

IDWeek, October 16-20, 2024, Los Angeles, CA, USA

Submission deadline: May 7, 2024, 11.59 PM ET

Lack of Association Between Cardiovascular Events and Tixagevimab/Cilgavimab for COVID-19 Pre-Exposure Prophylaxis: Potential Implications for Future Long-Acting Antibodies

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Character count: 1922 (limit: 1950 characters)

Background

In the PROVENT (NCT04625725) clinical trial of the long-acting monoclonal antibody combination tixagevimab/cilgavimab (AZD7442) versus placebo for pre-exposure prophylaxis (PrEP) against COVID-19, a numerical imbalance was observed in serious cardiac disorders between AZD7442 (23 [0.7%] participants) and placebo (5 [0.3%]) at the 6-month follow-up (2:1 randomization). No clinical/temporal patterns were observed, and no imbalance was observed in other AZD7442 trials. This retrospective cohort study assessed AZD7442 cardiovascular safety in immunocompromised patients who received AZD7442 PrEP, using data from a large US integrated health system.

Methods

Immunocompromised individuals eligible for AZD7442 PrEP under the previous US Emergency Use Authorization (EUA) between December 8, 2021, and January 26, 2023, were identified within the US Department of Defense Military Health System, including active military personnel and their beneficiaries. Individuals exposed to AZD7442 600 mg were propensity score (PS)-matched (1:1) to unexposed individuals using a “rolling cohort” approach. Conditional Cox regression was used to estimate hazard ratios and 95% confidence intervals for the effect of AZD7442 on each of heart failure, myocardial infarction, stroke, and deep vein thrombosis.

Results

Of 1,030,167 EUA-eligible individuals, 2362 AZD7442-exposed individuals were matched 1:1 to eligible unexposed individuals (**Table 1**). PS matching resulted in overall balance (standardized mean difference ≤ 0.1) in baseline characteristics between AZD7442-exposed and unexposed individuals. AZD7442 exposure was not associated with any of the assessed cardiovascular outcomes (**Table 2**), and results were similar among individuals who did versus did not have a history of these events.

Conclusions

After controlling for baseline cardiovascular risk, no difference was found in the rates of heart failure, myocardial infarction, stroke, or deep vein thrombosis among individuals who did versus did not receive AZD7442 600 mg. Similar results were observed among individuals with or without a history of cardiovascular events. These results further support the safety of AZD7442 PrEP and potential future long-acting COVID-19 PrEP monoclonal antibodies.

Disclosures

T.R. has no conflicts to disclose.

A.R.S. and A.W.C.K. are contractor and member, respectively, of Ikaika Health, which was funded by AstraZeneca for this work.

C.T., S.V., C.F., L.G., and S.T. are employees of, and may hold stock and/or stock options in, AstraZeneca.

N.M.S. is an employee of Health ResearchTx LLC, which received funding from AstraZeneca to execute this work on behalf of AstraZeneca.

E.S. is a retired military service member and has received no funding.

J.E. is a military service member and has received no funding. This work was prepared as part of his official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member or employee of the US Government as part of their official duties. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, DoD, or any component agency. The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy of the Defense Health Agency, Department of Defense, or the US Government.

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Presentation preference: Oral

Keywords (1-3 from prespecified options; need to log in to see options):

COVID-19, monoclonal antibody, patient safety

Abstract subject category (choose up to 2: <https://idweek.zendesk.com/hc/en-us/articles/1500002253822-Session-and-Abstract-Subject-Categories>):

Z2. COVID: Infection prevention

Acknowledgements/Funding: This study was funded by AstraZeneca.

