Title: Phase I, Randomized, Open Label, Three-arm, Single Dose, Parallel Group Study to Compare AZD7442 (AZD8895 + AZD1061) Pharmacokinetic Exposure Following Intramuscular Administration as a Coformulation versus Administration From Two Separate Vials of the Individual Monoclonal Antibodies in Adult Healthy Participants

Sponsor Study Code: D8850C00009

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AstraZeneca

D8850C00009

Phase 1, Randomized, Open label, Three-arm, Single Dose,Parallel Group Study to Compare AZD7442 (AZD8895 + AZD1061) Pharmacokinetic Exposure Following Intramuscular Administration as a Co-formulation versus Administration from Two Separate Vials of the Individual Monoclonal Antibodies in Adult Healthy Participants

Statistical Analysis Plan

Version: 5.0

Parexel Project Number: 265185

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
AUC	Area under the serum concentration-time curve
AUC0-31d	Area under the serum concentration-time curve from time zero to 30 days post-dose
AUC0-61d	Area under the serum concentration-time curve from time zero to 60 days post-dose
AUC0-91d	Area under the serum concentration-time curve from time zero to 90 days post-dose
AUC0-181d	Area under the serum concentration-time curve from time zero to 180 days post-dose
AUCinf	Area under the serum concentration-time curve from time zero to infinity
AUClast	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
BMI	Body mass index
CI	Confidence interval
CL/F	Apparent total body clearance of drug from serum after extravascular administration
Cmax	Maximum observed serum (peak) drug concentration
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	U.S. Food and Drug Administration
GMT	Geometric mean titer
gSD	Geometric standard deviation
ICF	Informed consent form

Abbreviation or special term	Explanation
ICH	International Council for Harmonisation
IM	Intramuscular
IMP	Investigational medicinal product
λz	Apparent terminal elimination rate constant
LLOQ	Lower Limit of Quantification
GLSM	Geometric least square means
mAb	Monoclonal antibody
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
nAb	neutralizing antibodies
NR	Not reportable
NQ	Not quantifiable
PD	Pharmacodynamics
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PT	Preferred term
Q1	first quartile
Q3	third quartile
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Standard error
SOC	System organ class
t½λz	Half-life associated with terminal slope (λz) of a semilogarithmic concentrationtime curve
tlast	time of last quantifiable concentration
TLFs	Tables, listings, figures
Tmax	time to maximum observed serum concentration
ULOQ	Upper Limit of Quantification

Abbreviation or special term	Explanation
Vz/F	volume of distribution based on terminal phase after extravascular administration

AMENDMENT HISTORY

Date	Brief description of change
07 Dec 2021	Initial approved SAP
10 Mar 2022	"Fully Vaccinated" changed to "Vaccinated" Added SoC to the description of adverse events causality summary
08 Jul 2022	Removal of IA
26 Jul 2023	Addition of text for sensitivity analysis
27 Oct 2023	Added text to Section 4.14 for additional statistical analysis and corresponding forest plot figures. Minor updates throughout text.

1 INTRODUCTION

This statistical analysis plan (SAP) documents the variables to be analysed and the statistical methods of the planned analyses and outlines the statistical programming specifications for the tables, figures and listings (TFLs). Any deviations after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP addendum and discussed in the Clinical Study Report (CSR). Any changes to this SAP prior to database lock will be described in a new version of the SAP.

The analyses described in this SAP are based upon the following study documents:

- Clinical Study Protocol (CSP), Version 1.0 (September 21, 2021)

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

Primary Objective:	**Endpoint:**
To evaluate the PK comparability between AZD7442 administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (clonal cell line material of AZD8895 and AZD1061) of the individual monoclonal antibodies (mAbs) in healthy adult participants	• AUCinf (final analysis), AUClast, Cmax, and AUC0-91d
To evaluate the PK comparability between AZD7442 administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (cell pool material of AZD8895 and AZD1061) of the individual mAbs in healthy adult participants	• AUCinf (final analysis), AUClast, Cmax, and AUC0-91d
To evaluate the PK comparability between the clonal cell line material and the cell pool material of AZD7442 administered as two	• AUCinf (final analysis), AUClast, Cmax, and AUC0-91d

separate sequential IM doses (AZD8895 and then AZD1061) of the individual mAbs in healthy adult participants

