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In vivo evaluation of ASC10 against SARS-CoV-2 virus in K18-hACE2 mouse SARS-CoV-2 model

Handan He, Jinzi J.Wu

Ascletis BioScience Co., Ltd.

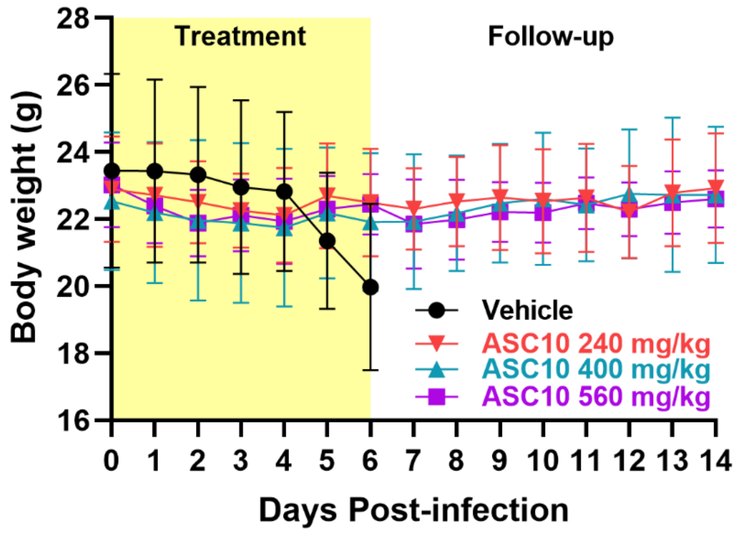
BACKGROUND

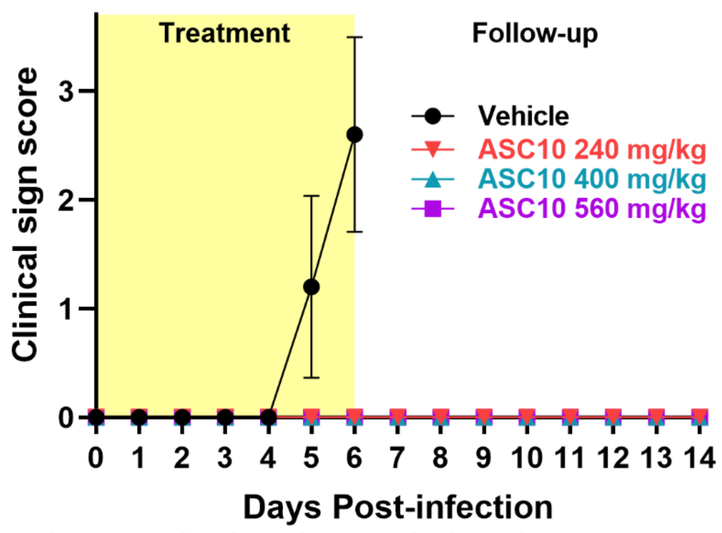
ASC10 is an oral double prodrug and rapidly converted into the same active metabolite of molnupiravir, ASC10-A, also known as β-d-N^4-hydroxycytidine (NHC) after oral administration. *In vitro* studies showed that ASC10-A had broad spectrum antiviral activities. Here we report the *in vivo* efficacy of ASC10 against SARS-CoV-2 virus in K18-hACE2 mouse SARS-CoV-2 model.

