Comparative Pharmacokinetics of Tixagevimab/Cilgavimab (AZD7442) Administered Intravenously Versus Intramuscularly in Symptomatic SARS-CoV-2 Infection

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AZD7442 (Evusheld) is a combination of two human anti-severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) monoclonal antibodies (mAbs), tixagevimab (AZD8895) and cilgavimab (AZD1061). Route of administration is an important consideration to improve treatment access. We assessed pharmacokinetics (PKs) of AZD7442 absorption following 600 mg administered intramuscularly (i.m.) in the thigh compared with 300 mg intravenously (i.v.) in ambulatory adults with symptomatic COVID-19. PK analysis included 84 of 110 participants randomized to receive i.m. AZD7442 and 16 of 61 randomized to receive i.v. AZD7442. Serum was collected prior to AZD7442 administration and at 24 hours and 3, 7, and 14 days later. PK parameters were calculated using noncompartmental methods. Following 600 mg i.m., the geometric mean maximum concentration (C_{max}) was 38.19 μg/mL (range: 17.30–60.80) and 37.33 μg/mL (range: 14.90–58.90) for tixagevimab and cilgavimab, respectively. Median observed time to maximum concentration (T_{max}) was 7.1 and 7.0 days for tixagevimab and cilgavimab, respectively. Serum concentrations after i.m. dosing were similar to the i.v. dose (27–29 μg/mL each component) at 3 days. The area under the concentration-time curve $(AUC)_{0-7d}$ geometric mean ratio was 0.9 for i.m. vs. i.v. Participants with higher weight or body mass index were more likely to have lower concentrations with either route. Women appeared to have higher interparticipant variability in concentrations compared with men. The concentrations of tixagevimab and cilgavimab after administration i.m. to the thigh were similar to those achieved with i.v. after 3 days from dosing. Exposure in the i.m. group was 90% of i.v. over 7 days. Administration to the thigh can be considered to provide consistent mAb exposure and improve access.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ AZD7442 (tixagevimab/cilgavimab; Evusheld) is a combination monoclonal antibody authorized by the US Food and Drug Administration (FDA) for the prevention of coronavirus disease 2019 (COVID-19), initially as 300 mg and updated to 600 mg in February 2022 (300 mg of each component) to the gluteal muscle (i.m.). Based on modeling, 600 mg combined dose was selected for phases II and III COVID-19 treatment trials without assessment of pharmacokinetics (PKs) in a phase I study.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study evaluated the PKs of 600 mg administered i.m. in the thigh and 300 mg i.v. in persons with mild to moderate COVID-19.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We demonstrated that 600 mg i.m. administered in the thigh achieves high levels within 24 hours and equivalent levels to 300 mg i.v. by 3 days with less variability and more rapid attainment of maximum concentration (C_{max}) with thigh injection than is expected when administered to the gluteal muscle.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Intramuscular administration of AZD7442 in the thigh may improve exposure in patients with mild to moderate COVID-19.

Received April 26, 2022; accepted June 28, 2022. doi:10.1002/cpt.2706

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Trial Registration: ClinicalTrials.gov Identifier: NCT04518410.

There is urgent need for therapeutics that can readily be administered early in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection to prevent severe coronavirus disease 2019 (COVID-19) outcomes. The first therapies authorized by the US Food and Drug Administration (FDA) for treatment of outpatients with COVID-19 were single-dose intravenous (i.v.) infusion monoclonal antibodies (mAbs), which are resource intensive to administer. Only two oral antiviral therapies have Emergency Use Authorization (EUA), and both have limitations, including drug–drug interactions (for nirmatrelvir/ritonavir), or relatively low efficacy (for molnupiravir).[1,2]

AZD7442 (Evusheld; AstraZeneca, Cambridge, UK), a combination of two human mAbs, tixagevimab (AZD8895) and cilgavimab (AZD1061), both cloned from B-cells isolated from the peripheral blood of COVID-19 convalescent patients, received FDA EUA for pre-exposure prophylaxis to be administered by intramuscular (i.m.) injection in the gluteal muscles.[3,4] These mAbs bind to unique, nonoverlapping epitopes at the human angiotensin-converting enzyme 2 (hACE2) interface of the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2, preventing viral entry into human cells. Both antibodies contain modifications in their Fc regions that extend their anticipated half-life to 70–130 days and reduce risk of antibody dependent enhancement (ADE) by limiting binding to Fc gamma receptors.[5–9] AZD7442 has been demonstrated *in vitro* to neutralize SARS-CoV-2 variants, including Omicron, with retained activity against the BA.1 and BA.2 subvariants.[10–12]

