PROTOCOL
#ESR 22-21698

Real World Evaluation of

the Effectiveness of AZD7442

for Prevention of SARS-CoV-2 Infection

in Immuno-Suppressed Cancer Patients

Short Title:

AZD Immuno-Suppressed Program (AISP)

FINAL

22 February 2022

AMENDED

7 September 2022

Confidential Document

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Program Abbreviations

AE	Adverse Event
AISP	AZD7442 Immuno-Suppressed Program
AZD7442	AstraZeneca combination monoclonal antibody
BP	Blood Pressure
CEC	Clinical Events Committee
cm	centimeter
COA	Clinical Outcome Assessment
COVID-19	SARS-Cov-2
EMR	Electronic Medical Record
FDA	Food and Drug Administration
g/dL	grams per deciliter
ICF	Informed Consent Form
Kg	Kilogram
Lb	Pounds
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mL	milliliter
mmHg	millimeters of mercury
ng	nanogram
OTC	Over-The-Counter
PCR	Polymerase Chain Reaction
QoL	Quality of Life
RBD-IgG	Semi quantitative measure of SARS-CoV-2 specific IgG spike protein antibody levels
REMS	Risk Evaluation and Mitigation Strategy
RWD	Real-World Data
RWE	Real-World Evidence
SAE	Serious Adverse Event
SARS-CoV-2	COVID-19 virus
SD	Standard Deviation

TIA	Transient Ischemic Attack

PROGRAM OVERVIEW

Title	**Real World Evaluation of the Effectiveness of AZD7442 for Prevention of SARS-CoV-2 Infection in Immuno-Suppressed Cancer Patients** Short Title: **AZD I**mmuno-**S**uppressed **Program** (**AISP**)
Phase	II-III
1.0 Rationale	**1.1 Rationale for Design** If a treated cancer patient cannot make antibodies to a SARS-CoV-2 EUA or approved vaccine, their risk for infection and its sequelae are significantly increased. The AZD Immuno-Suppressed Program (AISP) is designed to address whether a patient treated for cancer who receives a dose of AZD7442 600 mg IM or IV every 6 months will maintain a stable/protective effect against symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death up to 12 months post-baseline. SARS-CoV-2 qualifying symptoms are based on the definitions in the AstraZeneca PROVENT trial. In combination with a positive SARS-CoV-2 antigen test, symptomatic infection includes at least one of the following symptoms and duration: ➢ No minimum duration • Fever, shortness of breath, difficulty breathing, new onset confusion (only for patients ≥ 60 years), appetite loss or decrease food intake (only for patients ≥ 60 years), increased supplemental oxygen requirement (only for patients ≥ 60 years on baseline supplemental oxygen) ➢ Must be present for ≥ 2 days • Chills, cough, fatigue, muscle aches, body aches, headache, new loss of taste, new loss of smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea The program will focus on patients with cancer who have been treated with chemotherapy, immunotherapy, targeted therapy, other therapy or combination therapy with or without radiation therapy within 12 months prior to enrollment, are willing/able to receive one IM or IV injection of AZD7442, are able to complete 15

Patient Experience/COA surveys, 6 QoL assessments and are willing to allow blood to be drawn for serum concentration of AZD7442 5 times, blood to be drawn 5 times for SARS-CoV-2 RBD IgG antibody tests, and blood to be drawn 2 times for T-cell assays. In the event of a symptomatic break-thru SARS-CoV-2 positive infection by SARS-COV-2 RNA by RT-PCR test, the patient will have an additional AZD7442 serum concentration, SARS-CoV-2 RBD-IgG antibody level and T-cell assay obtained in a temporally related manner.

All currently EUA approved monoclonal antibodies for treatment or prevention of SARS-CoV-2 infection have side-effects that in most cases are mild and abate within 24 hours. A few isolated cases of anaphylaxis have been reported and there is a small chance of developing a symptomatic SARS-CoV-2 infection even after being treated with AZD7442. The AISP design is based on three elements:

- All patients treated with AZD7442 600 mg IM or IV
- Patients stratified by treatment with chemotherapy only, immunotherapy only, targeted therapy only or other therapy/combination therapy
- Patients sub-stratified based on currently on active treatment, ≤3 months post-treatment or >3 months and ≤12 months post-treatment

This national initiative, which includes key stakeholders in the healthcare system, is designed to prospectively collect data directly from patients via Patient Experience/Clinical Outcome Assessment surveys without third party interpretation. This is incorporated into a database that links and integrates these surveys with patient medical records, pharmacy fill /refill data and medical insurance claims data. These four main data sources comprise Real-Word Data.

1.2 Rationale for Program Population

At the time of evaluation of various currently or previously EUA approved monoclonal antibodies (Regeneron, Lilly, GSK/Vir, AstraZeneca), no data existed on whether or not sufficient numbers of treated cancer patients were included in their studies. The Phase III clinical trials were designed to demonstrate efficacy within a broad patient population and as a result were focused on achieving regulatory approval in the shortest possible timeframe. While scientifically sound, this approach left out vulnerable populations who might have benefited from monoclonal

	antibodies, in particular subjects with a history of cancer who were treated with chemotherapy, immunotherapy, targeted therapy, other therapy or combination therapies. Evaluations of real-world evidence are becoming increasingly important to healthcare providers and payers. These data analyses and interpretations are evolving in a direction that has the potential to become the standard for post-approval medication/vaccine evaluation including both comparative effectiveness and safety. In this program, the population will be broadly diverse with respect to age, gender, race, geography, socio-economic status, health literacy, and insurance coverage. This will allow for recruitment of patients considered to be comparable to those studied pre-approval but inclusive of the diverse nature of cancer patients. The program population will include a large number of patients with co-morbidities that may have a significant impact on their ability to maintain therapeutic levels of AZD7442 over 12 months post-baseline and, as a result, prevent a symptomatic SARS-CoV-2 infection. **1.3 Rationale for Immunological Profiling Using T-Cell (Thymocyte Derived Lymphocyte) Functional Testing in Immuno-Suppressed Cancer Patients** Post initial administration of AZD7442, breakthrough SARS-COV-2 RNA by RT-PCR positive SARS-CoV-2 infections could result from either failure of AZD742 to provide protection and/or intrinsic T-cell (Thymocyte Derived Lymphocyte) dysfunction. Relative to the latter possibility, it is known that in normal, healthy, immune-competent subjects, there is a significant T-cell response to COVID-19 virus that can result in (1) CD4 T-cell production and secretion of cytokines that activate other immune cells including B-cells, CD-8 T-cells and macrophages to combat the viral infection and/or (2) CD8 T-cell production and release of cytokines which destroy virus-infected cells by either lysis and/or apoptosis. Unfortunately, the relationship between neutralizing antibodies and T-cell activation/secretion is unknown in immuno-suppressed cancer patients at baseline as well as in response to active SARS-CoV-2 infection. As part of this program, a sub-study has been designed to provide systematic information to help address this critical issue.
2.0	**2.1 Primary Hypothesis**

Clinical Hypotheses to be Evaluated	The primary clinical hypothesis to be evaluated is that in patients treated for either solid tumor or hematologic malignancy cancer, a dose of AZD7442 600 mg IM or IV every 6 months will prevent symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death, independent of type of cancer therapy up to 12 months post-dose. The possibility of a break-through SARS-CoV-2 infection may be influenced by type of cancer, current cancer treatment or length of time post-baseline administration of AZD7442. **2.2 Serum Concentrations of AZD7442** We hypothesize that serum concentrations of AZD7442 will not be different between solid tumor or hematologic malignancy treatment regimens at any time point post-baseline. We believe that serum concentration of AZD7442 may be correlated with IgG antibody level to SARS-CoV-2 and CD4/CD8 level as a measurement of T-Cell function as well as symptomatic SARS-CoV-2 infection, including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death. We also expect to find that AZD7442 side-effects will not be significantly different between the four strata of cancer therapy (chemotherapy only, immunotherapy only, targeted therapy only, other therapy/combination therapy only). **2.3 T-Cell Function** We hypothesize that T-cell function obtained at Day 30 post AZD7442 administration in cancer patients will be within the normal range compared to historical healthy control patients' CD4/CD8 data. In addition, we hypothesize that patients who experience breakthrough SARS-CoV-2 infection will have an increase in T-cell function compared to data acquired on Day 30 post AZD7442 administration and that this increase will be in the range of expected results in historical control patients.
3.0 Study Objectives	**3.1 Primary Objective:** The primary objective is to quantify the serum concentration of AZD7442 at 1,3, 6, 9 or 12-months post-baseline in all qualified cancer patients treated with AZD7442 600 mg IM or IV every 6 months. **3.2 Secondary Objectives:** The secondary objectives of the study are as follows:

	• Compare the incidence of symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death between solid tumor and hematologic malignancy patients. • Compare of the incidence of symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death between patients treated with chemotherapy only, immunotherapy only, targeted therapy only or other/combination therapy only over 12 months post-baseline. • Compare the serum concentration of AZD7442 at 1, 3, 6, 9 and 12-months post-baseline between solid tumor and hematologic malignancy patients. • Compare the serum concentration of AZD7442 at 1, 3, 6, 9 and 12-months post-baseline between patients treated with chemotherapy only, immunotherapy only, targeted therapy only or other/combination therapy only. • Compare of the incidence of symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death to the levels of serum concentration of AZD7442 at 1, 3, 6, 9 and 12-months post-baseline in all patients. • Compare the incidence of severe SARS-CoV-2 (pneumonia or hypoxemia, and WHO score of ≥5) based on the TACKLE definition between solid tumor and hematologic malignancy patients. • Compare the incidence of severe SARS-CoV-2 (pneumonia or hypoxemia, and WHO score of ≥5) based on the TACKLE definition death between patients treated with chemotherapy only, immunotherapy only, targeted therapy only or other/combination therapy only over 12 months post-baseline. • Compare the incidence of severe SARS-CoV-2 (pneumonia or hypoxemia, and WHO score of ≥5) based on the TACKLE definition to the levels of serum concentration of AZD7442 at 1, 3, 6, 9 and 12-months post-baseline in all patients.

	• Compare time to first event (e.g., SARS-COV-2 RNA by RT-PCR positivity, symptomatic SARS-CoV-2 infection, hospitalization, death) between all four strata • Compare Quality-of-Life symptoms in all cancer patients, as measured by change from baseline (Day 2) to days 30, 90, 180, 270, and 360 post-baseline, and then compare the same Quality-of-Life metrics at each timepoint between each of the four strata • Assess patient safety and adverse events including medically attended visits, ER/urgent care/unplanned telehealth visits using Patient Experience/COA survey data for patients in each of the four strata • Evaluate whether solid tumor or hematologic malignancy patients have a greater incidence of AZD7442-related side effects • Assess the use of Machine Learning to predict the incidence of SARS-CoV-2 infection at days 30, 90, 180, 270 and 360 post-baseline in all cancer patients based on serum AZD7442 concentration levels **3.3 Exploratory Objectives:** • Virologic surveillance to detect all SARS-CoV-2 variants occurring during the study in patients that test positive for SARS-CoV-2 by SARS-COV-2 RNA by RT-PCR (polymerase chain reaction) testing • Detection of potential new variants identified by positive SARS-COV-2 RNA by RT-PCR testing •
4.0 Immunologic Profiling and T-Cell Function Objectives	**4.1 Immunologic Profiling and T-Cell Function Objectives** • Assess CD4 T-cell and CD8 T-cell function in immuno-suppressed cancer patients at 30 days post initial administration of AZD7442 compared to similar tests performed in normal healthy donor subjects. • Assess the relationship between different cancer treatment regimens and T-cell function in immuno-suppressed cancer patients at 30 days post administration of AZD7442.

