Onset in Index Patient to PEP Initiation (mITT)

	Ensitrelvir (N=1,030)	Placebo (N=1,011)
<48 hours, n	732	720
COVID-19 development, n (%)	18 (2.5)	74 (10.3)
Risk ratio*	0.26	
[95% CI]	[0.16, 0.41]	
48–72 hours, n	298	291
COVID-19 development, n (%)	12 (4.0)	17 (5.8)
Risk ratio*	0.69	
[95% CI]	[0.33, 1.42]	

COVID-19 development was defined as a CLC positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
*Risk ratio and its 95% CI was calculated using the GEE Poisson regression model.

Effect of Household Contact Age (mITT)

	Ensitrelvir (N=1,030)	Placebo (N=1,011)
<18 years, n	64	54
COVID-19 development, n (%)	1 (1.6)	2 (3.7)
Risk ratio*	0.42	
[95% CI]	[0.04, 4.57]	
18–64 years, n	867	867
COVID-19 development, n (%)	26 (3.0)	78 (9.0)
Risk ratio*	0.34	
[95% CI]	[0.23, 0.52]	
≥65 years, n	99	90
COVID-19 development, n (%)	3 (3.0)	11 (12.2)
Risk ratio*	0.25	
[95% CI]	[0.08, 0.82]	

COVID-19 development was defined as a CLC positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
*Risk ratio and its 95% CI was calculated using the GEE Poisson regression model.

Safety

TEAEs, n (%)	Ensitrelvir (N=1,190)*	Placebo (N=1,187)*
Any TEAE	180 (15.1)	184 (15.5)
Any serious TEAE	2 (0.2)	2 (0.2)
Any study drug–related TEAE	19 (1.6)	21 (1.8)
Any study drug–related serious TEAE	0	0
Any TEAE leading to treatment discontinuation	1 (<0.1)	1 (<0.1)
Any TEAE leading to study discontinuation	0	1 (<0.1)

*N represents the number of participating HHCs with each type of adverse event. Percentages are based on the number of participating HHCs in the safety analysis set within each treatment group.
TEAE, treatment-emergent adverse event.

Safety (Contd.)

TEAEs (≥1%) by preferred term, n (%)	Ensitrelvir (N=1,190)*	Placebo (N=1,187)*
Headache	35 (2.9)	30 (2.5)
Diarrhea	21 (1.8)	15 (1.3)
Nasopharyngitis	16 (1.3)	15 (1.3)
Cough	14 (1.2)	7 (0.6)
Influenza	13 (1.1)	19 (1.6)
Fatigue	13 (1.1)	12 (1.0)
Oropharyngeal pain	11 (0.9)	17 (1.4)

Both treatments had similar rates of TEAEs and serious TEAEs, with no deaths and hospitalisation

*N represents the number of participating HHCs with each type of adverse event. Percentages are based on the number of participating HHCs in the safety analysis set within each treatment group.

Summary

- Ensitrelvir post-exposure prophylaxis (PEP) ≤72 hours after symptom onset in index patients was well-tolerated and effective in significantly protecting household contacts from COVID-19.
  - ✓ Protection was consistently observed in at-risk groups, including elderly household contacts.
  - ✓ Ensitrelvir PEP efficacy was higher with earlier initiation in household contacts.
- These results suggest a potential for protection in other settings like outbreaks in acute and long-term care facilities.

Thank you!

We also thank the study participants, who generously gave their time, and the staff at the investigation site.

