Poster 1143

Prophylactic and Therapeutic Activity of AZD7442 (Tixagevimab/Cilgavimab) in SARS-CoV-2 Hamster Challenge Models

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Introduction

- AZD7442, a combination of two SARS-CoV-2–neutralizing monoclonal antibodies (mAbs; tixagevimab and cilgavimab), has received US Food and Drug Administration authorization for emergency use for prevention of COVID-19 in immunocompromised individuals.[1]
- YTE and triple modification (TM) amino acid modifications were introduced to the fragment crystallizable (Fc) regions to extend mAb half-life and reduce the potential risk of antibody-dependent enhancement of disease, respectively.[2]
- The hamster is a commonly accepted model for studying SARS-CoV-2, as they are susceptible to SARS-CoV-2 infection and develop lung pathology and clinical signs of COVID-19 (rapid breathing, lethargy, and weight loss).[3]

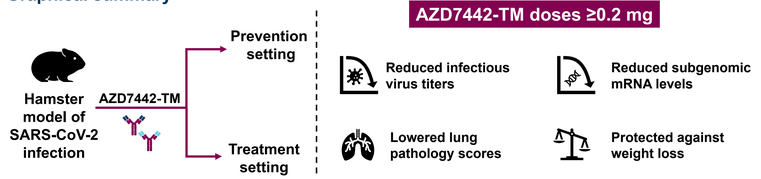
Objective

- We evaluated in vivo efficacy of AZD7442-TM in prevention and treatment settings in a Syrian hamster model of SARS-CoV-2 infection.

Conclusions

- In a Syrian hamster model of SARS-CoV-2 infection, AZD7442-TM (without YTE modification) given for prevention or treatment significantly lowered lung viral loads, with no evidence of antibody-dependent enhancement of disease or infection.
  - YTE modification extends half life of mAbs in humans but accelerates antibody clearance in rodents.
- In both prevention and treatment settings, AZD7442-TM provided protection against weight loss. Lung pathology scores indicated that AZD7442-TM protected against SARS-CoV-2–induced pulmonary inflammation and alveolar damage in the prevention and treatment settings.
- These findings support the continued clinical evaluation of AZD7442 for prevention and treatment of COVID-19 in humans, including immunocompromised populations.

Graphical summary



Supplementary Content

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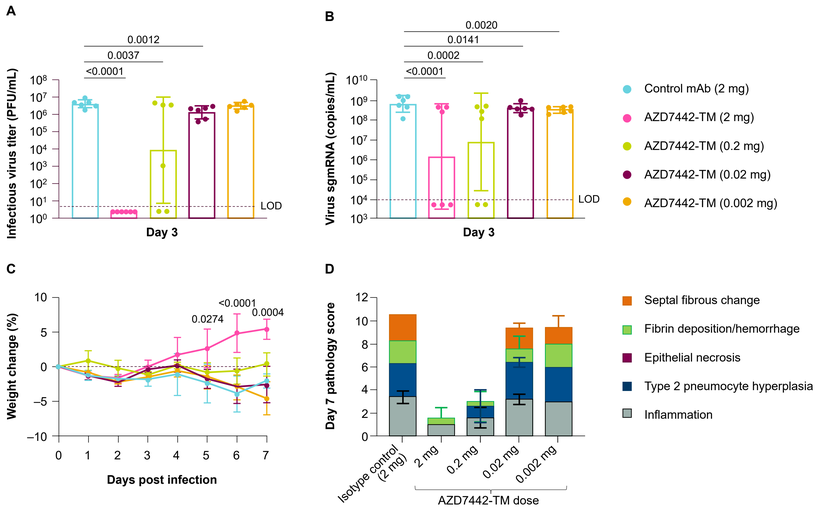
Results and interpretation

Prevention setting

- Serum concentrations of AZD7442-TM corresponded with dose (data not shown).
- At Day 3 post infection, the lowest infectious virus titer (**Figure 1A**) was seen with doses ≥0.2 mg AZD7442-TM; by Day 7, virus titers were below the limit of detection (LOD) for all doses tested.
- At Day 3, there was a dose-dependent reduction in viral subgenomic mRNA levels (**Figure 1B**); by Day 7, viral subgenomic mRNA levels were below the LOD at all doses tested.
- Doses ≥0.2 mg protected against virus-induced weight loss versus controls (**Figure 1C**).
- At Day 7, mean lung pathology score was <2 in hamsters treated with AZD7442-TM 2 mg versus >10 in controls, indicating AZD7442 protected from virus-induced inflammation and alveolar damage (**Figure 1D**).