	• Assess the relationship between type of cancer (solid vs. hematologic) and T-cell function in immuno-suppressed cancer patients at 30 days post administration of AZD7442. • In immuno-suppressed cancer patients who are subsequently diagnosed as having symptomatic SARS-COV-2 RNA by RT-PCR positive SARS-CoV-2 infection, assess the immunologic profile relating to AZD7442 serum level and T-cell function at the time of RT-PCR positive SARS-CoV-2 infection. • Assess the relationship between change from Day 30 in AZD7442 serum level, T- cell function and World Health Organization Ordinal Scale (WOS) for COVID-19 disease severity in the aggregated immune-suppressed cancer patients with documented SARS-COV-2 RNA by RT-PCR positive SARS-CoV-2 infection. • Assess the relationship between change from Day 30 in AZD7442 serum level, T- cell function and World Health Organization Ordinal Scale (WOS) for COVID-19 disease severity in immune-suppressed cancer patients with documented SARS-COV-2 RNA by RT-PCR positive SARS-CoV-2 infection based on cancer treatment. • Assess the relationship between change from Day 30 in AZD7442 serum level, T- cell function and World Health Organization Ordinal Scale (WOS) for COVID-19 disease severity in immune-suppressed cancer patients with documented SARS-COV-2 RNA by RT-PCR positive SARS-CoV-2 infection based on type of cancer.
	5.1 Overall Study Design This study is a multi-center, prospective, pragmatic evaluation of AZD7442 600 mg IM or IV for prevention of SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death in cancer patients. All qualified patients will receive active AZD7442 drug. **5.2 Screening Evaluation** Assessing the general level of immune competence in a patient includes: disease severity, duration, clinical stability, complications, comorbidities, and any potentially

5.0 Study Design	immune-suppressing treatment. The study begins with a screening evaluation of solid tumor or hematologic malignancy patients actively or previously treated for their oncologic disease. Enrollment will include patients who fulfill at least one of the following criteria (see Section 8.1; Inclusion Criteria): • Having received chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy) • On active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), as well as any FDA approved alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents) or any combination of these agents. • Previously treated but not on active treatment as defined in Section 8.1. The patient's clinical stability will be defined by the Investigator at the time of enrollment and applies to all solid tumor or hematologic malignancy patients. The categories for clinical stability are: (1) in remission, (2) stable or (3) progressing. These assessments of clinical stability will be repeated at month 3 and month 6 of patient follow-up. Hematologic malignancy patients may be enrolled even if their therapy is completed and their cancer status is considered stable or in remission. Solid tumor patients are excluded if their therapy has been completed more than 6 months prior to baseline and their cancer is either stable or in remission. All solid tumor or hematologic malignancy patients may be enrolled if their cancer status is considered as progressing, whether or not they are on active treatment. Enrolled patients will also fulfill one of the following criteria: (1) they have received any SARS-CoV-2 vaccination with an FDA EUA vaccine (Janssen, Moderna or Pfizer) and do not wish to receive an additional vaccine dose, or (2) they have received any SARS-CoV-2 vaccination with an FDA EUA vaccine (Janssen, Moderna or Pfizer) and wish to receive an additional Janssen, Moderna, Pfizer vaccine dose.

	The baseline evaluation will require SARS-CoV-2 specific RBD-IgG antibody testing in all vaccinated participants who are at least 4 weeks post their most recent vaccine dose. To qualify for enrollment into the program, each solid tumor cancer patient must be either on active treatment, up to 6 months post-treatment and/or has progression of his/her cancer. Hematologic malignancy patients may be enrolled on active treatment or up to 12 months post- treatment and if their cancer is in remission, stable or progressing. **5.3 Qualified Patients** Qualified solid tumor and hematologic malignancy patients will be stratified based on chemotherapy only, immunotherapy only, targeted therapy only or other/combination therapy only and then sub-stratified based on currently on active treatment, ≤3 months post-treatment or >3 months and ≤12 months post-treatment. **5.4 Vaccination** If a patient wishes to receive an additional dose of Moderna, Pfizer or Janssen vaccine after baseline treatment with AZD7442, they must wait 14 days before receiving any additional vaccine dose. It is not required that the patient's additional vaccine dose be provided from the same manufacturer as their original vaccination. There will be no attempt to balance the number of patients receiving an additional dose of Janssen, Moderna, or Pfizer vaccine. SARS-CoV-2 EUA or FDA approved vaccinations will be performed at a local pharmacy, community health center or health plan location **5.5 Study Activities** • All qualified patients will be treated with AZD7442 600 mg IM or IV at baseline. • All qualified patients will complete a baseline Patient Experience/Clinical Outcome Assessment (COA) survey (Day 1) prior to treatment with AZD7442 600 mg IM or IV. • All qualified patients will complete follow-up Patient Experience/COA surveys on days 2, 30, 60, 90, 120, 150, 180, 181, 210, 240, 270, 300, 330 and 360 post-baseline.

	• All qualified patients will complete QoL assessment on days 2, 30, 90, 180, 270, and 360 post-baseline. • All qualified patients will have serum concentration of AZD7442 obtained at days 30, 90, 180, 270 and 360 post-baseline. • All qualified patients will have SARS-Cov-2 RBD-IgG antibody level obtained at baseline, days 90, 180, 270 and 360 post-baseline • At Day 30 post-baseline, all patients will have blood obtained for T-cell assay. Measurements of CD4 T-cell and CD8 T-cell function will be performed. • Blood will be obtained for repeat T-cell assay (CD4/CD8) at Day 210 post-baseline in a selected subset of 120 hematologic malignancy and 60 solid tumor patients. • Repeat T-cell functional testing, SARS-CoV-2 RBD-IgG and serum concentration of AZD7442 will be performed in patients who become SARS-CoV-2 RNA by RT-PCR positive at approximately 10 days or according to study site guidelines after the patient develops a positive test. **5.6 Study Data** Study data for all qualified patients will be collected and stored on a proprietary data platform that has been tested and validated by a HIPAA compliant review system. This platform provides for role-based accountability. The platform is called the National Medication Safety, Outcomes and Adherence Platform (NMSOAP). The data collection for all study participants that receive AZD7442 treatment will include: one baseline Experience/COA survey, one baseline QoL assessment, 14 follow-up Experience/COA surveys, 5 follow-up QoL assessments, at least 5 serum concentrations of AZD7442, at least 5 SARS-CoV-2 RBD-IgG antibody levels, and at least 2 CD4/CD8 measurements. An additional AZD7442 serum concentration, SARS-CoV-2 RBD-IgG antibody level and CD4/CD8 assay will be performed if a symptomatic patient becomes SARS-CoV-2 RNA by RT-PCR COVID-19 positive. In this case, additional medical records will be obtained. These could include unplanned telehealth visit, Urgent Care/ER visit or hospitalization, pharmacy data and medical insurance claims data.

6.0 Sites, Subjects Stratification	**6.1 Sites** The study will be conducted at up to 75 hematology/oncology medical practice locations nationally. **6.2 Subjects** The program will enroll approximately 1,500 qualified patients divided into approximately 1,200 qualified solid tumor and approximately 300 qualified hematologic malignancy patients either on active therapy or treated within the past 12 months. **6.3 Stratification** Qualified solid tumor and hematologic malignancy patients will be stratified based on current or former treatment with chemotherapy only, immunotherapy only, targeted therapy only, or other therapy/combination therapy only and sub-stratified by: currently on active treatment, ≤3 months post-treatment or >3 months and ≤12 months post-treatment.
7.0 Study Duration	➢ Enrollment: Approximately 3 months ➢ Patient Follow-Up: 12 months from date of enrollment
8.0 Patient Eligibility Criteria	**8.1 Inclusion Criteria** Patients will be considered qualified for study enrollment if they meet the following inclusion criteria: ➢ Male or Female gender at birth ➢ Women who are not pregnant, not breast feeding and of child-bearing potential using contraception prior to enrollment in the study. Women of child-bearing potential must agree to continued use of contraception throughout the 12 months of study participation. ➢ Age at least 18 years ➢ It is preferable that a patient has access to a "smartphone" or tablet or laptop or desktop computer and/or an email address ➢ In the event that a patient does not have access to any of the above, the patient may complete all follow-up surveys via the study's Call Center or in written form in the offices of the Principal Investigator as specified in the protocol

	➢ Documented diagnosis of either hematologic malignancy or solid tumor as identified by standard ICD-10 diagnostic category ➢ Patients may be included with at least ONE of the following criteria: • **On active treatment** for solid tumor or hematologic malignancies. This can include: high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), as well as any FDA-approved alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents) or any combination of these agents. For patients on active oral, IM or IV therapy at the time of enrollment, treatments may have been initiated at any time prior to baseline • Hematologic malignancy patients may be included up to 12 months post-last day of last cycle of treatment with oral, IV, or IM therapy and either in remission, stable or progressing as determined by the Investigator • Solid tumor patients may be included up to 6 months post-last day of last cycle of treatment with oral, IV, or IM therapy and either in remission, stable or progressing as determined by the Investigator • Received chimeric antigen receptor (CAR-T) or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy) ➢ For patients not on active oral, IM or IV therapy at the time of enrollment, previous treatments may have been initiated at any time prior to treatment inactivity but must meet the hematologic or solid tumor post treatment requirements stated above ➢ Concomitant radiation therapy is permitted but cannot be the sole therapy ➢ Have been vaccinated with one or more doses of Janssen, Moderna or Pfizer COVID-19 vaccine at least 14 days prior to Baseline

	➢ If having been previously diagnosed with SARS-CoV-2 infection, the diagnosis has to be at least 90 days prior to study randomization. If previously diagnosed, previous treatment with Ivermectin or hydroxychloroquine is acceptable. ➢ Have a negative SARS-CoV-2 antigen rapid test performed in the office at screening ➢ Patient willing to receive treatment with AZD7442 600 mg IM or IV ➢ Patient willing to complete baseline and 14 post-enrollment Patient Experience/Clinical Outcome Assessment surveys. ➢ Patient willing to complete baseline (Day 2) and 5 follow-up QoL assessments ➢ Patient willing to have blood drawn for serum concentration of AZD7442 5 times post-baseline and repeated if patient becomes COVID-19 positive ➢ Patient willing to have blood drawn for T-cell assay at day 30 and at day 210 post-baseline and repeated if patient becomes SARS-COV-2 RNA by RT-PCR positive ➢ Patient willing to have RBD-IgG drawn at baseline, days 90, 180, 270 and 360 post-baseline and repeated if patient becomes SARS-COV-2 RNA by RT-PCR positive ➢ Patient willing to signed Informed Consent Form ➢ Patient willing to sign Authorization for Release of Health Information (including treating physicians' or other medical personnel's records, medication prescriber records, pharmacy records and medical insurance claims) **8.2 Exclusion Criteria** Patients meeting any of the following criteria will be excluded from study participation: ➢ Women who are pregnant, breast feeding or of child bearing potential and not using contraception ➢ Absence of a qualifying type of cancer as defined by standard ICD-10 diagnostic criteria ➢ Patient receiving only radiation therapy ➢ Patient with an ECOG performance status of 2 or higher

	➢ Patient with an expected cancer survival of less than 12 months by disease category ➢ Patient receiving adjuvant endocrine therapy as their only form of therapy for early-stage breast cancer ➢ Solid tumor patients more than 6 months post treatment and their cancer is considered to be stable or in remission as determined by the Investigator ➢ AZD7442 administration at any time prior to day of enrollment ➢ Have a positive test for SARS-CoV-2 antigen performed by either Rapid Test or SARS-CoV-2 RNA by RT-PCR (Polymerase Chain Reaction) less than 90 days prior to enrollment ➢ Patient with a prior (within 90 days), current, or planned use of any of COVID-19 convalescent plasma, other monoclonal antibodies against SARS-CoV-2 or any other EUA approved SARS-CoV-2 treatment ➢ Patient with fever >100.0 F, and/or cough, chills, loss of smell or taste or shortness of breath or any other signs or symptoms consistent with COVID-19 within 5 days prior to enrollment ➢ Patient who has any known active acute respiratory infection ➢ Patient who has persistent (refractory to treatment for ≥14 days) bacterial or fungal infection ➢ Patient who has a past SARS-CoV-2 infection within 90 days prior to randomization ➢ Patient who has received vaccination with any dose of Janssen, Pfizer or Moderna COVID-19 vaccine less than 14 days prior to baseline for this study ➢ Planned use of any investigational, authorized, or approved vaccine for COVID-19 less than 14 days prior to administration of AZD7442 600 mg IM or IV ➢ Patient who is unwilling to have SARS-CoV-2 RBD-IgG antibody levels drawn at least 5 times ➢ Patient who is unwilling to receive treatment with IM or IV AZD7442 ➢ Patient who is unwilling to complete baseline and up to 14 follow-up Experience/Clinical Outcome Assessment (COA) surveys.

	➢ Patient who is unwilling to complete baseline and up to 5 follow-up QoL assessments ➢ Patient who is unwilling to have blood drawn for AZD7442 serum concentration at least 5 times ➢ Patient who is unwilling to have blood drawn twice for T-cell assay ➢ Patient whose native language is not English and does not have a person who can translate the regulatory documents, surveys and QoL assessments. ➢ Patient who is unable to provide Informed Consent or Authorization for Release of Health Information due to mental illness that requires a Legally Authorized Representative. ➢ Patient who is legally blind and does not have a witness/caregiver who has agreed to assist the patient in his/her participation in the study. ➢ Patient with a history of a severe allergic reaction (i.e., anaphylaxis) to any of the components of AZD7442 ➢ Patient with a history of severe allergic reaction (hypersensitivity) to any SARS-COV-2 vaccination, Polyethylene Glycol (PEG) or Polysorbate 80 ➢ Patient who is illiterate and does not have a witness/caregiver who has agreed to assist the patient in his/her participation in the study. ➢ Patient who is participating in an interventional trial for prophylaxis or treatment of SARS-CoV-2
9.0 Study Activities	**9.1 Screening Activities** Total study enrollment will be based on approximately 80% of qualified enrolled subjects treated for solid tumors and approximately 20% of qualified enrolled subjects treated for hematologic malignancy. ➢ At the time of screening, all patients have (1) completed an FDA EUA or approved (Janssen, Moderna or Pfizer) COVID-19 single dose vaccine regimen, a two-dose vaccine regimen or one dose of a two-dose vaccine regimen; and/or (2) decided to receive or not receive an additional "booster" dose of Moderna, Pfizer or Janssen SARS-CoV-2 vaccine.

