The oral protease inhibitor ensitrelvir reduces SARS-CoV-2 transmission in a hamster model

Masaaki Nakashima[1], Takayuki Kuroda[1], Keita Fukao[1], Haruaki Nobori[1], Akane Hayashi[2], Mei Yoshida[2], Kazumi Matsumoto[2], Kaoru Baba[2], Teruhisa Kato[1]

[1] Shionogi & Co., Ltd., Osaka, Japan
[2] Shionogi TechnoAdvance Research, Co., Ltd., Osaka, Japan

COI: Authors are employees of Shionogi & Co., Ltd. or Shionogi TechnoAdvance Research, Co., Ltd. Some authors are shareholder of Shionogi & Co., Ltd.

Background

Novel coronavirus disease (COVID-19) continues to constitute a public health emergency of international concern. In addition to vaccination, antivirals also have a potential to be used as medical countermeasure to control severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread. Ensitrelvir is an orally available small molecule inhibitor of 3CL protease of SARS-CoV-2 which demonstrated antiviral efficacy in a randomized phase 3 study and was granted emergency use approval in Japan. We here established a hamster transmission model and evaluated the efficacy of ensitrelvir on reduction of virus transmission.

Methods

Male Syrian hamsters (6-weeks old) were intranasally inoculated with SARS-CoV-2 delta strain (hCoV19/Japan/TY11-927-P1/2021) (index). To evaluate efficacy of ensitrelvir on viral transmission, index hamsters were orally treated with 12.5, 50 and 200 mg/kg ensitrelvir or vehicle twice daily (bid) from eight hours post infection (hpi). One day post infection (dpi), index and naive hamster (contact) pairs were cohoused in separated two stainless wire cages to prevent direct viral transmission and in same container enable aerosol transmission for twelve hours. Viral titres in lung and Nasal lavage fluid (NALF), and RNA level in lung of index hamsters on 2 dpi and of contact hamsters on 4 days after cohousing were measured by $TCID_{50}$ assay using VeroE6/TMPRSS2 cells and qRT-PCR, respectively.

Figure 1a Design for evaluation of ensitrelvir against SARS-CoV-2 infection in a hamster model

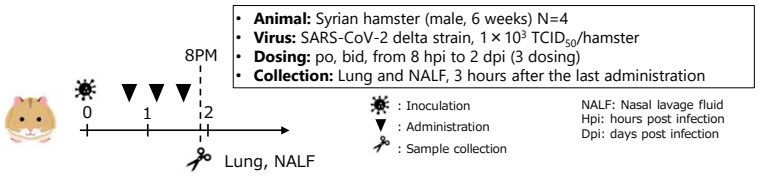
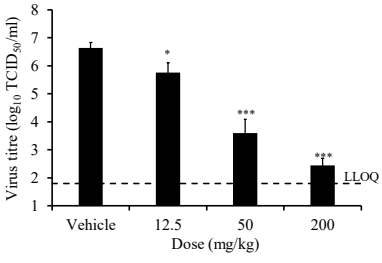
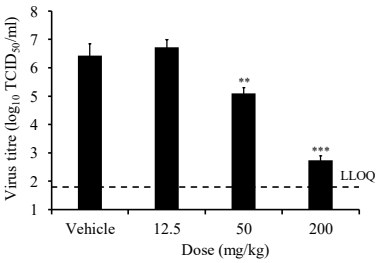


Figure 1b Lung virus titre



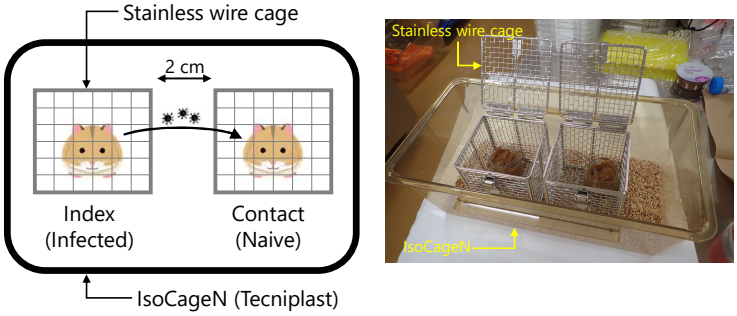
The following p-values were calculated by Dunnett's test.
* p < 0.05, *** p < 0.0001 vs vehicle.
LLOQ: Lower limit of quantification

Figure 1c NALF virus titre



The following p-values were calculated by Dunnett's test.
** p < 0.001, *** p < 0.0001 vs vehicle.
LLOQ: Lower limit of quantification

Figure 2 Transmission experiment system



Acknowledgement

SARS-CoV-2 was a kindly gift from National Institute of Infectious Diseases (NIID).