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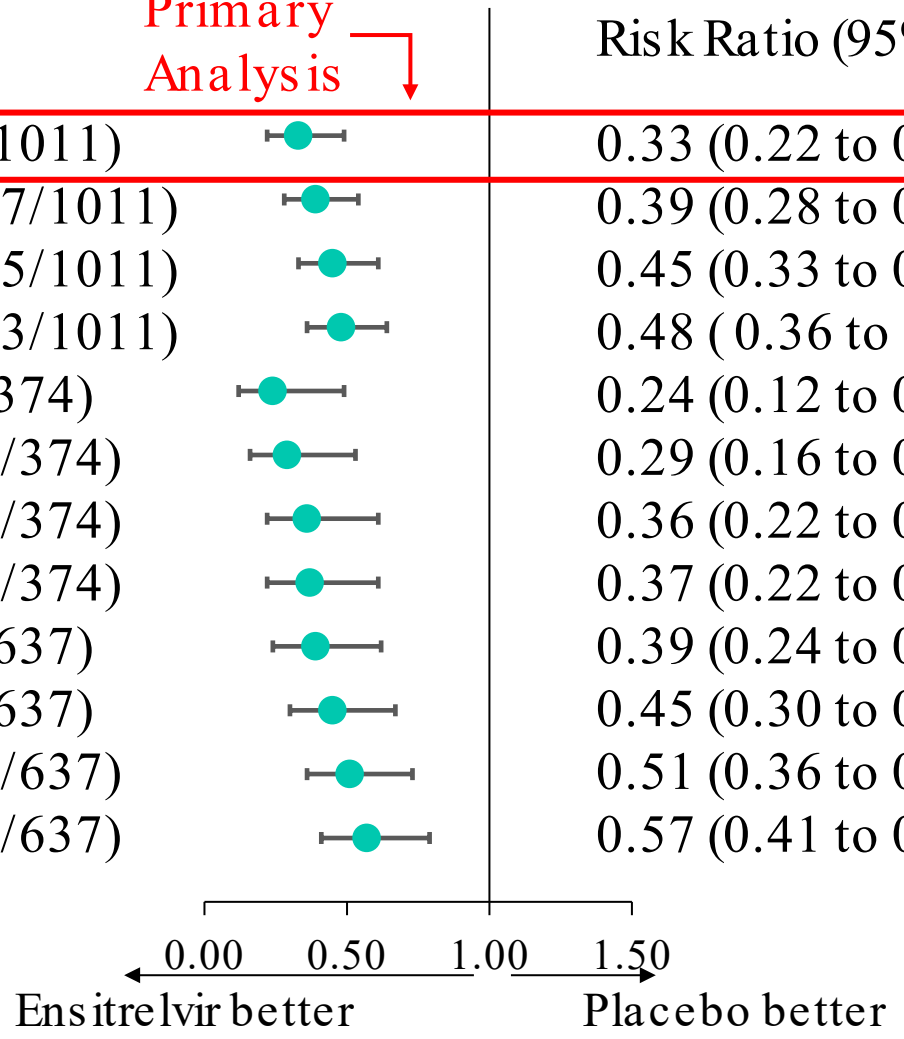
Back-up slides

Subgroup Analysis of w/wo Any Risk Factors – mITT Set, Symptom Duration: 48 hours