	➢ In vaccinated patients, screening may occur at any time after 14 days post vaccination. ➢ Site personnel will draw blood for SARS-CoV-2 specific RBD-IgG antibody level at least 4 weeks or longer after completion of the most recent dose of any FDA approved SARS-CoV-2 vaccine. ➢ Blood drawn for SARS-CoV-2 RBD-IgG in all patients will be sent to LabCorp for analysis. ➢ Once blood is obtained for SARS-CoV-2 RBD-IgG, the patient may proceed to the Baseline Visit and be offered treatment with AZD7442. The SARS-CoV-2 specific RBD-IgG level is without charge to the patient. ➢ Site personnel will perform a nasal or buccal SARS-CoV-2 rapid antigen test in the office at the time of screening. If the SARS-CoV-2 rapid antigen test is negative, the patient may proceed to the baseline visit. If the SARS-CoV-2 rapid antigen test is positive, the patient will be referred for SARS-CoV-2 by RT-PCR test. If the RT-PCR test is positive, the patient is disqualified from study participation. If the SARS-CoV-2 by RT-PCR test is negative the patient may proceed to the baseline visit. ➢ Patients will digitally sign and site personnel will witness the Informed Consent Form (ICF) ➢ Site personnel will obtain CBC (including platelet count) if not performed within prior 30 days ➢ Patients will digitally sign Authorization for Release of Healthcare Records Form. **9.2 Baseline Activities** Baseline Activities are as follows: ➢ Patients will complete the baseline Experience/Clinical Outcome Assessment (COA) survey ➢ For Patients Receiving IM Dose Administration: Site personnel will withdraw 1.5 mL of AZD8895 from each of two AZD8895 vials for a total of 3.0 ml into one syringe and in a separate syringe, withdraw 1.5 mL of

	AZD1061 from each of two vials of AZD1061 for a total of 3.0 ml in one syringe and administer 3.0 ml of AZD8895 and 3.0 ml AZD1061 separately in sequential order IM into each thigh or gluteal muscle, with no participant receiving 3.0 ml of IM AZD8895 without also receiving the matching dose of 3.0 ml of IM AZD1061. One IM injection must be given in each thigh or gluteal muscle in sequence for a total of 600 mg (6.0 ml) administered. ➢ For Patients Receiving IV Dose Administration: The criteria for IV administration of AZD7442 includes one or more of the following: platelet count ≤50,000, coagulation deficiency, intravenous medication port in place, limited gluteal or thigh muscle mass. The dose of AZD7442 for administration must be prepared using aseptic technique. The total time from needle puncture of the vial to the start of administration must not exceed: • 24 hours at 2 °C to 8 °C • 4 hours at room temperature AZD7442 is only stored refrigerated. The total time at room temperature prior to administration must not exceed 4 hours; otherwise, a new dose must be prepared using new vials. AZD7442 does not contain preservatives and any unused portion must be discarded. Use a single 50 to 100 mL 0.9% sodium chloride or 5% dextrose for injection IV bag for both AZD8895 and AZD1061 infusion. Use a soft IV bag made of polyolefin (PO), polyvinylchloride (PVC), or polyethylene (PE). Step 1: For 600 mg dose of AZD7442, retrieve two vials each of AZD8895 and AZD1061. Step 2: Accurately withdraw 1.5 mL from each of the two vials of AZD8895 and transfer to the IV bag. Then, withdraw 1.5 mL from each of the two vials of AZD1061 and transfer to the same IV bag. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Step 3:

	Administer the entire contents of the IV bag using IV administration sets containing low protein binding 0.2-µm or 0.22-µm filters made of polyethersulfone (PES). The target infusion time is 30 minutes and the target infusion rate is 20 mg/minute, which translates to IV pump programmable rates of approximately: • 100 mL/hr for a 50 mL IV bag • 200 mL/hr for a 100 mL IV bag Step 4: Flush the IV line according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time. Flush the catheter with 0.9% sodium chloride for injection at the end of the infusion. • Site personnel may administer AZD7442 600 mg IV ONLY under one of or more of the following conditions: ➢ at the discretion of the Investigator if the patient would have less discomfort with an intravenous route (i.e., has significant weight loss and little gluteal or thigh muscle mass) ➢ if the patient already has an indwelling medication "port" through which the patient receives intravenous drug administration. ➢ if the patient's platelet count ≤50,000/µl ➢ if the patient has a history of a coagulation disorder • AZD7442 may only be administered by IV infusion in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system as necessary. • Patients administered AZD7442 IV will be observed for immediate side effects and have vital signs measured every 15 minutes during the time of infusion and for the 60 minutes following the end of the infusion. All such vital signs will be record in the patient's medical record. • If an infusion-related reaction occurs, the AZD7442 infusion should be immediately terminated and appropriate medications including but not limited to diphenhydramine, other anti-histamines, methylprednisolone, epinephrine and/or other supportive care measures should be immediately provided.

- Patients will be observed for immediate side effects for 60 minutes following AZD7442 600 mg IM administration
- Site personnel will give all patients one SARS-CoV-2 Home Test Kit for at home testing of possible SARS-CoV-2 infection at the conclusion of the baseline visit
- Automatic request for patient medical records, pharmacy fill/refill data and medical insurance claims data for the 6 months prior to baseline will be sent and forwarded to MediMergent for analysis

9.3 Follow-Up Activities

Follow-Up activities are as follows:

- At Day 180 post-baseline, all patients will be administered a repeat dose of AZD7442 600 mg IM or IV. The window for this treatment will be +/- 5 days from the actual due date. The dose will be administered in the same manner as the baseline dose unless patient circumstances require a different route of administration. All requirements listed above for baseline AZD7442 administration both IV and IM will be followed for the repeat dose including the one-hour post-dose observation period.
- Patients will complete follow-up Patient Experience/COA surveys on days 2, 30, 60, 90, 120, 150, 180, 181, 210, 240, 270, 300, 330 and 360 post-baseline at home. The window for these surveys will be +/- 5 days from the actual survey due date except for day 2 survey which is +5 days only.

*NB - Study participants will complete all surveys via mobile phone, desktop, laptop, tablet computer or via Call Center. The study site is not responsible for patient completion of the surveys.

- Patients will complete QoL assessments on days 2, 30, 90, 180, 270, and 360 post-baseline at home. The window for these assessments will be +/- 5 days from the actual due date except for day 2 assessment which is + 5 days only.
- Site personnel will obtain blood for serum concentration of AZD7442 at days 30, 90, 180, 270 and 360 post-baseline in the office for all patients. The window for these blood draws will be +/- 5 days from the actual due date. All

	serum concentration measurements will be sent to PPD Bioanalytical Laboratory in Richmond, VA for analysis. ➢ Site personnel will obtain blood for RBD-IgG antibody level at days 90, 180, 270 and 360 post-baseline in the office for all patients. The window for these blood draws will be +/- 5 days from the actual due date. All RBD-IgG antibody levels will be sent to LabCorp for analysis. ➢ Site personnel will obtain blood for T-cell assay at Day 30 post-baseline in the office for all patients and send to Isoplexis in Branford, CT for analysis. A subset of patients will be selected including 120 patients with hematologic malignancy and 60 patients with solid tumors in order to have site personnel obtain blood for repeat T-cell assay at Day 210 post-baseline in the office and send to Isoplexis in Branford, CT for analysis. The window for these blood draws will be +/- 5 days from the actual due date. ➢ In the event that a patient develops any symptoms that could be possibly related to SARS-CoV-2 infection at home or out of the office, the patient must immediately test themselves using the SARS-CoV-2 Home Test Kit that was given to them at enrollment or go to a facility that can perform an EUA approved Breath Test for SARS-CoV-2 infection. ➢ In the event a positive test from the SARS-CoV-2 Home Test Kit or EUA approved Breath Test for SARS-CoV-2 infection is recorded, the patient must go a qualified testing center and receive a SARS-COV-2 RNA by RT-PCR nasal swab test. These include LabCorp or Quest Diagnostics or a location that uses one of these two labs for the analysis (e.g., CVS). ➢ A positive SARS-COV-2 RNA by RT-PCR test must be sent to a qualified genomics laboratory (LabCorp or Quest Diagnostics) for detailed virus analysis ➢ In the event that a patient tests positive for SARS-CoV-2 infection by SARS-COV-2 RNA by RT-PCR, the patient should be instructed to contact their oncology center immediately ➢ In the event that a patient tests positive for SARS COV-2 RNA by RT-PCR, the patient must have blood drawn for serum concentration of AZD7442, RBD-IgG antibody level and T-cell analysis in the office approximately 10

	days after the patient reported a positive test or in whatever timeframe is the acceptable protocol for a positive patient returning safely to the office of the Investigator. ➢ In the event that a patient develops a SARS-CoV-2 infection with symptoms, the patient should be immediately treated in accordance with Investigator judgement. Such treatment should include the current standard of care for symptomatic SARS-CoV-2 positive infection depending upon availability of immediate treatment. Such patient will be followed until day 360 of the study with all study procedures and assessments. ➢ Automatic request for patient medical records, pharmacy fill/refill data and medical insurance claims data for all patients for the 12 months post-baseline will be sent and forwarded to MediMergent for analysis.

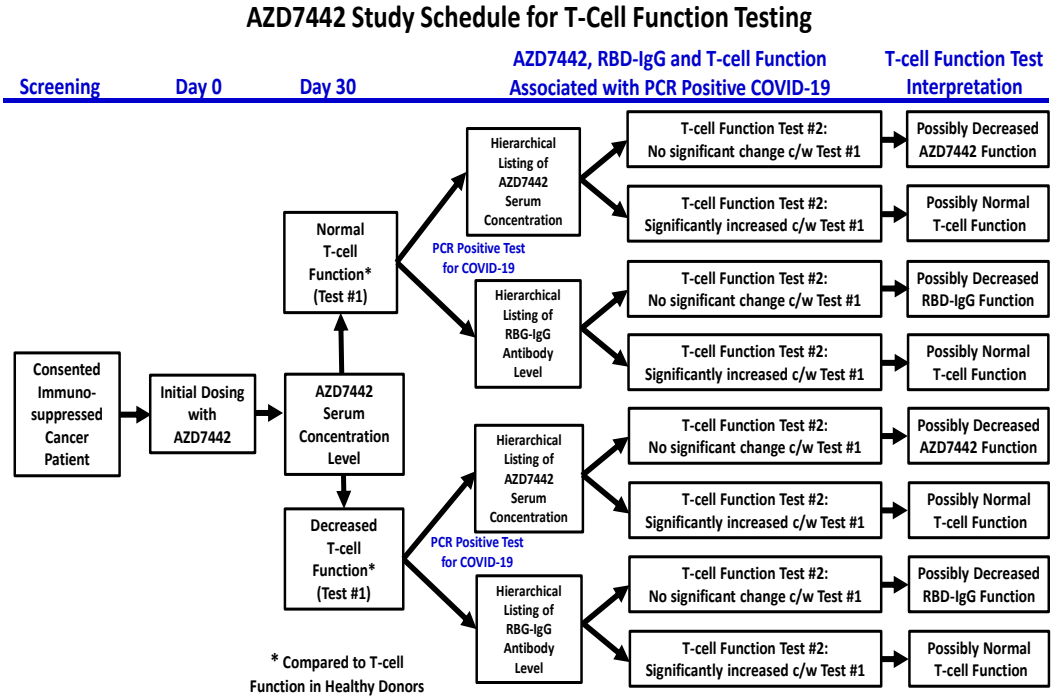
Schedule of Activities:

	Screening/ Day 1 Baseline	Day 2	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Day 181	Day 210	Day 240	Day 270	Day 300	Day 330	Day 360
Visit Window (Days)		+5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5
Informed Consent	X														
Authorization for Release of Health Info	X														
Inclusion/ Exclusion	X														
CBC including Platelet Count (if necessary)	X														
SARS-CoV-2 antigen test by nasal swab	X														
SARS-CoV-2 RBD-IgG Antibody level	X				X			X				X			X
T-Cell Assay			X							X					
AZD7442 Administration	X							X							
Baseline Survey	X														
QoL Surveys		X	X		X			X				X			X

Follow-up Patient Experience/COA Surveys		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Concentration of AZD7442			X		X			X				X			X
SARS-CoV-2 by RT-PCR if home test positive and/or symptomatic		NOTE: In the event that a patient tests positive for SARS COV-2 by RT-PCR at any time, the patient must have blood drawn for serum concentration of AZD7442, RBD-IgG antibody level and T-cell analysis in the office approximately 10 days after the patient reported a positive test or in whatever timeframe is the acceptable protocol for a positive patient returning safely to the office of the Investigator.													