2.2 Secondary Objectives

Secondary Objectives:	Endpoint:
To examine the serum PK profiles of AZD7442 when administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants	• Tmax, AUC0-31d, AUC0-61d, tlast, and for final analysis AUC0-91d, AUC0-181d, t½λz, CL/F, and Vz/F
To further assess the safety of AZD7442 when administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants	• AEs including serious AEs and AEs of special interest • Laboratory assessments (hematology, clinical chemistry, and urinalysis) • Physical examination • Electrocardiogram • Vital signs (systolic and diastolic blood pressure, pulse rate)
To evaluate the anti-drug antibody (ADA) responses to AZD7442 in serum following administration of a single IM dose as a co-formulation (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants	• Incidence and titers of anti-AZD8895 and anti-AZD1061 antibodies

2.3 Exploratory Objectives

Exploratory Objectives:	Endpoint:
CCI [redacted]	• CCI [redacted]

Exploratory Objectives:	Endpoint:
CCI [redacted]	

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open label, randomized, three-arm, parallel group, single dose, study in healthy participants (males and females), performed at multiple study centers to assess pharmacokinetic (PK) comparability between different formulations of AZD7442, which is a combination of two individual monoclonal antibodies (mAbs), AZD8895 and AZD1061. Each participant will receive AZD7442 as either a single IM dose (co-formulation; AZD8895 + AZD1061) from a single vial or as two separate IM doses of the individual mAbs (AZD8895 and then AZD1061) from two separate vials from either clonal cell line material or cell pool material as follows:

- Treatment A: 300 mg (total protein) AZD7442 as a single IM dose (co-formulation of 150 mg AZD8895 + 150 mg AZD1061) (clonal cell line material).
- Treatment B: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (clonal cell line material).
- Treatment C: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (cell pool material).

Additionally, within each of the treatment groups, participants will be randomized 1:1:1 to one of the three injection sites:

- Lateral thigh,
- Gluteal dorsal,
- Gluteal ventral.

Further, participants will be stratified based on the body weight and vaccination status at randomization as follows:

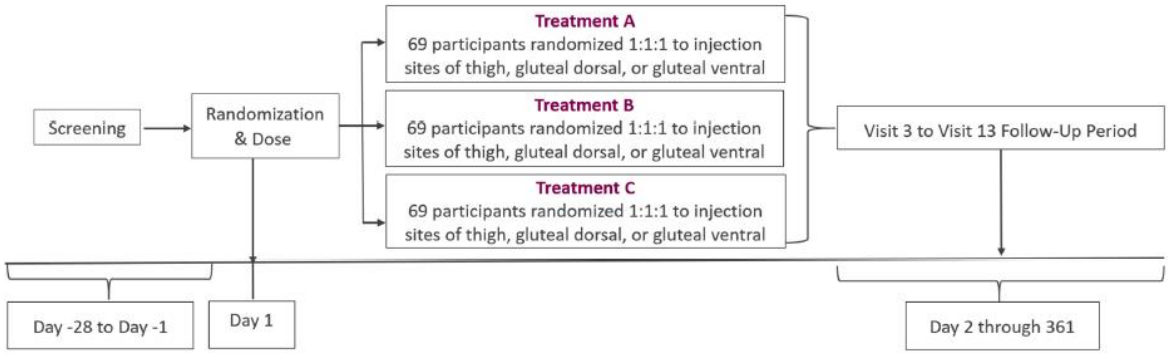
- Body weight at randomization: < 70 kg; 70 to < 80 kg; and ≥ 80 kg
- Anti-SARS-CoV-2 vaccination status at randomization: non-vaccinated or vaccinated (with one or more locally approved/authorized COVID-19 vaccine doses)

The study will comprise of:

- A Screening Period of up to 28 days that requires participants to visit the Clinical Unit (Visit 1).
- A Treatment Period of 1 day (Day 1; Visit 2) during which participants will be admitted to the study Clinical Unit and be randomized to receive their dose of IMP (AZD7442 as either a single IM dose or two separate IM doses). Participants will stay at the study clinic for at least 8 hours after dosing and will be discharged from the Clinical Unit at the discretion of the investigator, on the same day.
- A Follow-up Period of approximately 1 year consisting of regular visits to the study Clinical Unit starting from the day after dosing, Day 2 through to Day 361. The subsequent study visits total in 11 outpatient follow-up visits (Visits 3 to 13).

The end of study is defined as the last participant's last visit to the study Clinical Unit.