Injectable therapies via i.m. or subcutaneous routes, can improve equitable access to early treatment of COVID-19, as they allow for administration in a broad range of settings, including congregate living settings and clinics. However, injection of mAbs can potentially result in slower and more variable absorption. For SARS-CoV-2 infection, time to treatment from symptom onset may be important for mAbs and antivirals, with diminished efficacy observed in those treated after 5 or 7 days in some studies, and when provided to hospitalized patients compared with those with mild to moderate illness.[13–17] Therefore, evaluating whether route of administration impacts time to presumed minimum effective concentration is important for early treatment studies using mAb therapy. Of i.m. injection sites, gluteus medius absorption of small molecules is slowest and most variable, with variability related to body mass index (BMI), sex, and age, and reduced absorption in those with higher gluteal fat, especially if administered into adipose tissue rather than muscle.[18,19] Compared with gluteal sites, administration of small molecules in the thigh or deltoid has increased rate and decreased variability of absorption.[18] To our knowledge, no studies of anti-SARS-CoV-2 mAbs have compared pharmacokinetics (PKs) of i.m. administration in the thigh with other routes.

We assessed the PKs of these mAbs co-administered as 600 mg (300 mg of each component) i.m. in the thigh (vastus lateralis) once, compared with 300 mg i.v. (150 mg of each component) among adults with mild to moderate COVID-19 participating in a phase II study within the National Institutes of Health (NIH)-sponsored ACTIV-2 platform.

METHODS

ACTIV-2/A5401 (NCT04518410) is a randomized, placebo-controlled platform trial designed to evaluate the safety and efficacy of multiple investigational agents for treatment of non-hospitalized adults with COVID-19. Between February 17, 2021, and May 20, 2021, ACTIV-2 participants in the United States were randomized to tixagevimab/cilgavimab 600 mg or placebo (normal saline) administered i.m. in the thigh, or 300 mg or placebo i.v. once. Of 110 participants who received active drug in the i.m. arm, samples were available from 84 participants. For comparison, we included 16 with available samples of 61 participants who received active drug i.v.

The protocol was approved by a central institutional review board (IRB; Advarra (Pro00045266), US), with additional local IRB review and approval as required by participating sites. All participants provided written informed consent.

PK sampling

Serum samples for PK analysis were collected prior to study drug administration, 1-hour postdose, and at 3, 7, and 14 days postdose. An additional sample was taken from 15 participants at 24 hours after i.m. administration of the study drug.

Laboratory methods

Serum PK samples were analyzed (PPD Laboratories, Richmond, VA) using a validated hybrid LBA-liquid chromatography tandem mass spectrometry (LC-MS/MS) assay capable of distinguishing tixagevimab and cilgavimab in human serum, based on distinct complementarity-determining region (CDR) peptide sequences. Because tixagevimab and cilgavimab are too large for practical direct quantitative analysis using LC-MS/MS technology, the captured proteins were subjected to "on-bead" proteolysis with trypsin, following standard protein denaturation, reduction, and alkylation. After trypsin digestion, characteristic peptide fragments originating from tixagevimab and cilgavimab were produced and quantified as surrogates for tixagevimab and cilgavimab serum concentrations.

Statistical analysis

PK parameters of interest were observed maximum concentration (C_{max}) over 14 days, time of C_{max} (T_{max}), measured concentrations at 1, 3, 7, and 14 days postdose, and area under the concentration-time curve for 7 and 14 days post infusion (AUC_{0-7d}, AUC_{0-14d}). AUC calculations used actual sampling times and were based on the statistical moment theory using the trapezoidal rule (Phoenix WinNonlin, version 8.3; Certara,

Table 1 Pharmacokinetic characteristics of tixagevimab (AZD8895) and cilgavimab (AZD1061) after i.m. and i.v. administration