10.0 Immunologic Sub-Study Activities	**10.1 Sub-Study Secretome Assay** IsoPlexis' Single Cell Multiplex Secretome Assay application measures **T-cell polyfunctionality** (i.e., the number of cells secreting multiple cytokines). From these data, the **Polyfunctional Strength Index (PSI)** will be calculated as a numeric output generated as the product of T-cell polyfunctionality multiplied by the intensity of the measured signal using fluorescent imaging. These data generate functional information relating to: • **CD4 T-cells** (Helper T-cells) which produce cytokines to activate immune cells including B-cells, CD-8 T-cells and macrophages. • **CD8 T-cells** (Cytotoxic T-cells) which destroy virus-infected cells and tumor cells by either lysis and/or apoptosis. **10.2 CD4 and CD8 T-Cell Function** In general, CD4 and CD8 T-cell function increases during active SARS-CoV-2 infection reflecting stimulation and activation of T-cell immune response. The magnitude of this increase in T-cell function appears to be related to the severity of COVID-19 disease. Specifically, previous data acquired in immuno-competent subjects have reported that CD4 and CD8 T-cell function significantly increase in response to active SARS-CoV-2 infection in subjects with mild-to-moderate SARS-CoV-2 disease. However, subjects with moderate or more severe SARS-CoV-2 disease may have a blunted T-cell response due to "exhaustion" of the cells' ability to mount a sustained cellular immune response.

The following table uses the Day 30 T-cell test as an example for guidance relating to the clinical interpretation of the T-cell test responses.



11.0 WHO Ordinal Scale

11.1 COVID-19 assessment

In the current study, clinical severity of SARS-CoV-2 disease will be assessed throughout a patient's participation in the study in accordance with the 9-point World Health Organization (WHO) Ordinal Scale (WOS) consisting of the following categories:

WOS	Clinical Severity	Criteria
0	Uninfected	No evidence of infection
1	Mild	No limitation of activities
2	Mild	Limitation of activities
3	Moderate	Hospitalized, no oxygen therapy

<table>
<tr><td></td><td>
<table>
<tr><td>4</td><td>Moderate</td><td>Hospitalized, oxygen by mask or nasal prongs</td></tr>
<tr><td>5</td><td>Severe</td><td>Hospitalized, non-invasive ventilation or high-flow oxygen</td></tr>
<tr><td>6</td><td>Severe</td><td>Hospitalized, invasive ventilation without other organ support
(e.g., ECMO, CRRT, vasopressors)</td></tr>
<tr><td>7</td><td>Severe</td><td>Hospitalized, ventilation + additional organ support (e.g., ECMO, CRRT, vasopressors)</td></tr>
<tr><td>8</td><td>Dead</td><td>Death</td></tr>
</table>
Source: World Health Organization, 2020
</td></tr>
<tr><td>12.0
Program Products</td><td>
12.1 Program Product Dosage and Administration

AZD7442 600 mg (6.0 ml) dose for all participants will be provided by AstraZeneca and distributed to all sites from a central location.
AZD7442 will be administered by all AISP participating locations according to protocol guidelines.
AZD7442 600 mg IM will be administered according to FDA approved guidelines for administration.
AZD7442 600 mg IV will be administered only according to the instructions in Section 9.2 of this protocol.

12.2 Other Medications
Participants will continue administration and dose scheduling of all other medications as prescribed and in accordance with their normal medical practice
</td></tr>
<tr><td>13.0
Primary Endpoint</td><td>
13.1 Primary Endpoint
The study’s primary endpoint will assess AZD7442 serum concentration collected on days 30, 90, 180, 270, and 360 post-baseline in all patients.
13.2 Primary Endpoint Assessment
AZD7442 serum concentrations at 30, 90, 180, 270 and 360-days post-baseline will be assessed using a mixed model for repeated measures. The primary endpoint will be analyzed for the Intent-To-Treat (ITT) and Per-Protocol (PP) populations.
</td></tr>
</table>

14.0 Secondary And Exploratory Endpoints: Overall Study	**14.1 Definitions and Secondary Endpoints** **Definition of SARS-CoV-2 qualifying symptoms:** SARS-CoV-2 qualifying symptoms are based on the definitions in the AstraZeneca PROVENT trial. In combination with a positive SARS-CoV-2 antigen test, symptomatic infection includes at least one of the following symptoms and duration: ➢ No minimum duration • Fever, shortness of breath, difficulty breathing, new onset confusion (only for patients ≥ 60 years), appetite loss or decrease food intake (only for patients ≥ 60 years), increased supplemental oxygen requirement (only for patients ≥ 60 years on baseline supplemental oxygen) ➢ Must be present for ≥ 2 days • Chills, cough, fatigue, muscle aches, body aches, headache, new loss of taste, new loss of smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea **Secondary Endpoints will include the following:** • Incidence of symptomatic SARS-CoV-2 infections including but not limited to those with SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death compared between solid tumor and hematologic malignancy patients. • Incidence of symptomatic SARS-CoV-2 infection including but not limited to SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death compared between patients treated with chemotherapy only, immunotherapy only, targeted therapy only or other/combination therapy only over 12 months post-baseline. • Serum AZD7442 concentrations at 1, 3, 6, 9 and 12-months post-baseline compared between solid tumor and hematologic malignancy patients. • Serum AZD7442 concentrations at 1, 3, 6, 9 and 12-months post-baseline compared between patients treated with chemotherapy only, immune-therapy only, targeted therapy only or other/combination therapy only.

	• Correlation of the incidence of symptomatic SARS-CoV-2 infection including but not limited to those with SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death to the levels of serum concentration of AZD7442 at 1, 3, 6, 9 and 12-months post-baseline in all patients. • Incidence of symptomatic SARS-CoV-2 infection including but not limited to SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death compared between patients currently on active treatment, ≤3 months post-treatment and > 3 months and ≤12 months post-treatment regardless of treatment strata. • Incidence of Severe SARS-CoV-2 (pneumonia or hypoxemia) and WHO score of ≥5 compared between all four strata • Time to first event (e.g., SARS-COV-2 RNA by RT-PCR positivity, symptomatic SARS-CoV-2 infection, hospitalization, death) post-treatment compared between all four strata • Quality-of-Life metrics in all cancer patients, as measured by change from baseline to days 30, 90, 180, 270 and 360 post-baseline, compared between each of the four strata • Patient symptom safety and rate of adverse events including medically attended visits, ER/urgent care/unplanned telehealth visits using Patient Experience/COA survey data summarized and compared in each of the four strata • Incidence of AZD7442-related side effects compared between solid tumor and hematologic malignancy disease cohorts • Predict the incidence of SARS-CoV-2 infection based on serum concentration of AZD7442 at days 30, 90, 180, 270 and 360 post-baseline in all cancer patients using machine learning algorithms. **14.2 Secondary Endpoint Analysis** All secondary endpoints will be analyzed for the Intent-To-Treat (ITT) population with a Per-Protocol (PP) sensitivity analysis. **14.3 Exploratory Endpoints**

	• Determine the level of immunity (prevention of SARS-CoV-2 positive infection) over time provided by a combination of AZD7442 and antibodies that developed in response to prior SARS-CoV-2 vaccination or infection in this population. • Compare the AZD7442 serum concentrations and SARS-CoV-2 RBD-IgG antibody level collected prior to the event in subjects who do not develop SARS-CoV-2 infection versus those who develop SARS-CoV-2 infection overall and/or those who are hospitalized or die due to SARS-CoV-2 infection. • Virologic surveillance to detect all SARS-CoV-2 variants occurring during the study in patients that test positive for SARS-COV-2 RNA by RT-PCR (polymerase chain reaction) testing • Detection of potential new variants identified by positive SARS-COV-2 RNA by RT-PCR testing • Correlation of type of cancer and clinical stability with the following baseline and follow-up data: ➢ Baseline immunologic profile consisting of spike antibody (SARS-CoV-2 RBD-IgG) data and T-cell function data (CD4 and CD8 analyses) • SARS-CoV-2 clinical outcomes including: ➢ SARS-COV-2 RNA by RT-PCR positive test (symptomatic SARS-CoV-2 infection) ➢ Highest WHO SARS-CoV-2 Severity Classification ➢ TACKLE definition of severe SARS-CoV-2infection (pneumonia or hypoxemia, and WHO score of ≥5) ➢ Requirement for mechanical ventilation ➢ Death associated with SARS-CoV-2 infection
	15.1 Interim Analysis The interim analysis will be conducted in order to determine whether AZD7442 prevents a SARS-CoV-2 infection in the first 6 months post-treatment in solid tumor and/or hematologic malignancy patients. If break-through infections occur,

15.0 Interim Analysis	the analysis will determine which group is more likely to experience such infections. An interim analysis will be performed after the first 6-month assessments are completed for the first 50% of the targeted patient sample for each malignancy, i.e., 750 patients including 600 solid tumor and 150 hematologic malignancies. The primary endpoint of the interim analysis will be the serum concentration of AZD7442 for all patients with comparisons between disease categories. Secondary analyses will be conducted on the following measures in all patients included in the interim analysis set: • Incidence of break-through infections in all patients and then sub-divided into solid tumor and hematologic malignancy. • Time to infection compared between solid tumor and hematologic malignancy • RBD-IgG levels for all patients with comparisons between disease category • CD4/CD8 levels for all patients with comparisons between disease category
16.0 Immunological Sub-Study Endpoints	**16.1 Immunologic Sub-Study Endpoints** • Comparison of CD4 T-cell and CD8 T-cell function in all cancer patients at 30 days post initial administration of AZD7442 to similar tests performed in normal healthy donor subjects • Comparison of the relationship between different cancer treatment regimens and T-cell function in all cancer patients at 30 days post administration of AZD7442 • Comparison of the relationship between type of cancer (solid vs. hematologic) and T-cell function in all patients at 30 days post administration of AZD7442 • Comparison of the immunologic profile relating to AZD7442 serum level and T-cell function at the time of PCR positive SARS-CoV-2 infection in all cancer patients to Day 30 T-cell functionality • Comparison of the relationship between change from Day 30 in AZD7442 serum level, T- cell function and World Health Organization Ordinal Scale

	(WOS) for SARS-CoV-2 disease severity in all cancer patients with documented PCR positive SARS-CoV-2 infection • Comparison of the relationship between change from Day 30 in AZD7442 serum level, T- cell function and World Health Organization Ordinal Scale (WOS) for SARS-CoV-2 disease severity in all cancer patients with documented RT-PCR positive SARS-CoV-2 infection based on type of cancer treatment.
17.0 Statistical Considerations	**17.1 Sample Size Estimation** This program will recruit approximately 1,500 treated cancer patients divided into approximately 1,200 qualified solid tumor and 300 qualified hematologic malignancy patients from approximately 75 hematology/oncology medical practice locations throughout the United States. It is expected that on average, each site will enroll 16 solid tumor and 4 hematologic malignancy patients. **17.2 Sample Size Power** With a sample size of 1500 patients, the power to detect a non-inferiority margin of 5 mcg/ml with a standard deviation of 25 mcg/ml and Type I error rate of 1% is estimated to be approximately 80% when comparing the serum concentration levels between solid tumor and hematologic malignancy groups. The assumed comparison is between 1200 solid tumor and 300 hematologic malignancy patients. A target sample of 1500 patients will provide adequate size to analyze all of the secondary endpoints identified in the baseline and follow-up patient experience/COA surveys and the QoL surveys. At the time of interim analysis, the power to detect a 5 mcg/ml non-inferiority margin with a standard deviation of 25 mcg/ml and Type I error rate of 1% is estimated to be approximately 45%. This assumes a sample of 600 solid tumor and 150 hematologic malignancy patients. **17.3 Stratification** This is an open-label, pragmatic, multi-center study of participants receiving AZD7442 600 mg IM or IV for prevention of symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death.