Figure 1 Study Schema



IM: Intramuscular

3.2 Planned Analyses

The details of the analyses planned during the conduct of this study is outlined in the following table.

Analysis	Trigger
Final Analysis	The data cut-off for final analysis will be after the last participant's last visit to the study Clinical Unit. The analysis will be performed after Clinical Database Lock.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

Analyses will be performed by Parexel, except for the derivation of the PK parameters, which will be performed by Labcorp.

Continuous data, if not otherwise specified, will be summarized in terms of number of non-missing observations (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

Categorical variables will be summarized using frequencies and percentages.

The minimum and maximum values will be reported to the same number of decimal places as the individual values. The mean, median, SD, Q1 and Q3 will be reported to one more decimal place than the raw data recorded in the database and the same level of precision will be used for standard error (SE), and confidence intervals (CI). In general, the maximum number of decimal places reported shall be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Rounding should be the last operation in the treatment of data. There should be no rounding of intermediate results during the calculation of any derived value. Zeros at the end of a number should be retained.

All results will be presented by treatment period (if applicable) and overall with descriptive statistics.

CIs and p-values, when presented, will generally be constructed at the 2-sided 95% level, if not stated otherwise in the specific analysis description.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001". P-values equal to 1.000 will be reported as >0.999.

When change from baseline will be described, baseline is defined as the last reliable value prior to administration of the first dose of each treatment period.

Change from baseline will be defined as the value post-dosing minus the baseline defined, for each timepoint.

Percent change from baseline will be calculated as:

Percent change from baseline = ((visit value – baseline value)/baseline value) ×100

Depending on the extent of any impact, listings and/or summary tables of data relating to participants diagnosed with COVID-19 and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other protocol deviations) may be generated.

All other requirements and specifications for programming and presentation of TFLs will be specified in the TFL shells document.

4.3 General Variables

4.3.1 Study Day Definitions

Study day 1 is defined as the date of first dose of study treatment.

For visits (or events) that occur on or after first dose of study treatment, study day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] – date of first dose of study treatment). There is no study day 0 defined for this study.

For listings (such as for AEs) that include the derivation of "days since last dose", this is defined as (event date – date of last dose) where "date of last dose" is defined as the date of dosing immediately preceding the event occurrence. Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from last dose of study treatment.

4.3.2 Time Windows

A windowing convention will be used to determine the analysis value for a given study visit for visit-based assessments, which are as follows:

- serum sample for AZD7442 pharmacokinetic assessments (PK)
- serum sample for AZD7442 anti-drug antibodies (ADA) assessments
- serum sample for CCI [redacted]
- clinical chemistry, hematology, coagulation and urinalysis
- vital signs
- electrocardiogram (ECG)

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an odd number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

One or more results for a particular variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. In the event that two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

The visit windows are defined in the following tables.

Table 1a: Time window for serum sample for AZD7442 pharmacokinetic assessments

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 2	2	2 — 3
Day 5	5	4 — 6
Day 8	8	7 — 11
Day 15	15	12 — 18
Day 22	22	19 — 26
Day 31	31	27 — 45
Day 61	61	46 — 75

Day 91	91	76 — 135
Day 181	181	136 — 225
Day 271	271	226 — 315
Day 361	361	≥316

Table 1b: Time window for serum sample for AZD7442 anti-drug antibodies

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 31	31	15 — 60
Day 91	91	61 — 135
Day 181	181	136 — 270
Day 361	361	≥271

Table 1c: Time window for serum sample for CCI [redacted]

CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CCI [redacted]	[redacted]	[redacted]

Table 1d: Time window for clinical chemistry, hematology, coagulation, urinalysis, vital signs and ECG

Visit	Day Relative to Dose	Visit Window (Study Day)
Screening	≤ 1	≤ 1
Day 1	1	1
Day 5	5	2 — 6
Day 8	8	7 — 19
Day 31	31	20 — 196
Day 361	361	≥196

4.3.3 Handling of Missing Data

In general, other than for the below described, or where otherwise specified in the particular analysis, missing data will not be imputed and will be treated as missing.

4.3.3.1 Imputations of Partial Dates

Adverse events start dates

- AEs with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.
- AEs with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- Missing day: impute with the 1st of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
- Missing month: impute with the 1st month in which IMP was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known

year part is not a year in which IMP was administered, then the month will also be imputed with JAN.