Metric	T_{max}[a] (days)	C_{max} (μg/mL)	C_{max}/D (μg/mL)	C_{24h} (μg/mL)	C_{72h} (μg/mL)	C_{7d} (μg/mL)	C_{14d} (μg/mL)	AUC_{0-7d} (d*μg/mL)	AUC_{0-14d} (d*μg/mL)	AUC_{0-14d}/D (d*μg/mL/mg)
Intramuscular administration										
Tixagevimab										
Count	84	84	84	15	76	73	75	80	78	78
Geomean	7.1[a]	38.19	0.13	12.43	27.77	35.42	32.56	164.14	405.08	1.35
Geomean CV (%)		27.88	27.88	69.77	58.39	32.75	49.91	38.28	31.98	31.98
Min	1.8	17.30	0.06	5.15	1.17	14.10	1.28	51.89	168.17	0.56
Max	28.7	60.80	0.20	49.60	60.80	58.50	58.50	375.50	782.49	2.61
Cilgavimab										
Count	84	84	84	15	75	73	74	80	77	77
Geomean	7.0[a]	37.33	0.12	14.00	28.88	35.52	34.49	167.02	409.74	1.37
Geomean CV (%)		31.07	31.07	55.75	47.20	34.01	28.41	39.02	32.75	32.75
Min	1.8	14.90	0.05	5.87	3.35	11.10	14.90	44.50	135.69	0.45
Max	31.9	58.40	0.19	38.70	58.30	57.60	58.40	324.39	697.40	2.32
Intravenous administration										
Tixagevimab										
Count	16	16	16		16	16	16	16	16	16
Geomean	0.7 hours[a]	40.97	0.27		27.39	21.76	18.38	191.69	333.14	2.22
Geomean CV (%)		24.43	24.43		23.07	22.95	24.16	26.54	23.36	23.36
Min	0.3 hours	25.90	0.17		19.70	14.00	10.90	118.97	219.40	1.46
Max	6.9	61.90	0.41		39.50	28.30	26.20	279.64	459.41	3.06
Cilgavimab										
Count	16	16	16		16	16	16	16	15	15
Geomean	0.7 hours[a]	41.01	0.27		28.44	22.15	19.32	197.00	346.96	2.31
Geomean CV (%)		27.33	27.33		23.62	22.58	23.08	27.28	24.04	24.04
Min	0.3 hours	24.90	0.17		20.70	14.70	12.40	124.61	230.89	1.54
Max	6.9	64.70	0.43		42.70	32.60	28.00	310.82	533.85	3.56

AUC_{0-7d}, area under the concentration-time curve for 7 days after dose administration; AUC_{0-14d}, area under the concentration-time curve for 14 days after dose administration; AUC_{0-14d}/D, dose-adjusted area under the concentration-time curve for 14 days after dose administration; C_{24h}, C_{72h}, C_{7d}, and C_{14d}, measured concentrations at 24 hours (not obtained in those receiving i.v. administration), 72 hours, 7 days and 14 days after dose administration; C_{max}, maximum observed concentration; C_{max}/D, dose-adjusted maximum concentration; T_{max}, time postdose of maximum observed concentration.
[a]Median.

Princeton, NJ). Relationships among AUC_{0-14d} and participant demographics were explored.

RESULTS

In the 600 mg i.m. dose arm ($n = 84$), the median age was 39 years (range: 18–84) with a median BMI of 28.5 kg/m^2 (range: 17.8–48.1). The 300 mg i.v. dose arm ($n = 16$) was older (median age: 46 years, range: 21–65 years) and had a higher median BMI of 36.7 kg/m^2 (range: 20.3–57.9). Across the 2 dose groups, 52% of participants were women; 87% identified as White, 8% as Black, 5% as multi-racial/other, and 49% as Hispanic/Latino.

Following 600 mg i.m. administration, the geometric mean C_{max} was 38.19 µg/mL (range: 17.30–60.80) and 37.33 µg/mL (range: 14.90–58.40) for tixagevimab and cilgavimab, respectively. The T_{max} occurred at a median of 7.1 and 7.0 days, respectively (**Table 1**, **Figure 1**).