	Patients will be stratified based on type of cancer (solid tumor vs hematologic malignancy) with additional stratification for concomitant treatment regimen of chemotherapy only, immunotherapy only, targeted therapy only and other therapy/combination therapy. It is assumed that 80% of enrolled cancer patients will have solid tumors. Patients will be sub-stratified by: currently on active treatment, ≤3 months post-treatment or >3 months and ≤12 months post-treatment. **17.4 Populations for Analysis** The study will analyze two populations as defined by Intent-To-Treat (ITT) and Per Protocol (PP) criteria. • The ITT population includes all participants who complete enrollment, complete the baseline Patient Experience/COA survey, baseline QoL assessment, baseline SARS-CoV-2 RBD-IgG, undergo AZD7442 600 mg IM or IV administration, complete at least one serum concentration AZD7442 measurement post-baseline AZD7442 administration, one RBD-IgG post-baseline, complete the Day 30 T-Cell assay, complete at least one follow-up Patient Experience/COA survey and one QoL assessment. • The PP population includes all participants who complete all AZD7442 600 mg IM or IV administrations, complete the baseline Patient Experience/COA surveys, complete the baseline QoL assessment, complete the baseline SARS-CoV-2 RBD-IgG antibody level, complete the Day 30 and Day 210 T-Cell assay, complete 75% of follow-up Patient Experience/COA surveys, 75% of QoL assessments, 75% of RBD-IgG antibody levels and 75% of serum concentration of AZD7442 measurements post-baseline AZD7442 administration. **17.5 Missing Data** There are several potential missing data considerations within this study. These are outlined as follows with associated methods of handling the missing information. - Serum AZD7442 concentration: For both the ITT and PP populations, if a patient has serum AZD7442 at Day 30 and Day 90 but does not have an additional timepoint at Day 180 then the value for the missing serum AZD7442 concentration data point at Day 180 will be predicted from the linear regression of the log

	AZD7442 serum concentration from the Day 90 analysis. Otherwise, the missing AZD7442 serum concentration data will be treated as missing data. - SARS-CoV-2 infection: Will be determined through the documentation of SARS-CoV-2 diagnosis either through SARS-CoV-2 by Rt-PCR test, the medical record or claims information. Multiple locations of documentation will be considered a confirmed diagnosis. - Clinical Outcome Assessment/Quality of Life Assessment: If data are missing through the survey collection process, then only the relevant measures will be calculated. Appropriate consideration of missing values will be addressed for time points comparison either through the non-inclusion of the patient outcome in that time point and/or within regression model assessment. - RBG-IgG antibody level: Correlations will be determined where there is complete information only. **17.6 Evaluations of Primary and Secondary Endpoints** The primary and secondary endpoints will be evaluated for the intent-to-treat and per protocol patient populations. The primary comparisons will be the serum concentration of AZD7442 at Days 30, 90, 180, 270 and 360 post-baseline. Serum concentration comparisons of the log-adjusted serum AZD7442 concentration will be analyzed using linear mixed models for repeated measures. Models will include disease category, overall dose, and dose/kg accounting for concomitant treatment regimen category along with appropriate treatment and time interactions. An unstructured covariance matrix will be assumed, however, in the event of non-convergence, compound symmetry, and AR (1), covariance structures will be attempted, in that order. The Least Square Means Differences, and their 95% CIs, will be reported for each timepoint (e.g., Days 30, 90, 180, 270, and 360 post-treatment). Additional comparisons for Quality of Life (QoL) will be made between the disease category cohorts and concomitant treatment regimen categories. The disease category cohorts are solid tumor cancers and hematologic cancers. Concomitant treatment regimen categories will be defined as chemotherapy only, immunotherapy

only, targeted therapy only, other therapy/ combination therapy only. Differences in the primary endpoints will be assessed using a two-sided statistical significance level of 0.01, adjusting for planned multiple comparisons. All other differences will be assessed using a two-sided statistical significance level of 0.05.

The secondary endpoint comparisons will be made:

- between concomitant treatment regimen categories and
- between disease category cohorts

The between concomitant treatment regimen categories will account for the between disease category analyses. These secondary endpoint comparisons will be made using a logistic regression or linear mixed model accounting for potential patient and disease factors where appropriate. Additional secondary endpoints are as noted previously. The secondary endpoints will be analyzed for the Intent-To-Treat (ITT) population with a Per-Protocol (PP) sensitivity analysis.

17.7 Descriptive Statistics

Descriptive statistics will be generated for all primary, secondary, and outcome measurements. Ninety-five percent (95%) confidence intervals will also be provided.

17.8 Immunologic Sub-Study

In the immunologic sub-study, pre-specified analyses will evaluate CD4 T-cell and CD8 T-cell data including Polyfunctional Strength Index at Day 30 post-baseline in all 1,500 cancer patients and then compare these results against similar T-cell data for any patient who tests SARS-COV-2 RNA by RT-PCR positive at any timepoint post-baseline. In addition, results will be compared to prior data for these tests obtained from normal healthy donor subjects.

Relationships between AZD7442 serum concentration, RBD-IgG antibody level and T-cell function will be assessed as described in Section 10.2

Lab data will be extracted from the nearest time point to the blood draw associated with T-cell assay testing . An unpaired Wilcoxon-test will be used to determine the statistical difference between (1) WOS ≤2 and WOS = 3-4 and (2) WOS = 3-4 and WOS = 5-8 and (3) WOS ≤2 and WOS ≥3. Spearman correlation coefficient will be

	calculated to observe the associations between clinical data and WOS disease severity. In the current study, baseline T-cell polyfunctionality and PSI will be determined at two timepoints in immuno-compromised cancer patients: 30-days after initial administration of AZD7442 and in temporal proximity to the time that a patient has confirmed SARS-CoV-2 by RT-PCR evidence of SARS-CoV-2 infection. **17.9 Clinical Outcome Measurements** All other clinical outcome measurements will be analyzed for the ITT AZD7442 600 mg IM or IV treated groups for both solid tumor and hematologic malignancy population with a Per-Protocol (PP) sensitivity analysis. These include: • Rate of symptomatic SARS-CoV-2 infection including hospitalization and/or death • Rate of adverse events reported by the patient or investigator across the entire study observation period • Rate of symptoms and change from baseline in symptom severity over the observed time points. Correlation of symptom severity with log-adjusted serum concentration of AZD7442 levels, defined as the change over time from first measurement at Day 30 to Days 90, 180, 270 and 360. • Change in log-adjusted serum concentration of AZD7442 levels, defined as the change over time from first measurement at Day 30 to Days 90, 180, 270 and 360, relative to change in clinical status for individual disease category cohorts • Clinical treatment outcomes such as treatment discontinuation and time to treatment progression where possible • Health care resource utilization rates for ER, urgent care, hospitalization and unplanned telehealth visits • Rate of death will also be considered if there is sufficient information for analysis • Factor analysis to determine which factors (e.g., age, gender, type of cancer, cancer duration, type treatment, etc.) are related to higher levels of serum concentration of AZD7442

	17.10 Breakthrough Infection Descriptive Analysis All patients who experience a symptomatic breakthrough SARS-CoV-2 infection, defined as a positive SARS-COV-2 RNA by RT-PCR test with or without viral genomics and/or symptomatic clinical evidence of SARS-CoV-2 disease, will have a descriptive analysis that includes a clinical outcome (e.g., symptomatic infection, SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death), a profile of neutralizing antibody as measured by serum concentration of AZD7442, a functional analysis of T- characterized by cytokine stimulation and secretion and a genomic sequencing of the virus. In addition, relationship between these data and World Health Organization Ordinal Scale for Severity of SARS-CoV-2 Disease will be performed. **17.11 Patient Demographics, Disease and Treatment Attributes** Baseline patient characteristics for all enrolled participants include age, gender, race, weight and Body Mass Index (BMI) and will be analyzed using descriptive statistics for all strata and sub-strata. Patient demographics, disease and treatment attributes will be summarized and compared between the disease category cohorts and concomitant treatment regimens. Any attributes with significant differences will be considered for inclusion as factors in logistic regression and linear model analyses. Disease attributes will include stage of disease, time from initial diagnosis and performance status will be assessed. Treatment regimen attributes including type of therapy, cycle at time of study enrollment and cycle duration will be summarized. **17.12 Statistical Models** Statistical considerations for other endpoints will be treated on a case-by-case basis depending on the nature of the outcome variables and their distributions. Such approaches may include χ^2 cross-tabulations, t-tests, ANOVAs, negative-binomial regressions, logistic regressions, mixed model for repeated measures and linear regression.
18.0	**18.1 Identification of Non-Serious and Serious Adverse Events**

Safety and Adverse Events Analyses	Patient safety, non-serious and serious adverse events will be determined using Patient Experience/COA survey data, physician-reported events and lab data for all qualified patients treated with either chemotherapy only, immunotherapy only, targeted therapy only, or other therapy/combination therapy only. Individual symptom severity is assessed on a 3-point scale. In this study, safety will be assessed by evaluating non-serious and serious adverse events, chest x-rays, bacterial cultures, SARS-COV-2 RNA by RT-PCR and viral genomic test results. In addition, important infectious and oncologic safety events will be reviewed from CEC-adjudicated data for symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and SARS-CoV-2 related death. **18.2 Available Data** Safety data such as physical exams, labs and ECG data that are completed during the course of routine clinical care will be available to the MediMergent medical monitor through individual patient EMR data. Collection of non-serious adverse events will be limited only to answers on the follow-up survey questions as follows: (1) related to any event that occurred in the first 24 hours post AZD7442 administration, (2) symptoms of SARS-CoV-2 infection, (3) positive PCR-RT SARS-COV-2 test, (4) any unplanned telehealth visit, (5) any non-routine office visit, and/or (6) any ER/Urgent Care visit. Such events will be documented on the nonserious adverse event form. PCR test results will be reported digitally from the testing lab to the study site and the study site will report this result to MediMergent. If the Investigator considers that there was a causal relationship between treatment with AZD7442 or protocol design/procedures and a patient's underlying disease progression, then this must be reported as an AE or SAE. For all Serious Adverse Events, a separate data collection form, based on AstraZeneca guidelines, will be completed by the study site and submitted to MediMergent for data input and analysis. All Serious Adverse Events require collection of source documentation for review by the MediMergent safety team. Reporting of Adverse Events and Serious Adverse Events will follow FDA Guidelines and AstraZeneca reporting procedures.

18.3 Reporting Guidelines

As this is a pre-approval program, safety reporting guidelines for serious adverse events are expected to be followed. In the event that a reportable safety event is identified for one or more patients, MediMergent will immediately notify AstraZeneca of such an event for their reporting purposes. The AISP will report all known safety events that would be reported in a pre-approval clinical trial on an annual basis unless otherwise requested by the FDA. SUSARs will be reported to the FDA according to 7-day or 15-day reporting guidelines.

18.4 Likely SAEs

A program including 1,500 cancer patients followed for at least 12 months would be likely to encounter one or more of the following serious adverse events: sepsis, worsening of underlying cancer, respiratory failure, worsening of COPD, CHF, and death.

18.5 Hospitalization and Deaths

For purposes of this study, all hospitalizations and/or deaths will be considered a SAE. Hospitalization for a pre-existing condition that has not worsened (i.e., change a pacemaker battery) or for elective surgery will NOT be considered a SAE unless the hospitalization is prolonged by related SARS-CoV-2 therapy complications. These events will be collected and reported as SAEs only if the event is more severe than expected for the participant's current clinical status and medical history or if the Investigator feels that it is related to study drug. These will be collected and reported as SAEs as delineated below. Since it will not be possible to delineate in a single participant whether the hospitalization is directly related to SARS-CoV-2 infection complications, their underlying cancer, treatment for this cancer or could be related to AZD7442 causing more severe disease due to ADE, all hospitalizations for management of acute illness, regardless of cause, will be sent for evaluation to the Clinical Events Committee (CEC). See Section 20.1.

