Poster 1160

Treatment-Emergent Viral Variants in the Phase 3 TACKLE Trial Investigating Efficacy and Safety of AZD7442 (Tixagevimab/Cilgavimab) for the Treatment of Mild-to-Moderate COVID-19 in Adults

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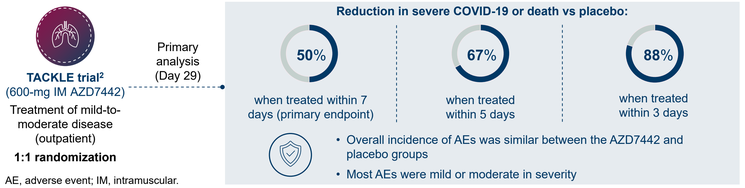
Introduction

- Due to ongoing SARS-CoV-2 intra-host evolution, viral variants carrying mutations may emerge during treatment with monoclonal antibodies (mAbs); some treatment-emergent variants may show decreased susceptibility to mAbs, and may be selected under treatment, especially in the setting of monotherapy.
- AZD7442 (tixagevimab/cilgavimab) is a combination of neutralizing mAbs that bind to distinct epitopes on the SARS-CoV-2 receptor-binding domain of the spike protein.[1]
- Tixagevimab and cilgavimab are individually capable of neutralizing SARS-CoV-2 and are used in combination to provide a higher threshold of protection against virus mutational escape from mAb neutralization. AZD7442 exerts neutralizing activity against the original SARS-CoV-2 strain and variants of concern, including Omicron.[2,3]
- In the Phase 3 TACKLE trial, AZD7442 significantly reduced severe disease or death in participants with mild-to-moderate COVID-19 and was well tolerated through Day 29 (**Figure 1**).[4]

Figure 1. Primary results from the TACKLE trial



AE, adverse event; IM, intramuscular.

Objective

- The objective of the current analysis was to assess emergence of SARS-CoV-2 variants in TACKLE study participants over 15 days after treatment with AZD7442 or placebo, and to determine in vitro susceptibility of identified variants to AZD7442 and individual mAb components.

Conclusions

- Following AZD7442 treatment, there was a low incidence of SARS-CoV-2 variants bearing mutations at tixagevimab/cilgavimab binding sites, with frequencies comparable to those seen in the placebo group.
- None of the tested treatment-emergent mutations with allele fraction (AF) ≥25% showed reduced susceptibility to AZD7442.
- These data indicate that a combination of two mAbs creates a high genetic barrier for resistance, supporting the use of mAb combinations that bind to distinct epitopes for the treatment of COVID-19.
- Monitoring to identify potential emerging resistance in ongoing AZD7442 clinical trials and use in clinical practice will continue.

Supplementary Content

Poster and video slides

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Presented at IDWeek, 19–23 October, 2022, Washington, DC, USA

Results and interpretation

Baseline prevalence of SARS-CoV-2 variants in TACKLE

- Baseline spike sequences were available for this analysis from 744 (82.4%) TACKLE participants (AZD7442, n=380; placebo, n=364).
- 87% of sequences corresponded to variants of concern/variants of interest (VOC/VOI).
- VOC/VOI diversity was in concordance with SARS-CoV-2 circulating at geographical locations of recruitment at that time.
- VOC/VOI were balanced between the AZD7442 and placebo groups (**Figure 2**).

Treatment-emergent SARS-CoV-2 mutations

- Baseline and follow-up sequences were available for 243 AZD7442 and 231 placebo participants.
- Treatment-emergent (post-dosing) viral variants were rare, with 11 (4.5%) AZD7442 and 3 (1.3%) placebo participants showing the emergence of ≥1 mutation at tixagevimab/cilgavimab binding sites, with an AF ≥25% (**Figure 3 and 4**).
- When tested in vitro, 13/13 treatment-emergent mutations showed susceptibility to AZD7442 (IC50 fold-change <5 compared to Wuhan-Hu-1+D614G) (**Table 1**).
- At AF ≥3%, 25 (10.3%) AZD7442 and 17 (7.4%) placebo participants carried at least one treatment-emergent mutation (**Figure 5**).

- **Overall, treatment-emergent mutations were rare, were observed in AZD7442 and placebo participants, tended to occur at day 6 post-dosing, and often involved the emergence of new variants which were not present at baseline.**

Figure 2. Incidence at baseline of SARS-CoV-2 variants of concern or interest, currently or formerly tracked by the World Health Organization

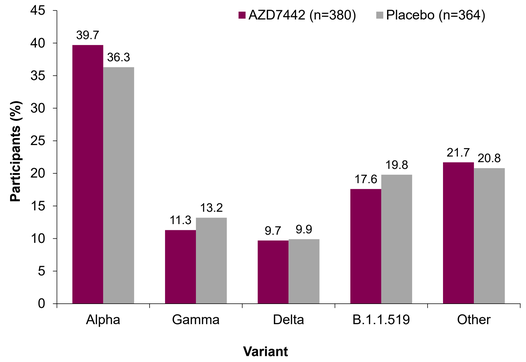


Figure 3. Treatment-emergent mutations in tixagevimab or cilgavimab by lineage at baseline detected at an allele fraction ≥25%

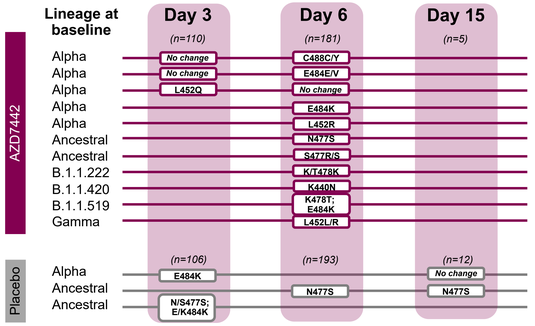


Figure 4. Location of treatment-emergent mutations in tixagevimab and/or cilgavimab binding sites (allele fraction ≥25%) in the SARS-CoV-2 spike protein