Following 300 mg i.v. administration, the geometric mean C_{max} of both tixagevimab and cilgavimab was 40.97 µg/mL (range: 25.90–61.90) and 41.01 µg/mL (range: 24.90–64.70), respectively. Concentrations of the 600 mg i.m. and the 300 mg i.v. dose were similar at 3 days (62.6 vs. 57.2 µg/mL combined AZD7442 concentrations, respectively); after day 3, concentrations after i.m. administration exceeded those after i.v. throughout the first 2 weeks.

The geometric mean ratio of AUC_{0-7d} was 0.9 and ratio of AUC_{0-14d} was 1.2 for 600 mg i.m. compared with 300 mg i.v. for both components.

Participants with higher weight or BMI showed a trend of lower concentrations for both i.m. and i.v. administration; participants weighing < 75 kg or with a BMI of < 30 kg/m^2 tended to have higher exposure. There was no clear trend in PKs based on age or sex, but interparticipant PK variability was higher in women compared with men: the percent coefficient of variation (CV) in tixagevimab AUC_{0-14d} with i.m. administration was 33% and 24%, respectively, for women and men, and was 32% and 24%, respectively, for women and men for cilgavimab (**Figure S1**).

DISCUSSION

In adults with early COVID-19, levels of AZD7442 rose quickly over 24 hours after administration of 600 mg i.m. to the thigh and were similar at 3 days to those achieved with 300 mg i.v. Following i.m. administration, concentrations of both mAb components continued to increase, achieving observed C_{max} around 7 days, and were sustained at > 85% of the C_{max} through 14 days postdose, as expected based on reported half-lives of ~ 90 days.[9]

The i.v. administration is typically performed at infusion centers or major medical centers; however, many patients eligible for treatment do not live in close proximity to such centers; space and staffing capacity are finite, especially during surges in cases. These hurdles act to delay or preclude treatment. Oral therapeutic options for outpatients with COVID-19 avoid administration issues but have their own challenges that limit their use. The i.m. administration can expand the availability of mAb treatment to beyond infusion centers, including outpatient or nonclinical settings.

As expected, there is a lag in achievement of peak concentrations of tixagevimab and cilgavimab following i.m. administration compared with i.v. infusion. Whereas providing therapeutic intervention as early as possible in COVID-19 has been suggested to maximize efficacy,[20,21] there are limited data available that define the optimal window for initiation of treatment for early COVID-19. Clinical trials demonstrating the efficacy of i.v. mAbs administered these agents within 3–5 days after symptom onset, limiting the opportunity to assess time-dependent effects.[17,22] Interim results from our ACTIV-2 phase III trial of the mAb