Figure 3a Design for evaluation of ensitrelvir against SARS-CoV-2 transmission in a hamster model

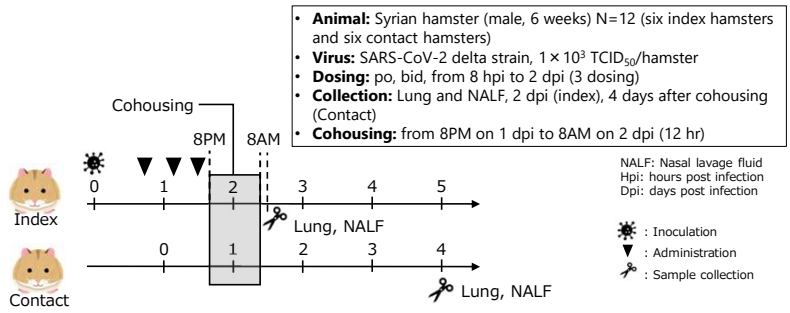


Figure 3b Lung virus titre of index hamsters

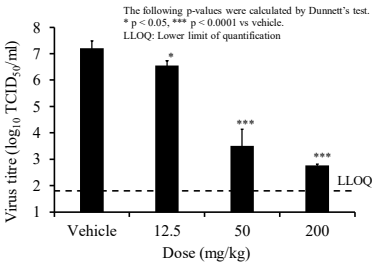


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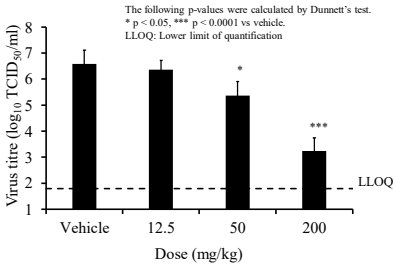
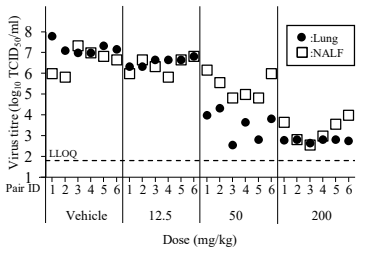
Figure 3c NALF virus titre of index hamsters



The following p-values were calculated by Dunnett's test.
* p < 0.05, *** p < 0.0001 vs vehicle.
LLOQ: Lower limit of quantification

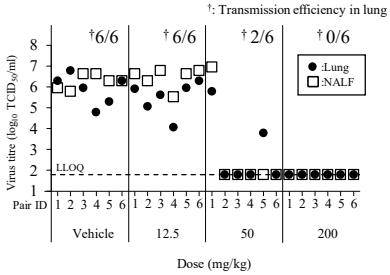
Figure 3d Virus titre of each index hamster



LLOQ: Lower limit of quantification

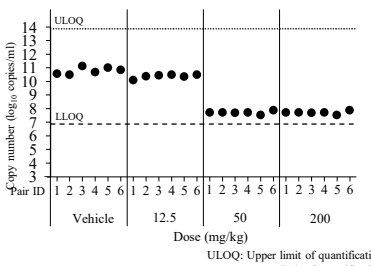
Figure 3e Virus titre of each contact hamster

†: Transmission efficiency in lung



LLOQ: Lower limit of quantification

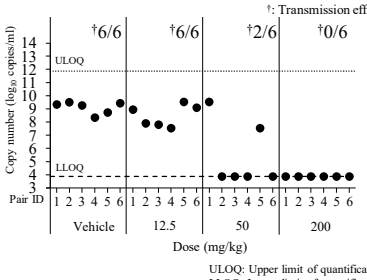
Figure 3f Lung virus RNA level of each index hamster



ULOQ: Upper limit of quantification
LLOQ: Lower limit of quantification

Figure 3g Lung virus RNA level of each contact hamster

†: Transmission efficiency



ULOQ: Upper limit of quantification
LLOQ: Lower limit of quantification

Results

Viruses were detectable in the lung collected from index hamsters and contact hamsters. Ensitrelvir significantly reduced virus titre in lung and NALF before and after cohousing in a dose-dependent manner in index hamsters. The detection rate of viral titres and RNA in lungs of contact hamsters (transmission efficiency) cohoused with vehicle administered index hamsters was 6/6. On the other hand, the detection rate among contact hamsters cohoused with ensitrelvir administered index hamsters decreased depending on the dose of ensitrelvir to index hamsters. These results indicate that indirect transmission occurred in hamster SARS-CoV-2 infection model and ensitrelvir reduces viral transmission from index hamsters.

Conclusion

We demonstrated that administration of ensitrelvir reduced the SARS-CoV-2 transmission in a hamster model.