18.6 Investigator Responsibilities

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the

	study intervention or the study, or that caused the participant to discontinue the study. Data on hospitalization or death should additionally be recorded on the Safety Report Form, for all relevant sections. The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in the Safety Reporting section of this document. **18.7 MediMergent Pharmacovigilance** The MediMergent Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities and AstraZeneca.
19.0 Quality of Life Data	**19.1 Quality-of-Life Evaluations** All Quality-of-Life data will be derived from questions in the baseline (Day 2) and follow-up QoL assessments. Each response will be given a numeric value and the sum of all responses will serve as the QoL "score" for a given patient at a given timepoint. The scoring will be determined such that the higher the score, the better the QoL. The comparison for all patients will use a change from baseline model. Scores at each time point for all patients for a given dose and cancer type will generate a mean, SD and SEM. The change from baseline at each post-baseline timepoint will be compared using two-tailed t-test comparison with P<.05 as significant. The mean change from baseline will be compared for all cancer patients treated with AZD7442 600 mg IM or IV and then sub-divided by comparisons between chemotherapy only, immunotherapy only, targeted therapy only and other/combination therapy only.
20.0 Adjudication: Clinical Events Committee (CEC)	**20.1 Clinical Events Committee Functionality** An independent Clinical Events Committee (CEC) will be assembled to adjudicate/evaluate using a pre-specified adjudication operations manual, all clinical events data associated with SARS-COV-2 RNA by RT-PCR positive symptomatic SARS-CoV-2 infection including SARS-CoV-2 infection relatedness and/or impact on hospitalizations and deaths. In addition, the CEC will use the available clinical

	data to establish a standardized assessment of SARS-CoV-2 disease severity using the World Health Organization Ordinal Scale (WOS). In SARS-COV-2 RNA by RT-PCR positive symptomatic SARS-CoV-2 patients, the WOS associated with the time of T-cell function blood draw will be determined by the CEC using manual review. The data to be evaluated using the patient's electronic health record (EHR) and other available information will include the components required to determine the World Health Organization Ordinal Scale (WOS).
21.0 Data Monitoring Committee (DMC)	**21.1 Data Monitoring Committee** A Data Monitoring Committee (DMC) will be established for the interim analysis. The DMC will be unblinded to therapy in this open-label study. It will oversee the study with primary responsibility for ensuring that all data meet regulatory standards for the goals and objectives of the interim analysis. Specific goals and responsibilities of the DMC include the following: • Oversight of the study with primary responsibility for review of all data generated for the interim analysis • Review of adverse event data as part of the interim analysis with special attention to the incidence of SARS-CoV-2 by RT-PCR positive patients • Conduct of the planned interim analysis including DMC recommendations relating to potential AZD7442 redosing.
22.0. Machine Learning	**22.1 Machine Learning Application** Machine Learning will be applied in order to predict the incidence of SARS-CoV-2 infection based on the serum concentration of AZD7442 at Days 30, 90, 180, 270 and 360 post-baseline for solid tumor and hematologic malignancy patients. Machine Learning will be used to integrate the data from Patient Experience/ COA and QoL surveys with medical records, pharmacy fill/refill and medical insurance claims data for all patients.

SUPPLEMENTAL INFORMATION

23.0 BACKGROUND INFORMATION

23.1 COVID-19 Vaccination in Immuno-Suppressed Cancer Patients

Are immuno-suppressed individuals, including those treated for cancer, adequately protected from SARS-CoV-2 mediated disease post-administration of an FDA Emergency Use Authorization (EUA) or approved COVID-19 vaccine regimen?

In the development of EUA or approved vaccines for COVID-19, immune compromised people and those on immunosuppressant therapies were not systematically enrolled or evaluated for safety and effectiveness of the study vaccine agent. Importantly, this includes patients with a history of cancer who were on active treatment for their disease (chemotherapy, immunotherapy, targeted therapy, any combination of drug therapies, radiation therapy).

This is especially important since patients treated for either solid tumors or hematologic malignancy may not be able to mount the robust vaccine mediated antibody and/or cellular immune responses needed to provide protection against the consequences of potentially life-threatening SARS-CoV-2 infection. These patients are at increased risk of severe illness from SARS-CoV-2.

- In a CDC study of 73 million patients in the USA of whom 273,000 had been diagnosed with cancer in the last year and 16,570 were diagnosed with COVID-19, patients with cancer had greatly increased odds of SARS-CoV-2 infection (adjusted odds ratio [aOR] of 7). Odds of infection were highest for patients with recently diagnosed leukemia (aOR 12.2), non-Hodgkin's lymphoma (aOR 8.5), and lung cancer (aOR 7.7). Mortality was also higher in patients with cancer who developed COVID-19. Indeed, patients with cancer and COVID-19 had a significantly greater risk of mortality (14.9%) than patients with COVID-19 without cancer (5.3%) and patients with cancer without COVID-19 (4.0%).
- For patients diagnosed with a hematologic malignancy in the last 5-years, the increased risk of death has been estimated to be at least 2.5-fold.

Clearly, there is a critical unmet clinical need for protective treatment in immuno-suppressed (i.e., high risk) patients for SARS-CoV-2 infection and subsequent progression to severe pulmonary disease complications including hospitalization or death. The following table

summarizes several recent clinical evaluations conducted in potentially immuno-suppressed patients with either a history of cancer or organ transplant.

SAR-CoV-2 Antibody Response to COVID-19 Vaccine Dosing in Cancer or Organ Transplant Patients

REF	Patient Population	# Pts	Vaccine	Antibody Testing	Results	Comments
Lancet Heme	• Myeloma	93	• Oxford AZ • PFE-BioNTech	• ≥3 weeks post 1st dose • No f/u post 2nd dose.	• Only 13% of myeloma patients had detectable Ab response at ≥3 weeks post 1st vaccination	• No control group.
Tel Aviv Sourasky Med. Ctr. in Israel	• Chronic Lymphocytic leukemia (N=167) • Healthy Controls (N=52)	219	• PFE-BioNTech (100%)	• All CLL and healthy Controls received 2 doses of the Pfizer vaccine approx. 3 weeks post 2nd dose.	• For the 167 CLL pts, 39.5% were Ab positive. • A comparison of 52 CLL and 52 healthy Controls showed 52% Ab positive for CLL pts and 100% Ab pos. for Controls. (p<0.001) • In CLL patients, Ab positive results were: ▪ 16% if currently under treatment ▪ 55.2% if treatment-naïve ▪ 79.2% if obtained clinical remission	• Several weeks after administration of the 2nd dose of PFE- BioNT vaccine, CLL patients continue to have reduced Ab positive response.
London School of Hygiene & Tropical Medicine	• 151 elderly pts with solid cancers (e.g., breast, prostate, heme cancers) and 54 heathy Controls	205	• PFE-BioNTech (100%)	• ≥3 weeks post 1st dose • 3 wks post 2nd dose in limited number of patients.	• 3 weeks after 1st dose, 39% of solid cancer pts and 13% of blood cancer pts had pos. Ab. 97% of Controls were Ab positive. • 5 weeks after dose #1, 43% of solid cancer pts and 8% of blood cancer pts had a positive Ab response. 100% of Controls were Ab pos. • 2 weeks after dose #2 (if given), Ab response was 95% in solid cancer pts. Insufficient data for blood cancer patients.	• Post dose 1 of Pfizer vaccine in immuno-compromised pts, most solid and heme cancer pts remained immunologically unprotected up until a least 5 weeks post the primary injection.
JAMA, Hopkins	• Kidney, liver or heart transplant. No prior COVID-19 or positive SARS-CoV-2 Ab. • Median age 55.9 yrs. • Median time since organ Tx was 6.2 yrs.	436	• Moderna (48%) • PFE/ BioNTech (52%)	• Median of 20 days after dose 1.	• 17% of Transplant pts had detectable Ab at a median of 20 days after dose 1. • 8% had detectable Ab if on an anti-metabolite like MMF or azathioprine	• Organ transplant pts have a high level of immunosuppression relative to COVID-19 Ab production. • Ab response most likely in pts <60 y.o.

23.2 COVID-19 Antibody Production

- It is assumed that immune competent, non-cancer patients who are vaccinated with either a single-dose or two-doses of a COVID-19 EUA or approved vaccine will produce antibodies to the SARS-CoV-2 spike protein at 4 weeks after complete vaccination. It is unclear if the EUA or approval for the Pfizer, Moderna or Janssen vaccines included a large enough cohort of cancer patients to statistically determine if they produced spike protein antibodies and if their antibody levels were comparable to age and gender-matched patients who did not have cancer. This is the dilemma for treated cancer patients: Does their current chemotherapy, immunotherapy, targeted therapy, other therapy, combination therapy and/or radiation therapy prevent them from making antibodies to a level similar to that seen in non-cancer patients?
- Is it possible that cancer patients cannot make antibodies at all or that their level of antibody production is lower than that observed in non-cancer patients?

If so, *can administration of a combination of two, long-acting, monoclonal antibodies provide protection against symptomatic SARS-COV-2 infection as well as COVID-19 related hospitalization and/or COVID-19 related death?*

These questions define the challenge and ultimate goal of this study.

23.3 Additional Dose of Covid-19 EUA Vaccine

The FDA has recently announced that patients who are considered immuno-compromised, such as treated cancer patients, whether they did or did not produce antibodies to SARS-CoV-2 spike protein (RBD-IgG) following their initial vaccination regimen with either the Pfizer, Moderna or Janssen vaccine will be permitted and encouraged to receive an additional dose of COVID-19 vaccine from either Pfizer, Moderna or Janssen. As a result of the recent FDA decision, patients may now receive the additional dose from either the same vaccine manufacturer that provided their original vaccination or from another FDA approved manufacturer (i.e., Janssen original and then Moderna additional). It is intended that this additional dose will provide protection against complications from SARS-CoV-2 infection. The fact remains that without quantitating the RBD-IgG, it is unknown whether this vaccination protocol will be protective for cancer patients.

23.4 AZD7442

AZD7442 (Evusheld) is a combination of two long-acting antibodies (LAABs) - tixagevimab (AZD8895) and cilgavimab (AZD1061) - derived from B-cells donated by convalescent patients after SARS-CoV-2 virus. Discovered at Vanderbilt University Medical Center and licensed to AstraZeneca in June 2020, the human monoclonal antibodies bind to distinct sites on the SARS-CoV-2 spike protein and were engineered and optimized by AstraZeneca with half-life extension and reduced Fc receptor and complement C1q binding. The half-life extension more than triples the durability of its action compared to conventional antibodies and could afford up to 12 months of protection from SARS-CoV-2 infection following a single administration. The reduced Fc receptor binding aims to minimize the risk of antibody-dependent enhancement of disease - a phenomenon in which virus-specific antibodies promote, rather than inhibit, infection and/or disease.
Data published in ***Nature*** in July 2020 showed in preclinical experiments that LAABs were able to block the binding of the SARS-CoV-2 virus to host cells and protect against infection in cell and animal models of disease.

23.5 AZD7442 Clinical Trial Results:

- AZD7442 is being studied in a comprehensive clinical trial program for both prevention and treatment of SARS-CoV-2 infection in over 9,000 participants. Ongoing trials include TACKLE COVID-19, a Phase III treatment trial in an outpatient setting and collaborator treatment trials in outpatient and hospitalized settings. TACKLE included 903 participants in a 1:1 randomization AZD7442 to placebo. AZD7442 is the first LAAB with Phase III data to demonstrate benefit in both prophylaxis and treatment of SARS-CoV-2 infection and is easily administered by IM injection. 90% of enrolled participants were from populations at high risk of progression to severe COVID-19, including those with co-morbidities. The primary analysis was based on 822 participants.
- AZD7442 was assessed using both IM and IV administration routes. Positive high-level results from the TACKLE Phase III COVID-19 treatment trial showed AstraZeneca's AZD7442, a long-acting antibody (LAAB) combination, achieved a statistically significant reduction in severe SARS-CoV-2 infection or death compared to placebo in non-hospitalized patients with mild-to-moderate symptomatic SARS-CoV-2 infection.
- The trial met the primary endpoint, with a dose of 600mg of AZD7442 given by intramuscular (IM) injection reducing the risk of developing severe SARS-CoV-2 infection or death (from any cause) by 50% compared to placebo in outpatients who had been symptomatic for seven days or less. The trial recorded 18 events in the AZD7442 arm (18/407) and 37 in the placebo arm (37/415). The LAAB was well tolerated in the trial.
- In a prespecified analysis of participants who received treatment within five days of symptom onset, AZD7442 reduced the risk of developing severe SARS-CoV-2 infection or death (from any cause) by 67% compared to placebo, with nine events in the AZD7442 arm (9/253) and 27 in the placebo arm (27/251).
- AstraZeneca has submitted a request to the US Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) for AZD7442, its long-acting antibody (LAAB) combination, for prophylaxis of symptomatic SARS-CoV-2 infection. The EUA request filing includes safety and efficacy data from the PROVENT and STORM CHASER Phase III trials and the Phase I trial. AZD7442 was optimized using

AstraZeneca's proprietary YTE half-life extension technology which more than triples the durability of its action compared to conventional antibodies.