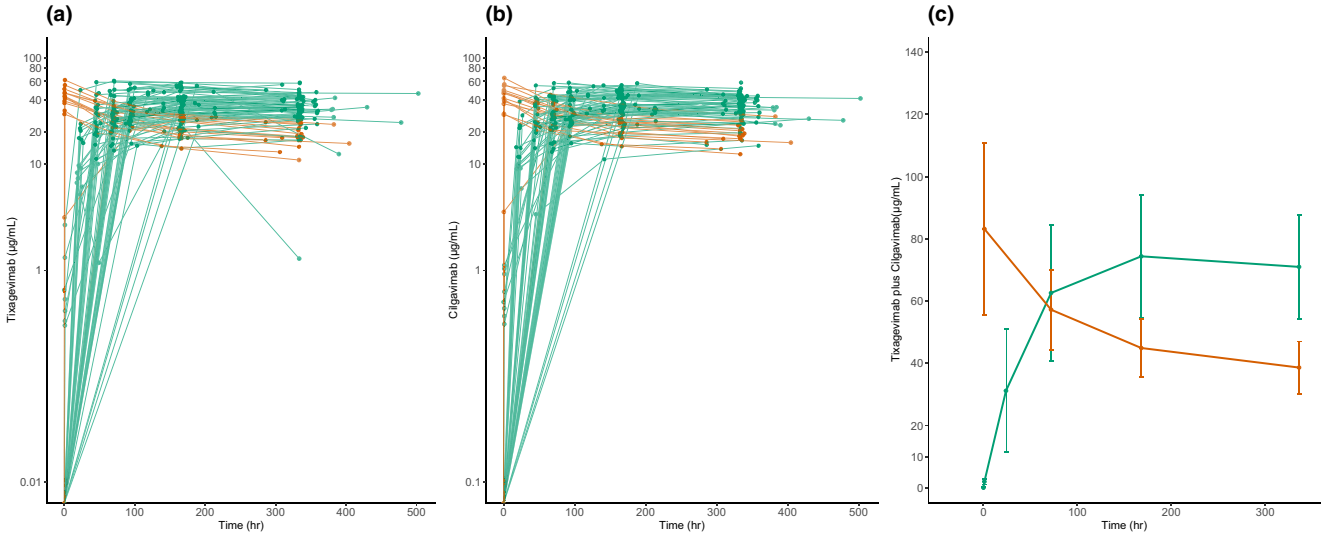

Figure 1 Concentration-time profiles of tixagevimab (**a**), cilgavimab (**b**) with concentration in log scale, and the sum of tixagevimab and cilgavimab concentrations as mean and SD (**c**). Serum concentrations following i.v. administration (150 mg of each component) are shown in orange and after i.m. administration (300 mg of each component) are shown in turquoise. For **c**, the mean values for the sum of tixagevimab and cilgavimab concentrations after i.m. administration were: 1 hour, 1.97 µg/mL; 24 hours, 31.17 µg/mL; 72 hours, 62.62 µg/mL; 7 days, 74.4 µg/mL, and 14 days, 71.0 µg/mL. After i.v. administration, the mean sums were: 1 hour, 83.2 µg/mL, 3 days, 72 hours, 57.23 µg/mL; 7 days, 44.93 µg/mL; and 14 days, 38.64 µg/mL.

combination of amubarvimab/romlusevimab (BRII-196/BRII-198) in outpatients with COVID-19 found that the efficacy in reducing hospitalizations and death was similar in those treated both within and beyond 5 days of symptom onset.[23] Additionally, the convenience of i.m. administration may shorten time to treatment initiation compared to i.v.

Our AZD7442 PK results after i.m. and i.v. administration are consistent with the those observed in a phase I study of this mAb, in which only the 300 mg i.m. dose (150 mg of each component in gluteal muscles) was tested (NCT04507256).[9] We found a more than doubling of the C_{max} when using 600 mg i.m. in the thigh compared with 300 mg i.m. in the gluteus, which may provide earlier achievement of effective concentration in those with acute SARS-CoV-2 infection. Similarly, a monoclonal antibody against *Bacillus anthracis* given i.m. in the gluteus and vastus lateralis also had higher dose-normalized C_{max} and AUC, and higher relative bioavailability (71–85%) with thigh administration.[24] It is notable that gluteal i.m. injection of 300 mg in SARS-CoV-2 uninfected participants resulted in a T_{max} of 14 to 28 days,[4] which is likely past the window of clinical benefit for treatment. The concentrations achieved with the 600 mg i.m. dose of tixagevimab and cilgavimab also exceeded the concentration associated with 300 mg i.v. after 3 days.

Our data also show that i.m. administration in the thigh produced more consistent absorption compared with gluteal injection based on data from the phase I study and PROVENT trials (28–31% vs. 36–39% CV).[4,9] Lower variability in concentrations and faster absorption compared with gluteal muscle administration may also lead to more rapid achievement of target concentrations in a wider range of people with thigh administration. Administration into the thigh, where there is higher probability of direct i.m., rather than adipose tissue administration, and which provides less intra-person variability, could further benefit patients with more adipose tissue at sites of administration, including those with higher body weight or BMI, and women.[18,19] Therefore, administration to the thigh may be a preferred route over the more commonly used gluteal site to achieve maximal clinical benefit for more patients.

