Poster 1110

AZD7442 (Tixagevimab/Cilgavimab) Demonstrates Potent In Vitro Activity Against SARS-CoV-2 Spike Variants Identified in Circulation and in Prophylaxis Clinical Studies

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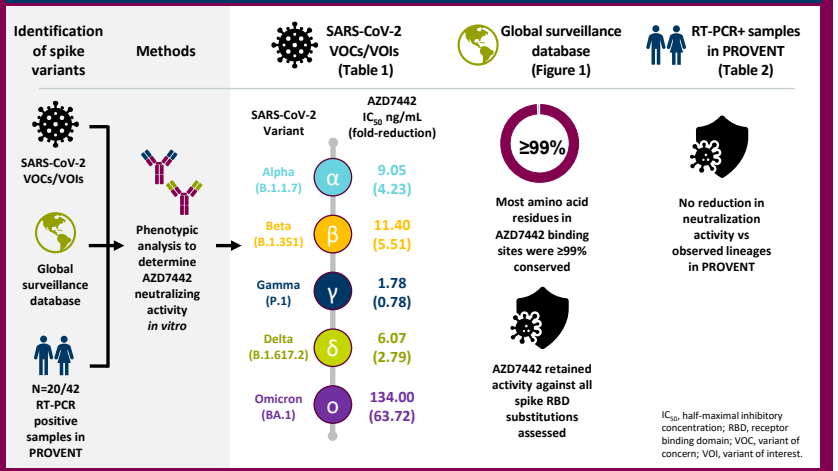
Graphical summary



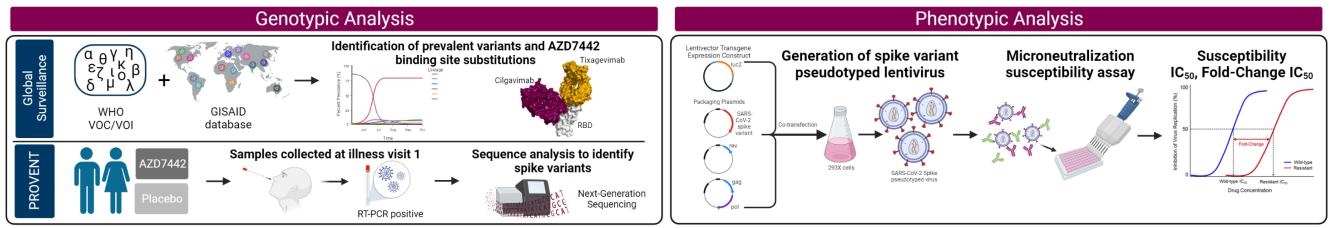
Introduction

- Although COVID-19 vaccines have been widely effective in combatting the pandemic, there remains a substantial population of immunocompromised individuals who do not elicit an adequate immune response to activate immunization via vaccination.[1]
- AZD7442 is a combination of extended half-life SARS-CoV-2–neutralizing monoclonal antibodies (mAbs) (tixagevimab/cilgavimab) that bind to distinct epitopes on the SARS-CoV-2 spike protein.[2]
- In the Phase 3 PROVENT prevention study, AZD7442 significantly reduced symptomatic COVID-19 versus placebo by 76.7% at primary analysis and was well-tolerated.[3]
- Despite the combination mAb approach of AZD7442 reducing the risk of viral escape, it is important to monitor for potential resistance-associated mutations.

Objective

- Evaluate the *in vitro* potency of AZD7442 and its components against SARS-CoV-2 VOCs/VOIs and assess the prevalence and impact that AZD7442 binding site substitutions had on variant susceptibility to neutralization.
- Determine whether variants identified from participants in the PROVENT trial (NCT04625725) exhibited a reduction in susceptibility.

Methods



- N=8,679,290 sequences from COVIDCG[4] (GISAID: December 1, 2019 through May 12, 2022) were evaluated to identify prevalently circulating spike variants and substitutions within the tixagevimab and cilgavimab binding sites.
- Globally prevalent circulating variants (WHO classification as of May 3, 2022) along with their characteristic RBD substitutions and the 7 SARS-CoV-2 spike-based lineages identified in 20/42 participants from PROVENT at illness visit Day 1 through the 6-month data cutoff were evaluated phenotypically for AZD7442 neutralization.[5]
- Spike substitutions were incorporated into SARS-CoV-2 Wuhan-Hu-1/2019 +D614G spike pseudotyped lentiviruses and assessed for susceptibility to AZD7442 and its component mAbs via microneutralization assay.

Results

Table 1. AZD7442 *in vitro* potency against globally prevalent SARS-CoV-2 spike variants

SARS-CoV-2 variants	Prevalence, %[a]	IC50, ng/mL (fold-reduction in susceptibility)[b]		
		Tixagevimab	Cilgavimab	AZD7442
Variants of concern				
Delta (B.1.617.2)	0.05	3.37 (2.99)	140.26 (47.07)	6.07 (2.79)
Omicron (BA.1)	2.46	1639.00 (1708.43)	2746.00 (919.39)	134.00 (63.72)
Previously circulating VOCs				
Alpha (B.1.1.7)	<0.01	3.87 (5.64)	11.89 (3.40)	9.05 (4.23)
Beta (B.1.351)	<0.01	9.96 (15.41)	7.28 (2.03)	11.40 (5.51)
Gamma (P.1)	0.00	1.09 (0.87)	1.67 (0.43	1.78 (0.78)
Previously circulating VOIs				
Epsilon (B.1.427/B.1.429)	0.00	0.83 (1.23)	8.05 (2.22)	2.05 (0.95)
Zeta (P.2)	0.00	11.80 (7.30)	6.38 (1.08)	10.38 (2.89)
Eta (B.1.525)	0.00	4.61 (4.19)	5.22 (0.94)	5.09 (1.85)
Iota (B.1.526)	0.00	9.41 (8.61)	3.26 (0.58)	5.24 (1.87)
Kappa (B.1.617.1)	<0.01	0.97 (0.89)	10.74 (1.93)	2.54 (0.92)
Lambda (C.37)	<0.01	0.10 (0.10)	11.70 (3.80)	0.30 (0.20)
Mu (B.1.621)	0.00	1.50 (1.50)	140.90 (45.50)	7.20 (4.50)