Table 1. Baseline characteristics for the PS-matched population

| | PS-matched study cohort | | |
|---|-------------------------|-------------|-------------|
| | Total | AZD7442 | Non-AZD7442 |
| | N=4724 | n=2362 | n=2362 |
| Baseline patient characteristics^a | | | |
| Age, mean, SD (years) | 63.8 (16.4) | 63.7 (14.4) | 64.0 (18.1) |
| Female, n (%) | 2402 (50.9) | 1203 (50.9) | 1199 (50.8) |
| VA Frailty Index, n (%) | | | |
| Non-frail | 1611 (34.1) | 752 (31.8) | 859 (36.4) |
| Pre-frail | 1647 (34.9) | 915 (38.7) | 732 (31.0) |
| Mildly frail | 954 (20.2) | 476 (20.2) | 478 (20.2) |
| Moderately frail | 395 (8.4) | 173 (7.3) | 222 (9.4) |
| Severely frail | 117 (2.5) | 46 (2.0) | 71 (3.0) |
| CCI score, mean (SD) | 6.3 (4.0) | 6.3 (3.7) | 6.3 (4.4) |
| Number of outpatient visits, mean (SD) | 46.6 (46.1) | 46.3 (38.5) | 46.9 (46.9) |
| Number of inpatient visits, mean (SD) | 0.5 (1.1) | 0.5 (1.1) | 0.5 (1.1) |
| Baseline CV conditions, n (%) | | | |
| Heart failure | 496 (10.5) | 257 (10.9) | 239 (10.1) |
| Deep vein thrombosis | 347 (7.4) | 174 (7.4) | 173 (7.3) |
| Myocardial infarction | 107 (2.3) | 56 (2.4) | 51 (2.2) |
| Stroke | 188 (4.0) | 95 (4.0) | 93 (3.9) |
| Immunocompromising conditions,^b n (%) | | | |
| Solid tumor malignancy | 597 (12.6) | 307 (13.0) | 290 (12.3) |
| Hematologic malignancy | 662 (14.0) | 331 (14.0) | 331 (14.0) |
| Organ transplant | 503 (10.7) | 269 (11.4) | 234 (9.9) |
| Stem cell transplant | 81 (1.7) | 55 (2.3) | 26 (1.1) |
| Primary immunodeficiency | 194 (4.1) | 104 (4.4) | 90 (3.8) |

| | | | |
|--|-------------|------------|------------|
| AIDS/HIV | 4 (0.1) | 2 (0.1) | 2 (0.1) |
| Therapeutically induced immunosuppression | 1319 (27.9) | 660 (27.9) | 659 (27.9) |
| <p>^aDemographics were assessed during the 1 year prior to the index date. Immunocompromising conditions were defined as at least one diagnosis code within the year prior to the index date. Medications were defined as at least one dispensing within 1 year prior to the index date.</p> <p>^bStudy eligibility required patients to have ≥ 1 baseline immunocompromising condition(s). AIDS, acquired immunodeficiency syndrome; CCI, Charlson Comorbidity Index; CV, cardiovascular; HIV, human immunodeficiency virus; PS, propensity score; SD, standard deviation; VA, Veterans Affairs.</p> | | | |

Table 2. AZD7442 exposure and CV outcomes

| CV Outcome | Number of patients | | Number of events | | HR | 95% CI |
|--|--------------------|-----------|------------------|-----------|------|--------------|
| | AZD7442 | Unexposed | AZD7442 | Unexposed | | |
| Heart failure | | | | | | |
| Overall | 2362 | 2362 | 223 | 215 | 1.04 | (0.87, 1.24) |
| Incident events | 2017 | 2049 | 61 | 58 | 1.07 | (0.75, 1.53) |
| Prevalent events | 345 | 313 | 162 | 157 | 0.88 | (0.71, 1.10) |
| Deep vein thrombosis | | | | | | |
| Overall | 2362 | 2362 | 113 | 96 | 1.18 | (0.91, 1.53) |
| Incident events | 2118 | 2152 | 40 | 26 | 1.57 | (0.96, 2.57) |
| Prevalent events | 244 | 210 | 73 | 70 | 0.86 | (0.62, 1.19) |
| Myocardial infarction | | | | | | |
| Overall | 2362 | 2362 | 36 | 45 | 0.79 | (0.52, 1.20) |
| Incident events | 2272 | 2270 | 21 | 34 | 0.61 | (0.35, 1.05) |
| Prevalent events | 90 | 92 | 15 | 11 | 1.39 | (0.64, 3.05) |
| Stroke | | | | | | |
| Overall | 2362 | 2362 | 73 | 95 | 0.76 | (0.56, 1.03) |
| Incident events | 2202 | 2195 | 42 | 54 | 0.77 | (0.52, 1.16) |
| Prevalent events | 160 | 167 | 31 | 41 | 0.74 | (0.46, 1.17) |
| CI, confidence interval; CV, cardiovascular; HR, hazard ratio. | | | | | | |