Figure 1. Effect of preventive treatment with AZD7442-TM on (A) Day 3 SARS-CoV-2 virus titers, (B) Day 3 SARS-CoV-2 subgenomic mRNA titers, (C) weight loss, and (D) Day 7 lung pathology

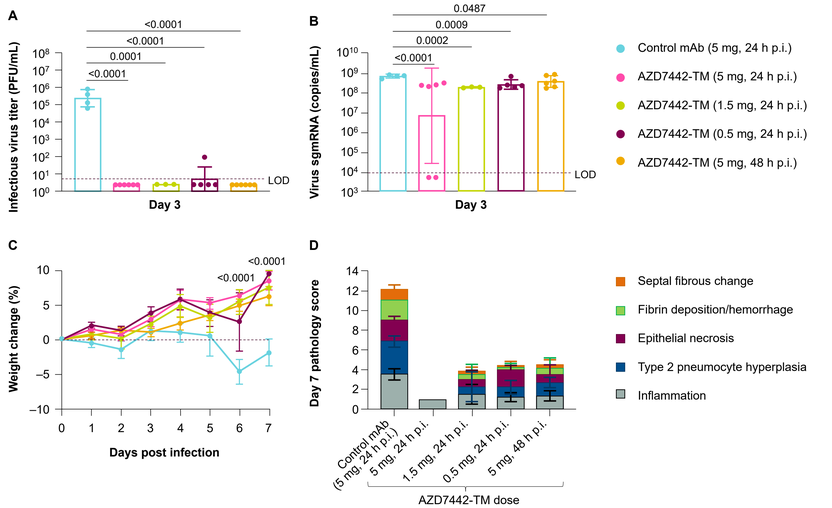


LOD, limit of detection; mAb, monoclonal antibody; PFU, plaque forming unit; sgmRNA, subgenomic mRNA; TM, triple modification.

Treatment setting

- At Day 3 post infection, infectious virus titers (**Figure 2A**) were below the LOD at all doses tested (P≤0.0001 versus controls) and remained that way; by Day 7, virus titers were below LOD for all doses tested.
- At Day 3, the lowest viral subgenomic mRNA levels (**Figure 2B**) were seen with doses ≥0.5 mg AZD7442-TM; by Day 7, subgenomic mRNA levels were below the LOD at all doses tested.
- Doses ≥0.5 mg protected against virus-induced weight loss versus controls (**Figure 2C**).
- At Day 7, mean lung pathology score was <2 in hamsters treated with AZD7442-TM 5 mg versus >12 in controls (**Figure 2D**).

Figure 2. Effect of post-infection treatment with AZD7442-TM on (A) Day 3 SARS-CoV-2 virus titers, (B) Day 3 SARS-CoV-2 subgenomic mRNA titers, (C) weight loss, and (D) Day 7 lung pathology



mAb, monoclonal antibody; PFU, plaque forming unit; p.i., post infection; sgmRNA, subgenomic mRNA; TM, triple modification.

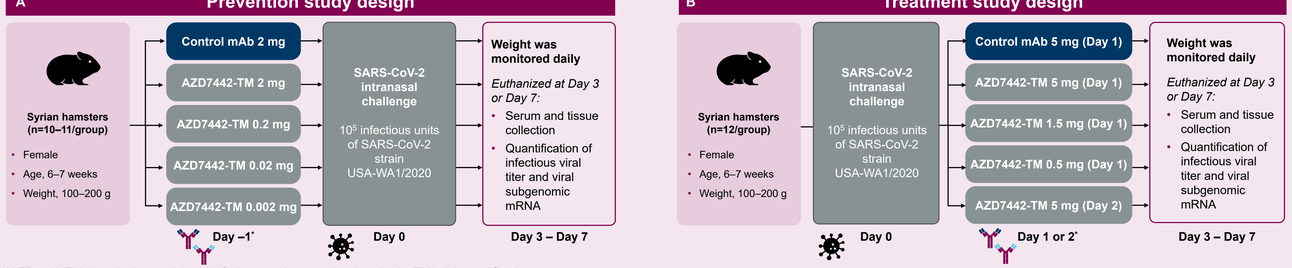
Limitations

- Limitations of this in vivo study include the short study period, restricting the ability to examine the potential impact of mAb administration on the natural immunity to virus infection, and use of a single SARS-CoV-2 strain.

Methods

- Syrian hamsters were challenged intranasally with SARS-CoV-2 strain USA-WA1/2020 on Day 0 for both the prevention (**Figure 3A**) and treatment (**Figure 3B**) settings.
- AZD7442-TM was administered by intraperitoneal injection. AZD7442-TM includes the TM but not the YTE modification, as YTE accelerates mAb elimination in rodents.[4]
- Serum and tissue were collected on Days 3 and 7 post infection; body weight was recorded daily.
- Tissue sections were stained with a rabbit mAb specific for SARS-CoV-2 nucleocapsid protein and were imaged and scored in blinded fashion by a veterinary pathologist.
  - Mean lung pathology scores were determined on a scale of 0 (normal) to 25 (most severe).

Figure 3. Study design for assessment of AZD7442-TM in hamsters in (A) prevention and (B) treatment settings



*AZD7442-TM given by intraperitoneal infusions. mAb, monoclonal antibody; TM, triple modification.

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Disclosures

- Patrick M. McTamney, Richard Roque, Yingyun Cai, Mark T. Esser, and Yueh-Ming Loo are current or past employees of, and hold or may hold stock in, AstraZeneca. Andrew S. Herbert, Ana I. Kuehne, Alicia M. Moreau, Russell Bakken, Christopher P. Stefan, Jeffrey W. Koehler, Korey L. Delp, Susan R. Coyne, Christopher D. Kane, and John M. Dye declare no competing interests.

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