- Preliminary 'in vitro' findings demonstrate that AZD7442 has broad anti-COVID activity, and in particular neutralizes recent emergent SARS-CoV-2 viral variants, including Delta and Mu variants.
- In June 2021, AstraZeneca announced results from the STORM CHASER trial assessing the safety and efficacy of AZD7442, a long-acting antibody (LAAB) combination, for the prevention of symptomatic SARS-CoV-2 infection in participants recently exposed to the SARS-CoV-2 virus. The trial did not meet the primary endpoint of post-exposure prevention of symptomatic SARS-CoV-2 infection with AZD7442 compared to placebo.
- Trial participants were unvaccinated adults 18 years and over with confirmed exposure to a person with a case of the SARS-CoV-2 virus within the past eight days. In the overall trial population, AZD7442 reduced the risk of developing symptomatic COVID-19 by 33% (95% confidence interval (CI): -26, 65) compared to placebo, which was not statistically significant.
- The trial included 1,121 participants in a 2:1 randomization AZD7442 to placebo, with 23 cases of symptomatic SARS-CoV-2 infection accrued in the AZD7442 arm (23/749) and 17 cases accrued in the placebo arm (17/372). All participants had a negative SARS-CoV-2 antibody test on the day of dosing to exclude prior infection, and a nasopharyngeal swab was also collected and subsequently analyzed for SARS-CoV-2 by RT-PCR to detect virus.
- Given the importance of finding therapies for SARS-CoV-2 infection and to help interpret trial results during the pandemic, additional analyses were performed and are being communicated.
- In a pre-planned analysis of SARS-CoV-2 PCR positive (detectable virus) and PCR negative (no detectable virus) participants in the STORM CHASER trial, AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 infection by 73% (95% CI: 27, 90) compared with placebo, in participants who were PCR negative at time of dosing. In a post-hoc analysis, in participants who were PCR negative at baseline, AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 infection by 92%

(95% CI: 32, 99) versus placebo more than seven days following dosing, and by 51% (95% CI: -71, 86) up to seven days following dosing.

- In August 2021, AstraZeneca announced preliminary results from the PROVENT pre-exposure prophylaxis trial which showed AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 infection by 77% (95% confidence interval (CI): 46, 90), compared to placebo. Importantly, the trial population included people with co-morbidities and who may be in need of additional protection from SARS-CoV-2 infection. Greater than 75% of participants in PROVENT presented with co-morbidities associated with an increased risk of severe disease or a reduced immune response to vaccination. The trial accrued 25 cases of symptomatic SARS-CoV-2 infection at the primary analysis. AZD7442 was well-tolerated.
- On December 8, 2021, AZD7442 (Evusheld) received initial emergency use authorization (EUA) in the US for the pre-exposure prophylaxis (prevention) of SARS-CoV-2 infection. The Food and Drug Administration (FDA) granted the EUA for AZD7442 for pre-exposure prophylaxis of SARS-CoV-2 infection in adults and adolescents (aged 12 and older who weigh 40kg or more) with moderate to severe immune compromise due to a medical condition or immunosuppressive medications and who may not mount an adequate immune response to SARS-CoV-2 vaccination, as well as those individuals for whom SARS-CoV-2 vaccination is not recommended. Recipients should not be currently infected with or had recent known exposure to a person infected with SARS-CoV-2. As a result of the prevalence of the omicron variants BA.1 and BA.1.1, the EUA was revised and updated on February 24, 2022 to increase the dose of AZD7442 (Evusheld) from 300 mg IM to 600 mg IM.
- AZD7442 is the only antibody therapy authorized in the US for SARS-CoV-2 pre-exposure prophylaxis and the only SARS-CoV-2 antibody delivered as an intramuscular dose (300 mg tixagevimab and 300 mg cilgavimab). About seven million people in the US are immunocompromised and may benefit from AZD7442 for pre-exposure prophylaxis of SARS-CoV-2 infection. This includes people with blood cancers or other cancers being treated with chemotherapy, and those taking medications after an organ transplant or who are taking immunosuppressive drugs for conditions including multiple sclerosis and rheumatoid arthritis.

- The primary data supporting the AZD7442 EUA are from the ongoing PROVENT Phase III pre-exposure prevention trial, which showed a statistically significant reduction (77% at primary analysis, 83% at median six-month analysis) in the risk of developing symptomatic SARS-CoV-2 infection compared to placebo, with protection from the virus continuing for at least six months. Data from the Phase III STORM CHASER post-exposure trial and the AZD7442 Phase I trial also supported the EUA.
- AZD7442 (Evusheld) has demonstrated reduced neutralization activity against the Omicron BA.1 variant (which is B.1.1.529), with a 132- to 183-fold reduction in neutralization activity seen in pseudotyped virus-like particle (VLP) assays and a 12- to 30-fold reduction in neutralization activity seen in authentic virus assays. Likewise, AZD7442 (Evusheld) demonstrated reduced neutralization activity against the Omicron BA.1.1 variant (which comprised 57% of circulating variants in the United States in the week ending 3/19/22 per https://covid.cdc.gov/covid-data-tracker/#variant-proportions), with a 424-fold reduction in neutralization activity seen in VLP assays and a 176-fold reduction in neutralization activity seen in authentic virus assays. Neutralization activity of AZD7442 (Evusheld) against the Omicron BA.2 variant is minimally impacted.
- Of the Omicron binding site substitutions relevant to AZD7442 that have been tested to date in preclinical assays, none have been associated with escape from AZD7442 neutralization. In vitro findings demonstrate that AZD7442 neutralizes other emergent SARS-CoV-2 viral variants, including the Delta and Mu variants.
- As of June 28, 2022 the EUA for AZD7442 has been modified and the dosing interval for AZD7442 has been adjusted to a repeat dosing of 600 mg IM or IV 6 months after the initial dose.

23.6 Population AZD7442 Pharmacokinetic Data

A Phase I pharmacokinetic trial of AZD7442 was conducted in 48 healthy volunteers in the UK in August 2020. A Phase I, double-blind, placebo-controlled pK trial in 40 healthy Japanese volunteers is currently ongoing in Japan. The results of the UK study are not yet published.

23.7 Potential Benefits of AZD7442 Treatment in Immunosuppressed Patients Without Adequate COVID-19 RBD-IgG Antibody Protection

- AZD7442 reduces the risk of hospitalization or death when given to “at risk” patients as pre-exposure prophylaxis for prevention of SARS-CoV-2 infection. Infusion of this antibody mimics naturally produced antibodies generated by subjects infected with the SARS-CoV-2 virus. It is important to systematically evaluate whether use of AZD7442 for prevention of SARS-CoV-2 infection in immunosuppressed patients is protective against the SARS-CoV-2 virus in patients who have low or no antibody response to a COVID-19 vaccine or who, for a myriad of reasons, have not been adequately treated with a COVID-19 vaccine regimen. In patients treated with hematologic malignancy, active, significant immunosuppression is expected and as a result, there will be reduced protection against SARS-CoV-2 infection.
- This Real-World Evidence study will compare the incidence of symptomatic SARS-CoV-2 infection as well as SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death in all cancer patients treated with AZD7442 600 mg IM or IV In addition, the study will compare Quality-of-Life metrics in all cancer patients treated with AZD7442 600 mg IM or IV as well as compare the same Quality-of-Life metrics between solid tumor and hematologic malignancy. To date, 300 mg IM has been tested as the dose for prevention while 600 mg IM has been tested as the dose for treatment post-infection, however, a recent FDA decision has requested that the dose of AZD77442 be increased to 600 mg for prevention.

24.0 REGULATORY OBLIGATIONS

24.1 Informed Consent

- An Informed Consent Form (ICF) will be prepared and approved by the IRB. The ICF will be signed digitally by all participants that can read or understand English at the time of enrollment. A paper version of the ICF may also be signed by a patient (1) if the site requires additional language that is only relevant for their site, (2) if it is needed for local regulatory requirements or (3) is in Spanish. Any updates to the ICF will be communicated to the PI at each study site. The ICF will be prepared in English.
- Before participation in the AISP, the site PI (oncologist) will be responsible for obtaining the digitally signed Informed Consent from the participant (or legally acceptable representative)

after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the program.

- The Informed Consent must be signed electronically and dated by the participant that can read or understand English (or caregiver/witness) and by the person who conducted the informed consent discussion. The digital ICF is retained perpetually in the participant's AISP digital record. (A hard copy of the Informed Consent Form may be provided to the participant (or caregiver/witness) upon request. If the patient only understands Spanish, they will sign the hard copy certified translation of the ICF. If a potential participant is either illiterate or legally blind and does not have a caregiver/witness who has agreed to assist the participant in his/her participation in the AISP, the participant is disqualified from program participation. If a participant is either illiterate or legally blind and has a caregiver/witness, both the participant and the caregiver/witness must electronically sign the ICF to attest that the Informed Consent was understood and that consent was freely given.

24.2 Authorization for Release of Health Information (including Prescriber Records, Pharmacy Records and Claim Information)

- All participants or their caregiver/witness will sign an Authorization for Release of Health Information Form (including Prescriber Records, Pharmacy Records and Medical Insurance Claims) that will be sent to the Prescriber, Pharmacy and Insurance Company that grants permission to release the participant's records to AISP.

24.3 Participant Confidentiality

- In order to comply with HIPAA, the oncologist must ensure that the participant's confidentiality is maintained. On documents submitted to the AISP or its designee, including medical record data, participants will be identified by use of a unique identification code that will be created at the time of participant's registration into the AISP. The participant's unique identification code will be printed on all hard-copy program related documents.

25.0 SAFETY REPORTING

25.1 Safety Overview

All safety events will be captured via Patient Experience/Clinical Outcome Assessment surveys. Safety data such as physical exams, labs and ECG data that are completed during the course of routine clinical care will be available to the MediMergent medical monitor through individual

patient EMR data. Safety events that occur as a result of an unplanned telehealth visit, non-routine office visit, ER/Urgent Care visit or hospitalization will be documented and all source documentation will be collected for review. PCR test results will be reported digitally from the testing lab to the site and the study site will report this result to MediMergent. For all Adverse Events or Serious Adverse Events, a separate data collection form, based on AstraZeneca guidelines, will be completed by the study site and submitted to MediMergent for data input and analysis. Reporting of Adverse Events and Serious Adverse Events will follow FDA Guidelines and AstraZeneca reporting procedures.

25.2 Reporting Guidelines

As this is an EUA pre-approval program, safety reporting guidelines for adverse events and serious adverse events are expected to be followed. In the event that a reportable safety event is identified for one or more patients, MediMergent will immediately notify AstraZeneca of such an event for their reporting purposes. The AISP will report all known safety events that would be reported in a pre-approval clinical trial on an annual basis unless otherwise requested by the FDA. Where expedited reporting is described, the sponsor will submit SUSARs to FDA within FDA required timelines for IND reports.

25.3 Expected SAEs

A program including 1,500 cancer patients followed for at least 12 months would be likely to encounter one or more of the following serious adverse events: sepsis, worsening of underlying cancer, respiratory failure, worsening of COPD, CHF, and death.

For purposes of this study, all hospitalizations and/or deaths will be considered a SAE. Hospitalization for a pre-existing condition that has not worsened (i.e., change a pacemaker battery) or for elective surgery will NOT be considered a SAE unless the hospitalization is prolonged by complications. These events will be collected and reported as SAEs only if the event is more severe than expected for the participant's current clinical status and medical history or if the Investigator feels that it is related to study drug. These will be collected and reported as SAEs as delineated below. Since it will not be possible to delineate in a single participant whether the hospitalization is directly related to SARS-CoV-2 complications, their underlying cancer or treatment for this cancer or could be related to AZD7442 causing more severe disease due to ADE, all hospitalizations for management of acute illness, regardless of cause, will be sent for evaluation by the Clinical Events Committee.

25.4 Investigator Responsibility

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study. Data on hospitalization or death should additionally be recorded on the Safety Report Form, for all relevant sections.

25.5 Recording, Evaluating and Assessing Causality

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in this document.

25.6 ASSESSMENT OF SAFETY

In this study, safety will be assessed by evaluating adverse events, chest x-rays, bacterial cultures and COVID-19 PCR and genomic test results. In addition, important infectious and oncologic safety events will be reviewed from CEC-adjudicated data for SARS-CoV-2 infection, hospitalization and death.

The MediMergent Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities and AstraZeneca.

25.7 ADVERSE EVENTS

25.7.1 Definition of an Adverse Event

- An adverse event is any untoward medical occurrence in a patient that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product and does not necessarily have a causal relationship to study product.
- In this study, any adverse event occurring after the patient has signed the informed consent document and received AZD7442 administration should be processed and reported as an adverse event. An adverse event can be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or any concurrent disease, whether or not considered related to study product. Stable chronic conditions (such as nausea) that are present prior to study entry and do not worsen during the study will not be considered adverse events. Accordingly, an adverse event could include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions.
- drug interactions
- laboratory or diagnostic test abnormalities occurring after the start of the study that result in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant.
  Note: Abnormal laboratory test results during the screening period that preclude a patient from entering the study or from receiving study treatment are not considered adverse events.