SARS-CoV-2 VOCs and VOIs per WHO classifications, May 3, 2022.
[a]Percent prevalence based on the ratio of whole genome sequences containing the set of corresponding SARS-CoV-2 spike substitutions from the designated lineage to all sequences collected to date (N=1,100,681 sequences; February 17, 2022, to May 5, 2022; source: https://covidcg.org).
[b]Versus the wild type reference strain (Wuhan-Hu-1/2019+D614G mutation);
Color coding (fold-changes in susceptibility): <10 (green), ≥10 to <100 (yellow), and ≥100 (orange).

Evaluation of AZD7442 *in vitro* potency against characteristic spike RBD substitutions within globally prevalent SARS-CoV-2 spike variants

- 23 characteristic individual RBD substitutions from the previously and currently circulating VOCs and VOIs (at time of this analysis) were phenotypically evaluated.
- Tixagevimab showed minor loss of neutralization activity against E484K and Q493R spike substitutions (6.16- and 7.86-fold, respectively).
- Cilgavimab showed reduced neutralization activity against L452R, G446S, and R346K substitutions (5.57-, 11.54-, and 25.90-fold, respectively).
- However, the tixagevimab and cilgavimab combination retained activity against all substitutions assessed.

Limitations

- Pseudovirus rather than a live virus assay was used, therefore results do not reflect live SARS-CoV-2 replication.
- Since the current study was conducted, new viral variants, such as Omicron BA.2.12.1 and BA.4/5, have emerged.

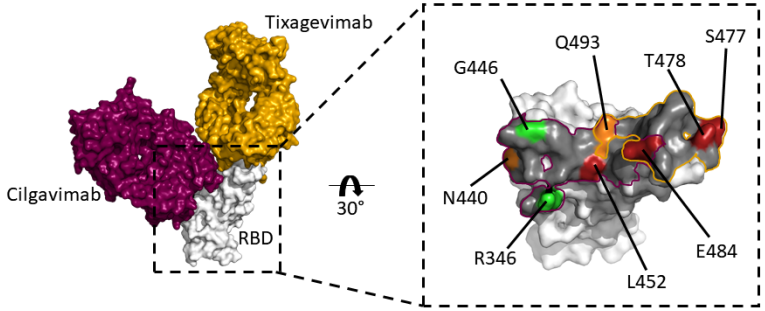


Figure 1. Conservation of AZD7442 binding site residues in the SARS-CoV-2 spike protein from 01 Dec 2019 through 12 May 2022. Conservation frequency based on ratio of whole genome sequences with observed SARS-CoV-2 spike binding site substitutions to all sequences collected from global surveillance to date

Table 2. Summary of AZD7442 *in vitro* neutralization against SARS-CoV-2 spike-based lineages detected at illness visit(s) through 6-month data cut, PROVENT

SARS-CoV-2 spike-based lineages	PROVENT participants with data, n (%)		IC50, ng/mL (fold-reduction in susceptibility)		
Set description	Placebo group (n=13)	AZD7442 group (n=7)	Tixagevimab	Cilgavimab	AZD7442
A_22	2 (15.4)	2 (28.6)	1.40 (1.00)	4.46 (1.00)	2.26 (1.00)
A_1	0 (0.0)	1 (14.3)	0.94 (0.54)	4.67 (0.81)	1.23 (0.35)
B.1.1.7_1 (Alpha)	5 (38.5)	0 (0.0)	3.78 (5.64)	11.89 (3.40)	9.05 (4.23)
B.1.351 (Beta)	0 (0.0)	1 (14.3)	13.58 (6.95)	5.32 (0.46)	11.73 (2.24)
B.1.617.2 (Delta)	5 (38.5)	1 (14.3)	3.37 (2.99)	140.26 (47.07)	6.07 (2.79)
B.1.429 (Epsilon)	0 (0.0)	2 (28.6)	0.83 (1.23)	8.05 (2.22)	2.05 (0.95)
B.1.526 (Iota)	1 (7.7)	0 (0)	9.41 (8.61)	3.26 (0.58)	5.24 (1.87)

Summary of AZD7442 in vitro neutralization against SARS-CoV-2 spike-based lineages detected at illness visit(s) through 6 months, from PROVENT.
Data cutoff: August 29, 2021.
Color coding (fold-changes in susceptibility): no reduction <5 or minimal reduction ≥5 to <10 (green), moderate reduction ≥10 to <100 (yellow).

Conclusions

- **AZD7442 retained in vitro neutralization activity against SARS-CoV-2 VOCs and VOIs with a moderate reduction against Omicron (BA.1) (Table 1)**
- **The majority of the amino acid residues in the tixagevimab and cilgavimab binding sites in the SARS-CoV-2 spike protein were ≥99% conserved (Figure 1)**
- **SARS-CoV-2 breakthrough infections in PROVENT were not due to AZD7442 resistance (Table 2)**

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Disclosures

All authors are employees of, and hold or may hold stock in, AstraZeneca.

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Supplementary Content

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