Limitations of these data include that we did not determine the elimination half-life due to limited postdose data that were immediately available; the goal of this evaluation was to investigate early PKs of i.m. absorption. The limited postdose concentration-time data also preclude, at present, a determination of relative bioavailability of i.m. compared with i.v. administration. When such data are available, the robustness of the relative bioavailability estimate will be limited by the sampling strategy and uncertainty about whether true C_{max} and T_{max} have been captured, and that a cross-over design was not used. Doses selected for these trials were informed by a viral dynamic model to simulate expected viral load clearance in the presence of AZD7442 with a measured potency of 10 ng/mL (half-maximal inhibitory concentration (IC_{50})) against the original SARS-CoV-2 strain, which was expected to have been achieved within respiratory epithelium by all participants in both cohorts within 24 hours. With the circulation of variants of concern, the required effective concentration is likely higher than previously determined.[10–12,25] The primary efficacy and safety outcomes of this mAb combination will be reported subsequently, together with investigations of relationships between concentration and outcomes. Last, whereas the study assessed PK parameters of tixagevimab and cilgavimab in participants with early COVID-19, this mAb is authorized by the FDA only for the prevention of SARS-CoV-2 infection and illness. Our findings, however, can guide the use of this mAb as pre-exposure prophylaxis and may apply to infused and injectable mAbs indicated for acute COVID-19.

CONCLUSIONS

The administration of tixagevimab and cilgavimab at a dose of 600 mg injected i.m. into the thigh is supported by rapid absorption and exposure comparable with i.v., in patients with early COVID-19. The i.m. administration of mAbs can facilitate access to treatment for those with symptomatic COVID-19 at risk for disease progression and is an alternative to i.v. administration that warrants further study.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank the study participants, site staff, site investigators, and the entire ACTIV-2/A5401 study team; the ACTIV-2 Community Advisory Board; the AIDS Clinical Trials Group, including Lara Hosey, Jhoanna Roa, and Nilam Patel; the Harvard Center for Biostatistics in AIDS Research (CBAR) and ACTG Statistical and Data Analysis Center (SDAC), the National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS (DAIDS), including Peter Kim; Bill Erhardt; the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, including Stacey Adam; and PPD. We especially thank the participants, site staff, and investigators from the following sites:

Absolute Clinical Research, LLC, Phoenix, AZ: Beach, Jason.
AIDS Research and Treatment Center of the Treasure Coast – (CRS), Vero Beach, FL: Pierone, Gerald.
Allegiance Research Specialists, Wauwatosa, WI: Samuel Idarraga.
Allied Biomedical Research Institute, Miami, FL: Michael Pfeffer.
Amber Clinical Research, LLC, Miami Shores, FL: Francisco Padron.
Ascension St. John Clinical Research Institute, Tulsa, OK: Anuj Malik.
Atella Clinical Research, La Palma, CA: Rafaelito Victoria.
Bozeman Health Deaconess Hospital, Bozeman, MT: David Taylor.
Bradenton Research Center Inc, Bradenton, FL: Eric Folkens.
Carolina Clinical Research, Charlotte, NC: Emeka Eziri.
Clinical Research Partners LLC, Richmond, VA: Robert Call.
Clinical Trials Center of Middle Tennessee, Franklin, TN: Aaron Milstone.
Clinical Trials of America, LLC, Monroe, LA: Clinton Guillory.
Clintheory, Orlando, FL: Moussly, Souheil.
Community Research of South Florida, Hialeah, FL: Carpio, Jose.
Cornell Clinical Trials Unit, New York Presbyterian Hospital-Weill Cornell Uptown, New York, NY: Teresa Evering.
Cullman Clinical Trials, Cullman, AL: Randall Quinn.
D&H National Research Centers, Miami, FL: Jorge Amaya.
Duke University Medical Center, Durham, NC: Nwora Okeke.
Fadi A. Haddad, MD, Inc, La Mesa, CA: Fadi Haddad.
Fairway Medical Clinic, Houston, TX: Mussaji, Murtaza.
Family Clinical Trials, Pembroke Pines, FL: Jeanne-Elyse Cedeno.
FOMAT Medical Research, Oxnard, CA: Augusto Focil.
Gonzalez MD & Aswad MD Health Services, Miami, FL: Yaneicy Gonzalez-Rojas.
IACT Health, Columbus, GA: Joseph Surber.
Infectious Disease Consultants of the Treasure Coast, Vero Beach, FL: Laurie Welton.
Innovative Health Medical Center, Hollywood, FL: Fernando Gonzalez Vergara.

