Reporting and Analysis Plan

Study ID: 214098

Official Title of Study: Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin (GSK2857916)

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STATISTICAL ANALYSIS PLAN

Protocol number 214098 – Amendment 02 TMF-11824254 dated 04FEB2021

Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin (GSK2857916)

AUTHOR: PPD

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 12OCT2022) for Protocol 214098 amendment 02.

	Name	Signature	Date (DDMMYYYY)
Author:	PPD	Refer to eSignature	
Position:	Biostatistician Team Lead		
Company:	IQVIA		
	Name	**Signature**	**Date (DDMMYYYY)**
Author:	PPD	Refer to eSignature	
Position:	Biostatistician Team Lead		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date (DDMMYYYY)
Approved By:	PPD	Refer to eSignature	
Position:	Study Lead Statistician		
Company:	GSK		

Approved By:	PPD	Refer to eSignature	
Position:	Study Lead Programmer		
Company:	GSK		
Approved By:	PPD	Refer to eSignature	
Position:			
Company:	GSK		
Approved By:	PPD	Refer to eSignature	
Position:	Senior Biostatistician Reviewer		
Company:	IQVIA		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	05MAY2021	PPD	Not Applicable – First Version
1.1	12AUG2021	PPD	Minor updates to Appendix 1 – ensured section refers to 'Prior/Concomitant **Ocular Therapy**/Medications' and that references are to end of study not end of treatment.
1.2	12APR2022	PPD	Updated to account for interim analysis (if 5 SK patients are not achieved by the planned final analysis timeline. Definition of all-treated, ICSK populations updated. Ocular history and risk factors summaries removed. Summary for multiple myeloma disease characteristics removed. Summary for histologic characterization removed. Summary for corneal imaging and sensation removed. Summaries for ocular examination and follow-up removed. AEs and SAEs summaries to be presented by All-Treated not ICSK population. Tear fluid summary updated to present detected/not detected (not quantitative data).
1.3	04MAY2022	PPD	Changed populations for primary, safety and

		PPD	pharmacokinetics analyses.
1.4	07JUN2022		Added in pharmacokinetics populations.
1.5	13JUN2022		Removed PKTEAR, PKPLAS and PDBIO from reasons for exclusion summary within disposition table. Grammar corrections.
1.6	15JUN2022		SAP version and date updated. Grammar corrections.
2.0	12OCT2022		Addition of summary statistics to be reported for mAb for plasma results

TABLE OF CONTENTS

ABBREVIATIONS

ADC	Antibody-Drug Conjugate
AE	Adverse Event
ATC	Anatomic Therapeutic Class
BCMA	B-Cell Maturation Antigen
GSK	GlaxoSmithKline
IC	Impression cytology
ICSK population	Impression cytology or superficial keratectomy procedure population
ISS	Investigator-Sponsored Study
mAb	Anti-BCMA monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MECs	Microcyst-like epithelial changes
MMAF	Monomethyl Auristatin-F
PK	Pharmacokinetic
PT	Preferred Term
SAP	Statistical Analysis Plan
SCR	All Participants Screened population
SK	Superficial keratectomy
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation, summarizing and analysis of data from participants receiving belantamab mafodotin (GSK2857916) in another GSK trial or patients on commercial prescriptions. This is an exploratory study, and only descriptive statistics apply.
This statistical analysis plan (SAP) is based on protocol 214098 amendment 02 (TMF-11824254), dated 04 February 2021.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to characterize corneal epitheliopathy in participants treated with belantamab mafodotin.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To correlate clinical data, including visual acuity and symptoms, as well as grade and appearance of corneal changes on imaging, with histopathologic findings.
- To describe safety profile of the impression cytology (IC) or superficial keratectomy (SK) procedure.

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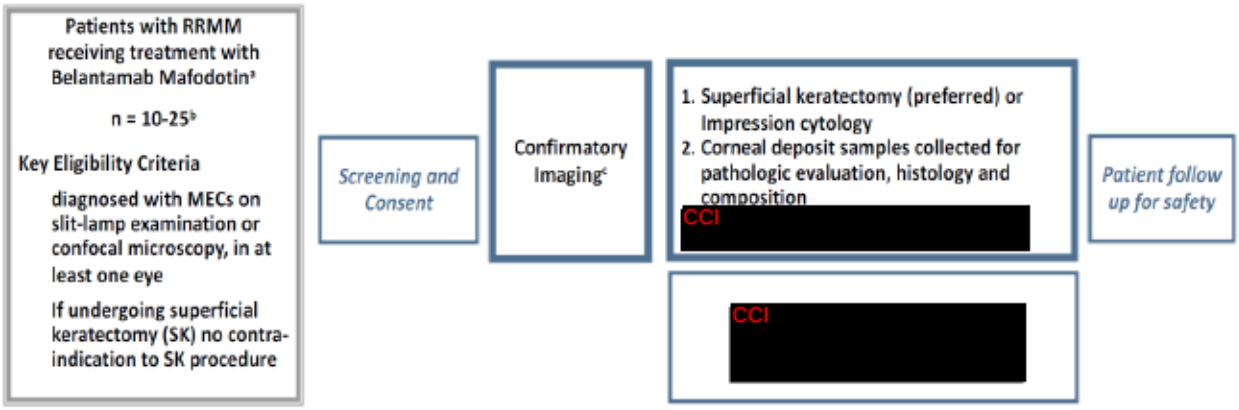
3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