- An unsolicited adverse event is an adverse event that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected following completion of the follow-up Patient Experience/COA survey by the participant and review of available medical records.
- Solicited AEs are predefined such as injection site reactions and systemic events for which the participant is specifically questioned in the follow-up Patient Experience/COA survey.

25.7.2 Events that Meet the AE Definition

- Any event that occurred in the first 24 hours post AZD7442 administration
- Symptoms of SARS-CoV-2 infection
- Positive PCR-RT SARS-COV-2 test
- Any unplanned telehealth visit
- Any non-routine office visit

- Any ER/Urgent Care visit
- Signs, symptoms, or the clinical sequelae occurring in the first 24 hours post administration
- If the Investigator considers that there was a causal relationship between treatment with AZD7442 or protocol design/procedures and a patient's underlying disease progression, then this must be reported as an AE or SAE.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will be reported as an AE/SAE even if it was not associated with AE/SAE. Intentional drug overdose with possible suicidal/self-harming intent will be reported as an AE/SAE. Such overdoses will be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

25.7.3 Events that do NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Elective treatment of a pre-existing condition that did not worsen from baseline.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

25.7.4 Method of Detecting AEs and SAEs

- Care should be taken not to introduce bias when detecting AE and/or SAE

- Patient reported outcomes/clinical outcome assessment surveys will be the method for detecting and reporting of adverse events

25.7.5 Recording and Follow-up of AEs and SAEs

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information. It is required for the Investigator to send photocopies or digital files of the participant's medical records to Sponsor in addition to of completion of the required AE/SAE form. There may be instances when medical records for certain cases are requested by pharmacovigilance staff. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in this document.
- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by pharmacovigilance to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide sponsor with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the participant's medical record and submitted as supplemental information to the original report. The Investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

25.7.6 Assessment of Event Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

25.7.7 Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Product Information (Package Insert), for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the participant's medical record that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

25.8 Recording and Reporting Adverse Events

- For the purpose of processing and reporting adverse events, the study period is defined as that time period from signature of the informed consent form through the last visit of the study. AEs may be reported by the study participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), the PI or the Study Coordinator.
- Reporting of non-serious adverse events will be limited to **ONLY** the following:
    - Any event reported by the patient on his/her follow-up survey in the first 24 hours post-administration of AZD7442
    - Any event reported by the patient on his/her follow-up survey that includes an unplanned telehealth visit, unscheduled physician office visit, ER/Urgent Care Visit
    - Any positive SARS-CoV-2 test by RT-PCR reported to the study site
    - Any symptoms of SARS-CoV-2 reported by the patient on any follow-up survey
    - If the Investigator considers that there was a causal relationship between treatment with AZD7442 or protocol design/procedures and a patient's underlying disease progression, then this must be reported as an AE or SAE.
- All AEs will be collected from baseline AZD7442 administration through day 360 post-baseline. SAEs will be collected from dose administration through the day 360 follow-up visit at the time points specified in the Schedule of Activities. However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedure, invasive tests or change in existing therapy) will be recorded from the time participant consents to participate in the study.
- Medical occurrences that begin before the start of study intervention but after obtaining Informed Consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she

considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the sponsor or designee.

- The primary mechanism for reporting SAEs will be the digital SAE Report Form. The site will use the digital SAE data collection tool to report the event within 24 hours. Details to be provided in the Study Specific SAE Reporting Guidelines. The Investigator must show evidence of review and verification of the relationship of each SAE to IP/study participation (causality) within 24 hours of SAE identification. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE, then the site can report this information on the digital SAE form or to the Sponsor by telephone or e-mail. Contacts for SAE reporting will be included in the Study Specific SAE Reporting Guidelines.
- All SAEs reported to the Sponsor (MediMergent) will simultaneously or not later than 24 hours following receipt by the Sponsor, be reported by the Sponsor to AstraZeneca.

25.9 Expedited Reporting

- Sponsor will promptly evaluate all serious adverse events and non-serious adverse events to identify and expeditiously communicate new safety findings to Investigators, IRBs, ECs, and health authorities based on applicable requirements as per the Safety Reporting Plan.
- To determine reporting requirements for single adverse event cases, Sponsor's Medical Monitor will assess the expectedness of these events using the AZD7442 Investigator Brochure and FDA approved prescribing information.
- All Sudden Unexpected Serious Adverse Events (SUSARs) will be submitted by MediMergent to the FDA. MediMergent will simultaneously send a copy of the initial SUSAR report and all follow-up reports to AstraZeneca.
- Where expedited reporting is described, the sponsor will submit SUSARs to FDA within FDA required timelines for IND reports.

25.10 Study Medication

- All adverse events that occur during the defined study period must be recorded in the patients' medical record regardless of the severity of the event or judged relationship to study medication. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state.
- A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single

diagnosis. The onset and end dates, duration (in case of adverse event duration less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event should be recorded in the patients' medical record.

25.11 Severity of an Adverse Event

- Standard toxicity grading according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) will be used to grade all AEs.
- The severity of each adverse event must be recorded as 1 of the choices on the following scale:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

25.12 Relationship of an Adverse Event to AZD7442

The relationship of an adverse event to AZD7442 is characterized as follows:

Definition of Adverse Event Relationship to AZD7442

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to AZD7442.	The relationship of an adverse event to AZD7442 may be considered to have no reasonable possibility if it is clearly due to extraneous cause(s) such as: • it does not follow a reasonable temporal sequence from the administration of AZD7442. • it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
Reasonable possibility (related)	This category applies to those adverse events for which there is evidence to suggest a causal relationship between the drug and the adverse even after careful medical consideration at the time they are evaluated, a connection with AZD7442 administration was felt with a high degree of certainty to be related to AZD7442.	The relationship of an adverse event to AZD7442 may be considered reasonable possibility related if: • it follows a reasonable temporal sequence from administration of AZD7442 and/or • conveys in general that there are facts (evidence) or arguments to suggest a causal relationship.

25.13 SERIOUS ADVERSE EVENTS

25.13.1 Definition of a Serious Adverse Event (SAE)

A SAE is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death

- a life-threatening adverse event (*i.e.*, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- in-patient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that inpatient hospitalization and/or prolongation of existing hospital stay occurred as a consequence of the adverse event. In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered SAEs.
- a persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions). The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent the outcomes listed in this definition. Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm,

blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

- An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

25.13.2 Serious criteria pertaining to hospitalization should include the following:

- Any formal inpatient admission (even if less than 24 hours).
- Chronic or long-term inpatient admission: transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit)

Serious criteria pertaining to hospitalization should NOT include the following:

- Emergency Room visits
- Outpatient/same-day/ambulatory procedures and observation/short- stay units
- Hospice facilities and Respite care (e.g., caregiver relief)
- Rehabilitation facilities, skilled nursing facilities, nursing homes, custodial care facilities.

The study period for the purposes of serious advent event reporting is defined as the period from when the patient provides written informed consent to participate in the study until the patient completes the end of the follow-up period or withdraws from the study.

25.13.3 Expectedness

- A SAE that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

25.13.4 Regulatory Reporting Requirements for SAEs

Sponsor is acting on behalf of AstraZeneca for the purposes of safety reporting for this study.

- Prompt notification by the Investigator to Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of study intervention under clinical investigation are met.
- Sponsor has a legal responsibility to notify AstraZeneca, local regulatory authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) as outlined in the ESRP will review and then file it along with the Investigator Brochure. The Sponsor will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator Safety Reports must be prepared for Suspected Unexpected Serious Adverse Reactions (SUSAR) according to local regulatory requirements and AstraZeneca policy and forwarded to Investigators as necessary.

25.13.5 Deaths

- All deaths will be SAEs and will require completion of the SAE Report Form. This form includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.
- The Death related SAE form should be completed after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

25.13.6 Investigator Responsibility

To satisfy regulatory requirements, all SAEs that occur during the study (including the protocol-defined follow-up period) regardless of judged relationship to treatment with study product must be reported to MediMergent by the investigator within 24-hours of when the investigator learns about it or, if the event occurs on a weekend or national holiday, on the next working day. The following information should be provided to record the event accurately and completely:

- study name or number
- investigator and study site identification
- patient number
- patient initials
- name of SAE(s)
- investigator's assessment of the relationship of the SAE to the study drug (no reasonable possibility or reasonable possibility)
- Additional information may include the following:
    - age and gender of patient
    - date of study drug administration

- date and amount of administered dose of study product
- onset date and end date of SAE
- description of clinical course of SAE
- action taken
- outcome if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory test data, or other diagnostic test data

- medical history
- if the adverse event results in death
    - cause of death (whether or not the death was related to study product)
    - autopsy findings (if available).

The investigator must ensure that the IRB is also informed of the event in accordance with local regulations.

Note: Although pregnancy is not a SAE, the process for reporting a pregnancy is the same as that for reporting a SAE but using the pregnancy form.

25.14 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Adverse events related to signs, symptoms or positive RT-PCR testing for SARS-CoV-2 infection, and/or resulting in hospitalization should be reported as an AE or SAE. If the Investigator considers that there was a causal relationship between treatment with AZD7442 or protocol design/procedures and a patient's underlying disease progression, then this must be reported as an AE or SAE.

For example, the following constitute events meeting the AE definition and that should be considered as expected progression, signs, or symptoms of COVID-19:

- hypoxemia requiring supplemental oxygen
- hypoxemia requiring non-invasive ventilation or high flow oxygen devices
- respiratory failure requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

NOTE: If either of the following conditions apply, then the event must be recorded and reported as an AE or SAE (instead of a disease-related event):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the natural history of the disease, or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with study treatment(s).

25.15 Adverse Events of Special Interest

Adverse events of special interest are defined in the study protocol as relevant known toxicities as a result of signals observed from previous studies in the non-clinical programs of AZD7442. These will be updated during the course of the study based on accumulating safety data. AESI include:

- Reactions including hypersensitivity reactions occurring on same day as vaccination
- Local injection site reactions
- Coronary Ischemia
- Myocardial Infarction
- Congestive Heart Failure
- Thrombotic events-coronary, cerebral, abdominal, pulmonary or peripheral vascular

25.16 Systemic Reactions and Hypersensitivity Reactions

Please refer to local or institutional guidelines for monitoring relevant adverse events encompassing hypersensitivity, angioedema, anaphylaxis, acute anaphylactic shock and minor allergic episodes. Pre-medications will be permitted at the Investigator's discretion and will be appropriately documented.

25.17 Local infusion/injection site reactions (LI/ISR)

Injections may be associated with local reactions (e.g., swelling, induration, pain, bleeding, numbness). Local tolerability assessment is defined in this document.

25.18 Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study at any time at the discretion of the Investigator. The patient will be monitored until the event has resolved or stabilized, until a determination of a cause related to the study product is made, or until the patient is referred to the care of a local health care professional. Additional reports must be provided when requested.

25.19 Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment for the emergency to protect patient safety has been administered, the investigator or other physician in attendance in such an emergency must contact the individual patient as soon as possible to discuss the circumstances of the emergency. The investigator will decide whether the patient should continue to participate in the study. Any protocol deviation related to adverse events should be noted in the patients' medical record along with the reason for such deviations.

25.20 Pregnancy

Pregnancies that occur during the study are to be reported immediately to the Investigator of this protocol and the Investigator must provide the MediMergent Pharmacovigilance team with this information. The process for reporting a pregnancy is the same as that for reporting a serious adverse event.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until day 360 post-baseline.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to Sponsor within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy and for up to 1 year after birth. The Investigator will collect follow-up information on the participant and the neonate/child and the information will be forwarded to Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to MediMergent as described in this document. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

25.21 Laboratory Tests

Laboratory test results for this protocol (RBD-IgG, T-cell and serum AZD7442 concentration data) are for research purposes only and do not have a defined normal range. The results do not need to be reviewed, interpreted or signed off by the Investigator.

An adverse event includes a laboratory or diagnostic test abnormality that requires medical treatment or further diagnostic work-up.

25.22 Clinical Endpoints Committee

An independent **Clinical Endpoints Committee (CEC)** will adjudicate all potential clinical events relating to symptomatic SARS-CoV-2 infection including SARS-CoV-2 related hospitalization and/or SARS-CoV-2 related death in accordance with pre-specified criteria.

25.23 MediMergent Pharmacovigilance Team

The MediMergent Pharmacovigilance team will be responsible for oversight of all safety data and for determining the expectedness of all SAEs, expedited reporting of individual cases, and safety updates to regulatory authorities. During the course of the study, SAEs and pregnancies will be entered into a pharmacovigilance safety database, which will be separate from the clinical database. The pharmacovigilance safety database has restricted user access and is controlled.

26.0 LANGUAGE

All participant entries for the baseline and follow-up surveys must be completed in English or Spanish. All written information and other material to be used by participants and investigative staff must use vocabulary and language that are clearly understood by the program participants.

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