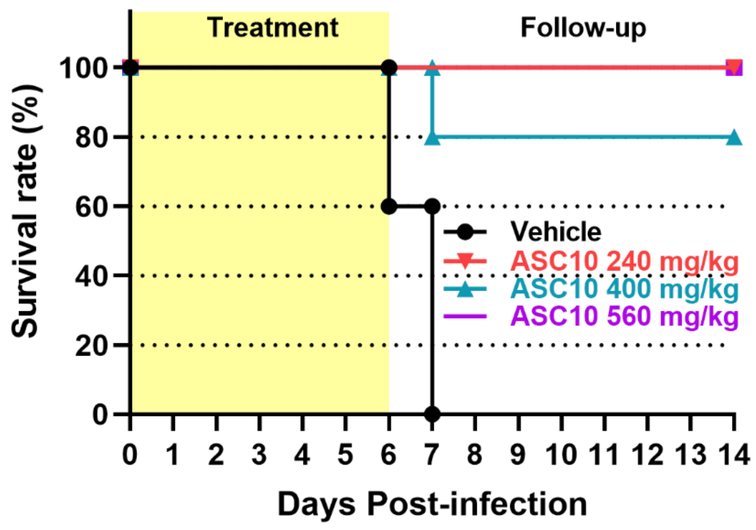
METHODS

This animal study included 2 parts, health monitor and lung viral titration parts. Each part consisted of 4 groups with 5 mice per group. K18-hACE2 mice were infected intranasally with SARS-CoV-2 viruses at 5×10^3 PFU/mouse on Day 0, and then treated with 240, 400, 560 mg/kg ASC10 or vehicle (100% PEG400) by gavage twice daily (BID). In health monitor part, mice were treated from Days 0-6, and followed until Day 14. All animals were euthanized on Day 14. Mice were monitored for body weight changes, clinical signs and survival. Clinical sign score was calculated by a set of four animal symptoms including ruffled fur, hunched gesture, lethargy/low activity and labored breath, and each symptom scored as 1 point. In lung viral titration part, mice were treated from Days 0-3, and euthanized on Day 4. Fresh lung tissue was collected for measurement of viral load by immuno-plaque assay.

RESULTS

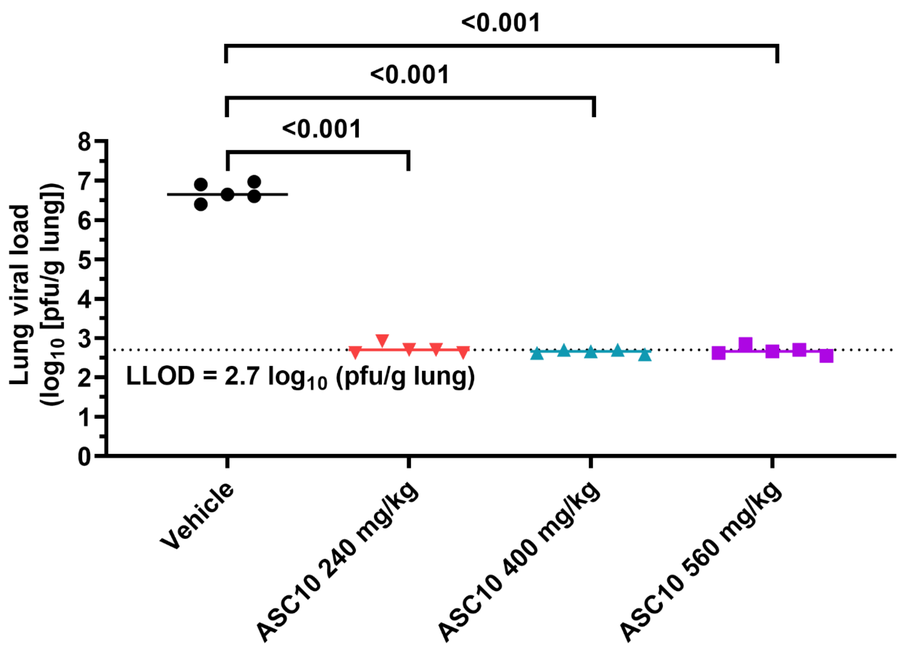






Mice treated with the vehicle showed a dramatic body weight decrease on Day 5 post virus infection and all died on Day 7, while the body weight of mice treated with ASC10 remained stable during 14-day study. Only one mouse in 400 mg/kg group died on Day 7, while the rest of mice treated with ASC10 survived until the end of study. Mice treated with the vehicle experienced a significant increase of clinical sign scores from Day 5, with average scores of 1.2 and 2.6 on Days 5 and 6, respectively.

Mice treated with the vehicle had an average viral titer of 6.7 $\log_{10}$ (pfu/g lung), whereas mice treated with 240, 400 and 560 mg/kg ASC10 showed an average viral titer decrease of 3.99, 4.05 and 4.02 $\log_{10}$, respectively. The viral titer of mice treated with ASC10 all reduced to approximately 2.7 $\log_{10}$ (pfu/g lung), which was the lower limit of detection (LLOD) of plaque assay, suggesting that ASC10 at 240 mg/kg dose had already reached the maximum antiviral effects and could potentially eliminate infectious viruses in mouse lungs and inhibit viral replication.



CONCLUSION

Results of this study showed that ASC10 could potently eliminate SARS-CoV-2 viruses in the lungs, and therefore protect animals from weight losses, development of clinical symptoms and deaths. Combined with the positive phase 1 data in human, further clinical investigation is warranted.

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