- Missing day and month: impute with the day and month of dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered, then the day and month will also be imputed with 01JAN.
- Missing year: impute with the year of dosing.
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

When imputing a start date care should be taken to ensure the start date is sensible, i.e., prior to the end date.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for AEs or concomitant for medications. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, durations and study days will not be calculated.

4.3.3.2 Imputation of Adverse Events in tabulations

- AEs with unknown intensity will be treated as “severe” for the tabulations.
- AEs with unknown relationship will be treated as “related” for the tabulations.
- AEs with unknown seriousness will be treated as “serious” for the tabulations.

There will be no imputation of AE data for the data listings. All data will be listed as recorded in Medidata Rave.

4.3.3.3 Imputation of PK elapsed times

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the raw data. If actual elapsed times are missing, nominal times will be used.

4.3.3.4 Imputations of Laboratory Values

Values of the form “< x.x” (i.e., below the lower limit of quantification [LLoQ]) or “> x.x” (i.e., above the upper limit of quantification [ULoQ]) will be imputed as “x.x” in the calculation of summary statistics but displayed as “< x.x” or “> x.x” in the listings.

4.4 Software

All report outputs will be produced using SAS® version 9.4 in a secure and validated environment.

The PK parameters will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara).

4.5 Analysis Sets

4.5.1 Randomized set

The Randomized Set will consist of all participants randomized into the study.

4.5.2 Safety analysis set (SAF)

The safety analysis set will include all participants who were randomized and received any amount of IMP.

4.5.3 PK analysis set (PKS)

The PK analysis set will consist of all participants in the safety analysis set who received IMP and have evaluable serum PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

Data from participants for whom the pre-dose concentration is > 5% of their respective Cmax for AZD8895 or AZD1061 may be excluded from the summary tables and figures and from the statistical analysis.

4.5.4 CCI

CCI

4.5.5 AZD8895 ADA Evaluable Analysis Set

The AZD8895 ADA Evaluable Analysis Set will include participants with at least 1 baseline and 1 post-baseline AZD8895 ADA measurement.

4.5.6 AZD1061 ADA Evaluable Analysis Set

The AZD1061 ADA Evaluable Analysis Set will include participants with at least 1 baseline and 1 post-baseline AZD1061 ADA measurement.

4.5.7 AZD7442 ADA Evaluable Analysis Set

The AZD7442 ADA Evaluable Analysis Set will include participants with either at least 1 baseline and 1 post-baseline AZD8895 or at least 1 baseline and 1 post-baseline AZD1061 ADA measurement.

4.5.8 Analysis sets summary

Upon database release, protocol deviation and the analyses population will be produced for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which participants and/or participant data will be excluded from certain analyses. Decisions made regarding the exclusion of participants and/or participant data from analyses will be documented and approved by the sponsor.

A summary on which analysis set will be used for each outcome variable is provided in Table 2.

Table 1 Summary of Outcome Variables and Analysis Sets

Outcome Variable	**Analysis Set**
PK Data	
PK concentrations	PKS
PK parameters	PKS
Study Population/Demography Data	
Disposition of participants	Randomized
Demography characteristics	SAF
Baseline and disease characteristics	SAF
Important protocol deviations	SAF
Medical history	SAF
Concomitant medications	SAF
Safety Data	
Exposure	SAF
AEs	SAF
Laboratory measurements	SAF

Outcome Variable	Analysis Set
Vital signs	SAF
ECGs	SAF
Injection site reaction	SAF
Anti-drug antibodies	
ADA assessments	AZD8895 ADA Evaluable Analysis Set; AZD1061 ADA Evaluable Analysis Set; AZD7442 ADA Evaluable Analysis Set
CCI [redacted]	
CCI [redacted]	CCI [redacted]

4.6 Study Participants

4.6.1 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion.

Participant disposition will be listed and summarised for the Randomized Set.

A randomization listing will be presented and include the following: each participant's randomization number, the participant's full enrollment number, the treatment to which the participant has been randomized and the country where the study Clinical Unit is located.

Participants and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Participant disposition will be summarized and will include the following information: number of participants randomized and dosed, number and percentage of participants completing the study and the number and percentage of participants who were withdrawn (including reasons for withdrawal).

Participant discontinuations will be listed including the date of study exit, duration of on-study follow-up, duration of safety follow-up and reason for discontinuation. A listing of informed consent response will also be presented.