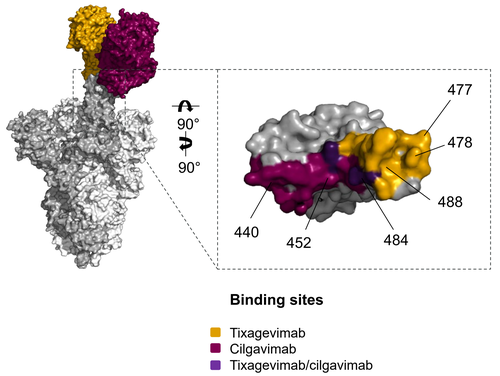


Table 1. In vitro susceptibility of individual SARS-CoV-2 spike substitutions identified in treatment-emergent mutation analysis (allele fraction ≥25%)

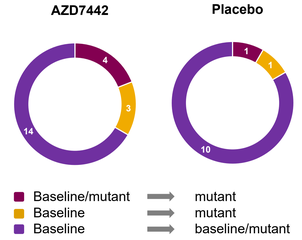
Mutation	mAb	Fold change in susceptibility, IC_{50}
K440N	Cilgavimab	1
L452L/R	Cilgavimab	1
L452Q	Cilgavimab	0.28
L452R	Cilgavimab	1
S477R/S	Tixagevimab	1.1
N477S	Tixagevimab	1
N/S477S	Tixagevimab	1
K478T	Tixagevimab	1
K/T478K	Tixagevimab	1.2
E484E/V	Tixagevimab/cilgavimab	2.6
E484K	Tixagevimab/cilgavimab	2.1
E/K484K	Tixagevimab/cilgavimab	2.1
C488C/Y	Tixagevimab	QNS*

*D, day; IC50, half maximal inhibitory concentration; mAb, monoclonal antibody; QNS, quantity not sufficient: produced lentiviral pseudoparticles did not achieve high enough titer for in vitro susceptibility testing

Figure 5. Incidence of treatment-emergent mutations in tixagevimab or cilgavimab detected at an allele fraction ≥3%

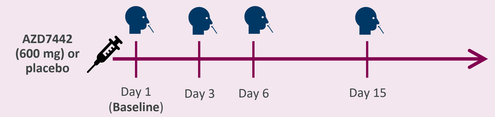
Participants, n (%)	AZD7442	Placebo
Day 3	4/110 (4)	6/106 (6)
Day 6	21/181 (12)	12/193 (6)
Day 15	0/5 (0)	2/12 (17)

Treatment-emergent mutational profiles at day 6



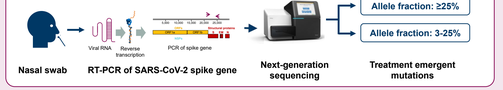
Methods

- In TACKLE (NCT04723394), non-hospitalized adults with mild-to-moderate COVID-19 were randomized and dosed ≤7 days from symptom onset with a single 600-mg dose of AZD7442 (2 consecutive intramuscular injections, 300 mg of each antibody; n=452) or placebo (n=451).
- Samples (nasal swabs taken at baseline and Days 3, 6, and 15) were available from the TACKLE primary analysis (data cutoff, August 2021).



- Next-generation sequencing of the spike gene was performed on SARS-CoV-2 reverse-transcription polymerase chain reaction–positive nasal swabs.
- SARS-CoV-2 lineages were assigned using spike nucleotide sequences. Amino acid substitutions, insertions, and deletions were analyzed at AF (% of sequence reads represented by mutation) ≥25%, and 3–25%.

Genotypic analysis



- Fold-changes in susceptibility were assessed by pseudotyped lentivirus microneutralization assays.

Phenotypic analysis

Funding and Acknowledgments

The TACKLE study and this analysis were funded by AstraZeneca. We thank Kevin Tuffy, MSc, for generating structural models of the SARS-CoV-2 spike protein. Medical writing was provided by Rob Campbell, PhD and India Wright, MSc, and editorial support was provided by Jess Galbraith, BSc, and Sharmin Saleque, MSc, all of Core, London, UK, supported by AstraZeneca according to Good Publication Practice guidelines.

Disclosures

Gustavo H. Kijak, Bahar Ahani, Douglas Arbetter, Tyler Brady, Fernando Chuecos, Vancheswaran Gopalakrishnan, Tiffany Roe, Nicolette Schuko, Elizabeth J. Kelly, and Katie Streicher are employees of, and hold or may hold stock in, AstraZeneca. F.D. Richard Hobbs reports funding from AstraZeneca to cover meeting attendances and operationalization of TACKLE in the UK. He has received funding from United Kingdom Research and Innovation/National Institute for Health Research (NIHR) for national urgent public health coronavirus disease 2019 trials, and as director of the NIHR Applied Research Collaboration, Oxford Thames Valley, and investigator of the Oxford Biomedical Research Centre and NIHR MedTech. Francisco Padilla has received personal fees and grants from Amgen, AstraZeneca, Boehringer Ingelheim, Ferrer, Kowa, Medix, Merck, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Servier, and Silanes. Hugh Montgomery has received consultation fees from AstraZeneca and is supported by the UK NIHR Comprehensive Biomedical Research Centre at University College London Hospitals. He has consulted for Millfield Medical Ltd. on the development of a new continuous positive airway pressure machine.

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