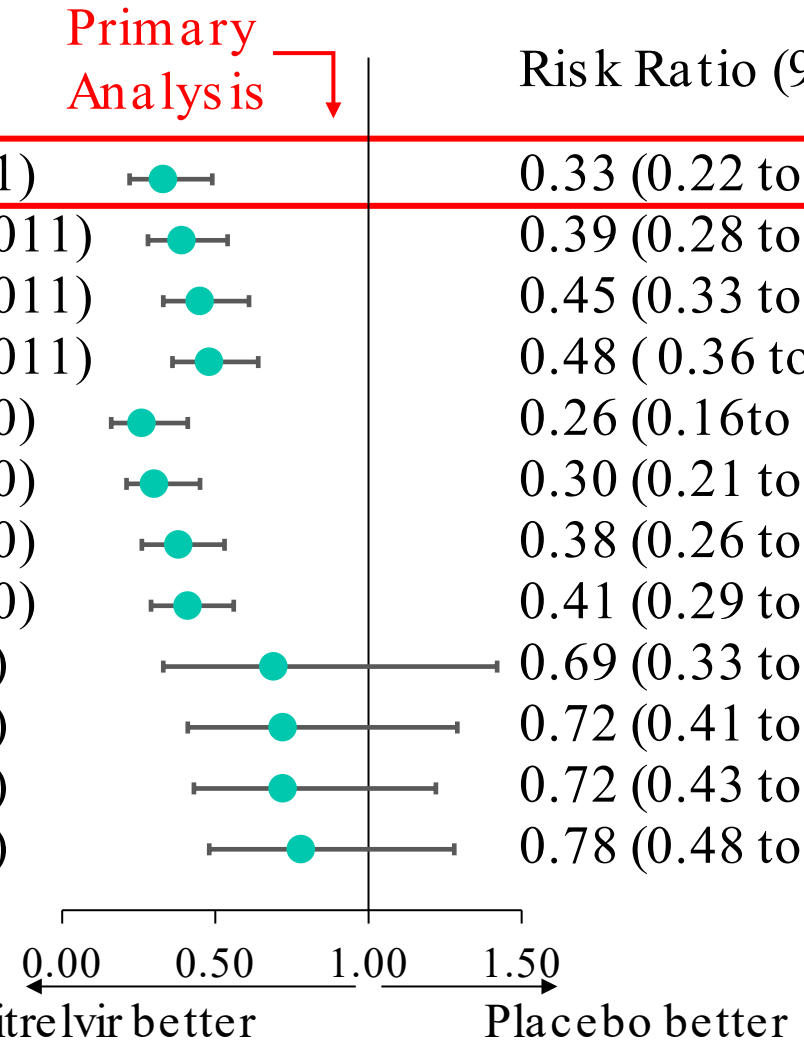
With/ without HR factor	Evaluation Period	Ensitrelvir	Placebo	Risk Ratio (95% CI)
Overall	Day 10	2.9% (30/1030)	9.0% (91/1011)	0.33 (0.22 to 0.49)
	Day 15	4.0% (41/1030)	10.6% (107/1011)	0.39 (0.28 to 0.54)
	Day 21	5.0% (52/1030)	11.4% (115/1011)	0.45 (0.33 to 0.61)
	Day 28	5.8% (60/1030)	12.2% (123/1011)	0.48 (0.36 to 0.64)
With HR Factor	Day 10	2.4% (9/382)	9.9% (37/374)	0.24 (0.12 to 0.49)
	Day 15	3.4% (13/382)	11.8% (44/374)	0.29 (0.16 to 0.53)
	Day 21	4.5% (17/382)	12.6% (47/374)	0.36 (0.22 to 0.61)
	Day 28	4.7% (18/382)	13.1% (49/374)	0.37 (0.22 to 0.61)
With HR Factor	Day 10	3.2% (21/648)	8.5% (54/637)	0.39 (0.24 to 0.62)
	Day 15	4.3% (28/648)	9.9% (63/637)	0.45 (0.30 to 0.67)
	Day 21	5.4% (35/648)	10.7% (68/637)	0.51 (0.36 to 0.73)
	Day 28	6.5% (42/648)	11.6% (74/637)	0.57 (0.41 to 0.79)



Arobust & favourable trend was observed regardless of w/wo any risk factors & symptom duration

Subgroup Analysis by Time from Onset of Index Patients to Enrolment - mITT Set, Symptom Duration: 48 hours

Time from IP onset	Evaluation Period	Ensitrelvir	Placebo	Risk Ratio (95% CI)
Overall	Day 10	2.9% (30/1030)	9.0% (91/1011)	0.33 (0.22 to 0.49)
	Day 15	4.0% (41/1030)	10.6% (107/1011)	0.39 (0.28 to 0.54)
	Day 21	5.0% (52/1030)	11.4% (115/1011)	0.45 (0.33 to 0.61)
	Day 28	5.8% (60/1030)	12.2% (123/1011)	0.48 (0.36 to 0.64)
<48 hours	Day 10	2.5% (18/732)	10.3% (74/720)	0.26 (0.16to 0.41)
	Day 15	3.3% (24/732)	11.7% (84/720)	0.30 (0.21 to 0.45)
	Day 21	4.5% (33/732)	12.4% (89/720)	0.38 (0.26 to 0.53)
	Day 28	5.2% (38/732)	13.2% (95/720)	0.41 (0.29 to 0.56)
≥48 hours	Day 10	4.0% (12/298)	5.8% (17/291)	0.69 (0.33 to 1.42)
	Day 15	5.7% (17/298)	7.9% (23/291)	0.72 (0.41 to 1.29)
	Day 21	6.4% (19/298)	8.9% (26/291)	0.72 (0.43 to 1.22)
	Day 28	7.4% (22/298)	9.6% (28/291)	0.78 (0.48 to 1.28)