4.6.2 Protocol Deviations

Important protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. A full list of protocol deviations can be found in the study-specific Protocol Deviation Specification.

Deviations from the protocol will be assessed as “important” or “not-important” during a data review meeting prior to database lock. Important deviations from the protocol may lead to the exclusion of participants or data from the PKS. Deviations will be assessed before database lock.

Important deviations will include the following at a minimum:

- Violation of key inclusion and/or exclusion criteria
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.
- Dosing deviations that are expected to influence the measurement of the primary endpoint.
- Time window deviations for safety and/or PK assessments
- Other procedural and study conduct deviations recorded by the study Clinical Unit on a protocol deviation log

All important protocol deviations will be listed.

4.7 Demographic and baseline characteristics

Demographic and baseline characteristics will be listed and summarised for all participants in the SAF by treatment group:

- Demographics (age [years], gender, race and ethnicity)
- Participant characteristics at baseline (height [cm], weight [kg], and body mass index [BMI] [kg/m^2])
- Stratification factors, as reported on the CRF (weight group and vaccination status)

The denominator for percentages will be the number of randomized participants.

4.8 Medical and surgical history

Disease related medical/surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All disease related medical/surgical history (past and current) will be listed including visit, description of the disease/procedure, MedDRA SOC, MedDRA PT, start date and stop date (or ongoing if applicable) .

4.9 Prior and concomitant medications

Information on any treatment that the participant is receiving at the time of enrolment and all concomitant medications with reasons for the treatment, will be recorded in the Electronic Case Report Form (eCRF).

Prior and concomitant medications are defined based on start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to first dose of study treatment.
- Concomitant medications are those with no stop date (ongoing) or a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).

Prior and concomitant medications will be listed for the SAF using the AstraZeneca March 2022 dictionary. They will be listed by participant and will include the following information: reported name, preferred term, the route of administration, dose, frequency, start date/time, duration, and indication.

The duration of the medication will be calculated as:

Duration = (end date/time) – (start date/time) +1

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

4.10 Pharmacokinetics

4.10.1 Analysis and Data Conventions

All summary tables and figures of PK concentrations and parameters, as well as all statistical analyses will be presented for the PKS, unless otherwise indicated. All PK listings and individual PK concentration versus time figures will be based on SAF, unless stated otherwise.

For PK parameters other than tmax and tlast, the following descriptive statistics will be presented: n, geometric mean (gmean), geometric standard deviation (gSD), geometric coefficient of variation (gCV), arithmetic mean, arithmetic standard deviation (SD), median, minimum, and maximum. For tmax and tlast, only n, median, minimum, and maximum will be presented.

The geometric mean will be calculated as e^{μ} where μ is the mean of the data on the logarithmic scale.

The geometric CV will be calculated as $100 \times \sqrt{\exp s^2 - 1}$ where s is the SD of the data on the logarithmic scale.

gmean ± gSD will be derived as $\exp(\mu \pm s)$ where μ and s has been defined as above.

Individual concentrations below the Lower Limit of Quantification (LLOQ) of the bioanalytical assay will be reported as NQ (Not Quantifiable) in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings.

Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean, gmean ± gSD and gCV% will be set to NC. The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, minimum, median and maximum will be reported as NQ and the gCV% and gmean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter (e.g. Cmax, Cmin, Clast) to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

If data are available for less than three participants, no summary statistics other than minimum, maximum and n will be presented.

4.10.2 Serum Concentrations

For the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061), the serum concentrations for each scheduled time point will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category using appropriate descriptive statistics, based on the PKS. A listing of all concentration-time data, ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations will be presented by treatment group (with injection site, and bodyweight category listed) for all participants in the SAF.

For AZD7442 concentration derived as the sum of AZD8895 and AZD1061 concentrations, the following cases of <LLOQ hold:

AZD1061 concentration	**AZD8895 concentration**	**Result of AZD7442 concentration**
<LLOQ	<LLOQ	<LLOQ
<LLOQ	XX	XX
YY	<LLOQ	YY
YY	XX	YY+XX
Missing	XX	Missing
YY	Missing	Missing
Missing	Missing	Missing

4.10.3 Pharmacokinetic Parameters

All PK parameters for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061) will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category using appropriate descriptive statistics, based on the PKS.

All reportable PK parameters for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061), including individual diagnostic and λz-related parameters, will be listed for each participant by treatment group (with injection site, and bodyweight category listed) based on the SAF.

