Review 1: "Antisense oligonucleotides target a nearly invariant structural element from the SARS-CoV-2 genome and drive RNA degradation"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

Claims are generally supported by the data and methods used. Decision-makers should consider the claims in this study actionable with limitations based on the methods and data. Also, this research is well-structured and well-written by using clear and accurate language. The manuscript has a high degree of novelty which contributes to broader research understandings. I can recommend it for publishing.

Reviewer recommendations:

1. Figure 1D-E requires more clear explanation like "what was the main purpose to do these experiments", and "how does it contribute to support the idea in case of structures formed."
2. Figure 2C is not clearly explained. There are some questions coming to mind there; what are the meanings of multiple bands in +all, +some, and +RNaseH samples, how is it possible to be a degradation in +all and +some samples without RNaseH enzymes. These must be answered.
3. There is no in vivo study in this manuscript, so don't use in vivo terms, as studies on cell lines are mostly accepted as in vitro studies as they are happening inside a tube.
4. Figure 5D should be discussed more. Possible questions: How do you explain the saturated replicon activity between 50 and 500ul doses in gapmer 6 sample for HEK293T cell lines? Why does the replicon activity significantly decrease in gapmer scr samples for HEK293T cell lines from 0 to 500ul dose?
5. The discussion section seems incomplete and more like a conclusion. That's why there should be more efforts in that section to build a compact study.