James J. Peters VA Medical Center Clinical Research Site, Bronx, NY: Michael Gelman.
Johns Hopkins University, Baltimore, MD: Kelly Dooley.
Lakes Research, Miami Lakes, FL: Jose Perez.
Las Vegas Medical Research, Las Vegas, NV: Bharat Mocherla.
Loma Linda University Health, Loma Linda, CA: Jennifer Veltman.
Massachusetts General Hospital, Boston, MA: Rajesh Gandhi.
Miami Clinical Research, Miami, FL: Keila Hoover.
Moore Clinical Research, Inc., Brandon, FL: George Monlux.
Northwestern University, Chicago, IL: Babafemi O Taiwo.
Ohio State University Medical Center, Columbus, OH: Carlos Malvestutto.
Orlando Immunology Center Clinical Research Site, Orlando, FL: Edwin DeJesus.
Pro Live Medical Research Corp, Miami, FL: Rosa Suarez.
Puerto Rico AIDS Clinical Trials Unit, San Juan, PR: Santana-Bagur, Jorge.
QC Trials, Miami Beach, FL: Gene Neytman.
Rush University Medical Center, Chicago, IL: Mariam Aziz.
Sanford USD Medical Center, Sioux Falls, SD: Susan Hoover.
Savin Medical Group LLC, Miami Lakes, FL: Manuel Hernandez.
Snake River Research, PLLC, Idaho Falls, ID: Buitrago, Martha.
Stanford University, Palo Alto, CA: Upinder Singh.
STAT Research, Springboro, OH: Joshua Ordway.
The Miriam Hospital Clinical Research Site (TMH CRS) – (CRS), Providence, RI: Ryback, Natasha.
The University of Pittsburgh, Pittsburgh, PA: Madhu Choudhary.
Triple O Research Institute PA, West Palm Beach, FL: Olayemi Osiyemi.
University at Buffalo, Emergency Medicine, Buffalo, NY: Brian Clemency.
University of California Los Angeles, Los Angeles, CA: Kara Chew.
University of California San Diego Antiviral Research Center, San Diego, CA: Constance Benson.
University of Florida Jacksonville, Jacksonville, FL: Mobeen Rathore.
University of Kansas Medical Center, Kansas City, KS: Mario Castro.
University of North Carolina at Chapel Hill, Chapel Hill, NC: David Wohl.
University of Pennsylvania, Philadelphia, PA: Pablo Tebas-Medrano.
University of Washington AIDS Clinical Trials, Seattle, WA: Rachel Bender Ignacio.
UT Southwestern HIV/ID Clinical Trials Unit, Dallas, TX: Mamta Jain.
Vida Clinical Studies, Dearborn, MI: Derrick Williamson.
Vanderbilt Therapeutics Clinical Research Site, Nashville, TN: David Haas.
Zion Medical Center, San Diego, CA: Schwartz, Adam.

FUNDING

This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number 3UM1AI068636-14S2, UM1AI068634, UM1AI068636, and UM1AI106701. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Investigational agent was supplied by AstraZeneca.

CONFLICT OF INTEREST

R.B.I. is a consultant for Abbvie and SeaGen, unrelated to this topic. K.W.C. has received research funding to the institution from Merck Sharpe & Dohme, unrelated to this topic. V.P.R., A.R., and G.M. are full-time employees of and hold shares of AstraZeneca. D.W. is a consultant for Gilead Sciences as well as for Janssen Pharmaceuticals and ViiV Healthcare unrelated to this topic, and his university receives research funding from Gilead Sciences, Merck Sharpe & Dohme, Eli Lilly, and ViiV. A.C.J., Y.M., C.V.F., M.D.H., J.S.C., J.E.E., and D.S. report no conflicts of interest.

AUTHOR CONTRIBUTIONS

R.B.I., D.W., C.V.F., M.D.H., J.J.E., J.S.C., K.W.C., and D.S. wrote the manuscript. R.B.I., D.W., C.V.F., M.D.H., J.J.E., J.S.C., K.W.C., A.C.J., and D.S. designed the research. R.B.I., D.W., C.V.F., M.D.H., J.J.E., J.S.C., K.W.C., A.C.J., and D.S. performed the research. Y.M., C.V.F., V.P.R., and R.A. analyzed the data. M.G. contributed new reagents/analytical tools.

DATA AVAILABILITY STATEMENT

The authors confirm that all data underlying the findings are fully available. Due to ethical restrictions, study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group and the manufacturer of the investigational product.

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