Table 3 PK Parameters

Parameter	Definition
AUCinf	Area under serum concentration-time curve from time zero to infinity (final analysis only)
AUClast	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC0-31d	Area under the serum concentration-time curve from time zero to 30 days post-dose
AUC0-61d	Area under the serum concentration-time curve from time zero to 60 days post-dose
AUC0-91d	Area under the serum concentration-time curve from time zero to 90 days post-dose
AUC0-181d	Area under the serum concentration-time curve from time zero to 180 days post-dose
Cmax	Maximum observed serum concentration
tmax	Time to reach maximum observed serum concentration
t½ λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve (final analysis only)
tlast	Time of last quantifiable serum concentration
CL/F	Apparent total body clearance of drug from serum after extravascular administration (final analysis only)
Vz/F	Volume of distribution (apparent) based on terminal phase after extravascular administration (final analysis only)

The following diagnostic parameters will be provided as appropriate for the final analysis:

Parameter	Definition
λz	Apparent terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination

Parameter	Definition
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

4.10.4 Primary Endpoint

The primary endpoints for evaluation of pharmacokinetic comparability will be assessed using a linear fixed effects analysis of variance model with the natural logarithm of primary PK parameters (eg, AUCinf [for final analysis only], AUClast, Cmax and AUC0-91d [for IA only]) for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061) as the response variables, treatment, injection site, anti-COVID-19 vaccination status (as reported on the CRF), and continuous baseline body weight on the log scale as fixed effects and participant as a random effect.

Transformed back from the logarithmic scale, geometric least square means (GLSM) together with CIs (2-sided 95%) will be estimated and presented by treatment. Also, ratios of geometric least square means together with CIs (2-sided 90%) will be estimated and presented.

The following treatment comparisons will apply:

- Treatment A vs Treatment B
- Treatment A vs Treatment C
- Treatment B vs Treatment C

where:

- Treatment A: 300 mg (total protein) AZD7442 as a single IM dose (co-formulation of 150 mg AZD8895 + 150 mg AZD1061) (clonal cell line material).

- Treatment B: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (clonal cell line material).
- Treatment C: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (cell pool material).

One statistical model will be fitted for each PK parameter, including all study data. Estimating parameters for the comparisons listed above will be done from this one model making use of the appropriate contrasts.

A variance component covariance structure will be used for the within-participant errors. Degrees of freedom will be determined using Kenward-Roger approximation.

If the estimating algorithms do not converge, these covariance structures will be tried: first-order autoregressive, compound symmetry, unstructured and Toeplitz.

Missing values will not be imputed. In this analysis it is thus assumed that any missing values are missing at random (MAR).

The following figures, in black and white, will be generated:

Figure	Analysis set	Presented by
Individual profiles, serum concentration versus actual elapsed time data – linear and semi-log scale, separate plot for each participant for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061)	SAF	n/a
Combined individual serum concentration versus actual elapsed time data – linear and semi-log scale for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061)	PK	• treatment
GMean (+/-gSD), serum concentration versus planned nominal time data – linear and semi-log scale for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs	PK	• treatment • treatment and injection site • treatment and bodyweight category

of AZD7442 (AZD8895 + AZD1061)		• treatment, injection site, and bodyweight category
Individual PK parameter with geometric mean (95% CI) for Cmax, AUClast, AUCinf (for the final analysis only), and AUC0-91d (for the IA only) for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061)	PK	• treatment • treatment and injection site • treatment and bodyweight category • treatment, injection site, and bodyweight category
Geometric least square means with 95% CIs for all treatments	PK	• primary PK parameters
Geometric least square means ratios with 90% CIs for all comparisons	PK	• primary PK parameters

4.10.4.1 Methods to minimize bias

This is a controlled open-label study, the sponsor will be blinded to summary outputs until formal database locks occur in order to minimize bias.

4.10.4.2 Adjustment for multiple comparisons

No adjustments for multiple comparisons or multiplicity will be made.

4.10.5 Secondary Endpoints

4.10.5.1 PK Parameters

The following PK parameters will be listed and summarised by means of descriptive statistics:

- Tmax, AUC0-31d, AUC0-61d, tlast, and for final analysis AUC0-91d, AUC0-181d, t½λz, CL/F, and Vz/F
- Diagnostic parameters: λz, λz lower, λz upper, λzN, λz span ratio, Rsq adj, AUCextr

4.10.5.2 Immunogenicity

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in CSP section 3.1. ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of nAb will be tested for all ADA-positive samples. The nAb results will be reported as positive or negative. A participant is defined as being ADA-positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise the participant is defined as ADA negative.