Arobust &favourable trend was observed regardless of time from onset of index patient &symptom duration
Effect size in <48 hours of time from index onset was larger than that in ≥48 hours

Key Inclusion Criteria

	For Index Patients	For Household Contacts
Inclusion criteria	✓ Have ≥1 of 14 COVID-19 symptoms* within 24 hours ✓ Must have positive SARS-CoV-2 test from a sample collected ≤72 hours prior to randomisation; have positive SARS-CoV-2 test from any respiratory tract specimen at the local lab (antigen or RT-PCR) ✓ Have the first positive test for SARS-CoV-2 or the earliest onset of COVID-19 symptoms within the household	✓ ≥12 years of age with a negative screening SARS-CoV-2 test at the local lab (antigen or RT-PCR) ✓ Be randomised ≤72 hours from the onset of COVID-19 symptoms in the index patient ✓ Has lived/continues to live in the same household with index patient and shares common areas such as dining rooms and bathrooms until the end of the study
Exclusion criteria	✗ Documented respiratory infection other than COVID-19 ≤14 days prior to the screening visit	✗ Have tested positive for SARS-CoV-2 in the past 6 months ✗ Received any SARS-CoV-2 vaccine in ≤6 months ✗ Fever or COVID-19 symptoms ✗ Respiratory illness within the past 2 weeks ✗ Systemic corticosteroid use ✗ Pregnancy ✗ Severe liver disease ✗ Use of strong CYP3A inducers

*Fever, shortness of breath or difficulty breathing, cough, sore throat, nasal congestion or runny nose, chills, fatigue, body or muscle pain or aches, headache, nausea, vomiting, diarrhea, change in sense of taste, change in sense of smell.
CYP, cytochrome P450.

Index Patient Characteristics (mITT)

Characteristics	Total (N=1,319)
Age—yr, mean (SD)	39.7 (19.9)
Age categories—yr, n (%)	
<12	73 (5.5)
≥12 to <18	141 (10.7)
≥18 to <65	968 (73.4)
≥65	137 (10.4)
People per household, excluding the IP, n (%)	
1	225 (17.1)
2	273 (20.7)
3	275 (20.8)
≥4	546 (41.4)
IPs receiving antiviral treatment, n (%)*	241 (18.3)
Treatment details	
• Ensitrelvir	176 (73.0)
• Nirmatrelvir/ritonavir	43 (17.8)
• Molnupiravir	22 (9.1)

*Number of index patients with antiviral treatment was used as the denominator.

Distribution of High-risk Factors mITT Set

HR Factors, n(%)	Ensitrelvir N=1,030	Placebo N=1,011
Any of HR factors	382 (37.1%)	374 (37.0%)
BMI ≥30 kg/m^2	223 (21.7%)	208 (20.6%)
Smoking (current or former)	98 (9.5%)	97 (9.6%)
Age ≥65 years	99 (9.6%)	90 (8.9%)
Heart disease	56 (5.4%)	41 (4.1%)
Diabetes (type 1 or type 2)	43 (4.2%)	40 (4.0%)
Chronic lung disease	10 (1.0%)	5 (0.5%)
Hypertension	5 (0.5%)	6 (0.6%)
Chronic liver disease	4 (0.4%)	2 (0.2%)
Stroke	3 (0.3%)	2 (0.2%)
Immunocompromising conditions	2 (0.2%)	0
Hypothyroidism	1 (0.1%)	1 (0.1%)
Chronic kidney disease	1 (0.1%)	0

HR Factors, n(%)	Ensitrelvir N=1,030	Placebo N=1,011
Down syndrome	1 (0.1%)	0
Sickle cell disease	0	1 (0.1%)
Asthma controlled	0	1 (0.1%)
Hyperthyroidism	0	1 (0.1%)

More frequent risk factors:

- BMI ≥30 kg/m^2
- Smoking (current or former)
- Age ≥65 years
- Heart disease
- Diabetes (type 1 or type 2)