The number and percentage of participants in the following ADA categories in each treatment group will be determined for the individual mAbs AZD8895 and AZD1061, as well as for AZD7442 based on the respective ADA evaluable analysis set (Section 4.5). The number of ADA-evaluable participants in the treatment group will be used as the denominator for percentage calculation.

• ADA positive at any visit (at baseline and/or post-baseline). The percentage of these participants in a population is known as ADA prevalence. For AZD7442, either AZD8895 and/or AZD1061 is ADA positive.
• Treatment-emergent (TE) ADA positive (either treatment-induced ADA positive or treatment-boosted ADA positive). The percentage of these participants in a population is known as ADA incidence. For AZD7442, either AZD8895 and/or AZD1061 is TE ADA positive.
• Non-TE ADA positive, ADA-positive but not fulfilling the conditions for TE ADA-positive.
• Treatment-induced ADA positive:
  - For AZD8895, ADA negative at baseline and ADA positive at >=1 post-baseline assessments with ADA titer >=160.
  - For AZD1061, ADA negative at baseline and ADA positive at >=1 post-baseline assessments with ADA titer >=80.
  - For AZD7442, either AZD8895 and/or AZD1061 is treatment-induced ADA positive.
• Treatment-boosted ADA positive (baseline ADA titer that was boosted by ≥4-fold following drug administration). For AZD7442, either AZD8895 and/or AZD1061 is treatment-boosted ADA positive.
• ADA positive post-baseline and positive at baseline.
• ADA positive at baseline and not detected post-baseline.
• TE ADA persistently positive, defined as TE ADA positive participants having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment. For AZD7442, either AZD8895 and/or AZD1061 is TE ADA persistently positive.
• TE ADA transiently positive, defined as treatment-emergent ADA positive participants having at least one post-baseline ADA positive measurement and not fulfilling the conditions for TE ADA persistently positive.

To evaluate the ADA responses to AZD7442 in serum the following analyses will be presented:

- A summary of the number and percentage of participants who developed detectable ADA to AZD7442 (ADA results to AZD8895 and AZD1061 will be reported separately) by ADA categories listed above in the different treatment arms will be presented based on the ADA evaluable analysis set. Descriptive statistics of the maximum titer will also be presented by ADA category. ADA results and titers will be summarized by visit and treatment group. ADA results (positive/negative, ADA titer and nAb data for ADA positive samples) will be listed for all participants in the safety analysis set regardless of ADA-evaluable status. AEs in ADA positive participants by ADA positive category will be listed

4.10.5.3 Safety Evaluation

The safety evaluation is presented in the section 4.11 of the SAP.

4.10.6 Exploratory Endpoint

CCI

CCI

CCI

CCI

CCI

4.11 Safety Evaluation

All safety data (scheduled and unscheduled) will be presented in the data listings sorted by treatment group and participant. Continuous variables will be summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarized in frequency tables (frequency and proportion) treatment group.

The analysis of the safety variables will be based on the safety analysis set.

4.11.1 Extent of Exposure

The IMP administration date and time will be listed for each participant.

4.11.2 Adverse Events

AEs and SAEs will be collected throughout the study from date of informed consent until the end of the follow-up. MedDRA (using the latest or current MedDRA version) will be used to code the AEs.

Adverse events with onset (start date/time) after dosing will be summarized by treatment group (dose level or administration process of AZD7442, Total AZD7442). Tabulations will include causality (related, not related) and severity (mild, moderate and severe). All tabulations will be presented by MedDRA SOC and PT with the exception of the severity tables, which will be presented by PT only. Furthermore, listings of SAE and AEs that led to withdrawal will be made and the number of participants who had any AE, SAEs, and discontinuation events will be summarized. Adverse Events of Special Interest (related to Anaphylaxis and other serious hypersensitivity reactions, and injections site reactions) will be listed and summarized. The AEs that occur before dosing will be excluded from the summary tables.

Adverse events will be listed by each dose of AZD7442. The following information will be included in the listings: verbatim term, MedDRA SOC, PT and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of participants.

4.11.3 Vital Signs

The results of the vital signs measurements will be listed by participant and time point including the date/time of the assessment, changes from baseline, repeat/unscheduled measurements and clinical significance. The baseline for vital signs measurements will be the pre-dose assessment on Day 1. Descriptive statistics will be presented by treatment group and time point for both observed values and changes from baseline, which will exclude unscheduled assessments. The number and percentage of participants with a clinically significant vital sign result will be tabulated by parameter.

4.11.4 Resting 12-lead Electrocardiogram

12-lead ECG results will be listed for each participant with interpretation by the investigator as “Normal”, “Abnormal CS” (clinically significant) or “Abnormal NCS” (not clinically significant). Descriptive statistics will be presented by treatment group and time point for both observed values and changes from baseline. The number and percentage of participants who meet the following conditions for QTc and QTcF will tabulated by treatment group: >450 msec, >480 msec, >500 msec, >30 msec increase from baseline, and >60 msec increase from baseline. The shift from baseline Overall ECG Evaluation to worst Overall ECG evaluation will be tabulated for each treatment group.

Since triplicate ECGs will be performed for this study, the mean of the 3 measurements collected on a visit will be used in the by-visit summaries for that visit, but the highest of the 3 measurements collected at baseline and the highest among all post-baseline measurements will be used for the shift from baseline summaries.

4.11.5 Laboratory assessments

Hematology and clinical chemistry values will be listed by participant and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations will be presented by treatment group, which will exclude unscheduled measurements. The baseline for the measurements will be the pre-dose assessment on Day 1. Shift tables will also be presented, and will consider unscheduled assessments.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (eg, AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)
- The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

4.11.6 Physical Examinations

The baseline/screening results of the physical examination will be documented in medical history for each participant.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

4.11.7 Injection Site Reaction

Results of the injection site reaction assessment (including assessment of size, redness/erythema, swelling, itching/pruritus, pain or tenderness, induration, discoloration) will be listed by treatment group and participant.

4.11.8 COVID-19 Symptoms

Protocol defined COVID-19 symptoms reported during the study will be summarized by treatment group, and will be listed.

4.12 Determination of Sample Size

Preliminary analysis of PK data from the first-in-human study, D8850C00001, indicated that after an IM dose of IMP (separate AZD8895 and then AZD1061 doses) at a dose of 300 mg total protein, the CV% for Cmax of the individual mAbs, AZD8895 and AZD1061 were 35.6% and 38.5%, respectively, while the CV% for AUCs of both individual mAbs, AZD8895 and AZD1061 were < 36.4%. Therefore, assuming a mean ratio of 1 between comparators, 69 participants per group will provide at least 95% power to demonstrate comparability (90% CI contained within 0.8 and 1.25).

4.13 Interim Analysis

There will be no interim analyses in the study.

4.14 Changes to Protocol-planned Analyses

During scheduled audits of the sites #7808 and #7809, irregularities and critical findings were observed regarding collection and handling of study data. A subsequent FDA inspection also had several critical findings for data quality at these sites. Hence a sensitivity analysis is deemed necessary to analyze the robustness of the primary analysis of the trial. The sensitivity analysis will be performed on the primary and secondary endpoints including safety data and ADA endpoints.

The sensitivity analysis will be performed on the primary PK endpoints evaluating the comparability between the three treatment arms. Secondary PK endpoints, safety and ADA endpoints will also be analyzed. Demographic summary tables (excluding site #7808 and #7809) will be produced to provide details for the sensitivity analysis.

The sensitivity analysis will repeat planned analyses of the above-mentioned endpoints by excluding the sites: #7808 and #7809 to provide evidence for the robustness of the primary analysis, which include all sites (including sites: #7808 and #7809). A complete list of repeated analyses will be included in the TFL shells.

Additional PK analysis of AUCinf, AUClast and Cmax similar to that described in Section 4.10.4 will be performed for specified subgroups of lateral thigh group, gluteal dorsal group and gluteal ventral group for each compound AZD8895, AZD1061 and AZD7442.

Further subgroup analysis will be performed by injection site within treatment group, by vaccination status within treatment group, and by body weight category within treatment group for each compound AZD8895, AZD1061 and AZD7442.

The mixed model specifications will be described in the footnotes of each subgroup analysis table.

Forest plots of the additional comparisons will present the geometric mean ratio point estimate and corresponding 90% CI. These will include the injection site vaccination status, and body weight category subgroup comparisons grouped by treatment.

Approval Signatures

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