- This study is available to any participant who has received or is currently receiving belantamab mafodotin treatment through a clinical trial (including an investigator- sponsored study (ISS), or an access program) or a Physician prescription; they do not need to be on active treatment as long as they meet inclusion criteria (See protocol amendment 02 (TMF-11824254) – Section 5 STUDY POPULATION).
- Up to 25 participants will complete the procedure. Once a total of 5 participant samples from SK procedure has yielded evaluable material for pathologic examination and composition analysis of the corneal epithelial changes, further enrollment will cease.
- Each patient will have a total of 3 (IC) to 6 (SK) visits. Additional follow-up visits may be required in the event of delay in healing from the ocular procedures.
- One eye will be the study eye. The study eye will be the eye most affected with the corneal epithelial changes. If both eyes are equally affected, the poorer-seeing eye will be selected.
- CCI [redacted]
- Impression cytology: Following topical anesthesia, an eyelid speculum, will be placed. Next, the filter paper will be pressed to a preidentified region on the corneal surface of the study eye with a glass rod (or similar instrument) for 5–10 seconds. The filter papers obtained from the procedure will contain epithelial layers from areas of the cornea with microcyst-like changes and will be analyzed through histologic techniques.
- Superficial keratectomy: Following topical anesthesia (such as proparacaine hydrochloride 0.5%) and a drop of povidone iodine 5% for antisepsis, an eyelid speculum will be placed. The eye will then be visualized using a slit-lamp or operating microscope in a procedure room. The corneal epithelium of interest (the region that contains the MECs) will be carefully removed using either a Weck-Cel/dry cellulose sponge or small blade; Jeweler or 0.12 forceps may be required in some cases. The tissue will be submitted in formalin for histologic analysis.
- Study Duration: approximately 4 weeks.

Table A: Study schema



[a] Patients on a DREAMM clinical trial, the compassionate use program, or a Physician Prescription are eligible.
[b] Up to 25 patients will be enrolled. The goal is to obtain 5 evaluable SK pathologic samples. Once 5 evaluable SK samples are obtained, enrollment will cease.
[c] An ophthalmic examination that includes best-corrected visual acuity, slit-lamp examination, and confocal microscopy (if available) must be performed prior to the impression cytology or keratectomy procedure to document site and size of corneal epithelial changes and to correlate imaging with pathologic findings. The slit-lamp examination must include orbit/lid/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous. Confirmatory anterior segment photography is also required unless acceptable corneal images are available from an examination performed <14 days prior to impression cytology or SK.
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3.2. SCHEDULE OF ACTIVITIES

Procedure	Screening	Pre–IC or SK procedure	IC or SK procedure (day of procedure)	Post–IC or SK procedure[e]	Safety follow-up (up to 1 week after SK procedure)	Safety follow-up (2 weeks after SK procedure)[f]	Additional follow-up at ophthalmologist's discretion[g]
Informed consent	X						
Eligibility criteria	X						
Slit-lamp examination and confocal microscopy (if available)[a] with imaging		X			X[d]		
Snellen eye test [a]			X		X	X	
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Corneal tissue sampling[c]			X				
Pathology review of corneal sample				X			
Ophthalmology post-procedure checkup							X
Vital signs (pulse and blood pressure)			X				
AEs/SAEs			X	X	X	X	
Data Collection[h]	X	X	X	X	X	X	X
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AE, adverse event; CCI IC, impression cytology; SAE, serious adverse event; SK, superficial keratectomy.

[a] An ophthalmic examination that includes best-corrected visual acuity, slit-lamp examination, and confocal microscopy (if available) must be performed prior to the impression cytology or keratectomy procedure to document site and size of corneal epithelial changes and to correlate imaging with pathologic findings. The slit lamp examination must include orbit/lid/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous. Confirmatory anterior segment photography is also required unless acceptable corneal images are available from an examination performed <14 days prior to impression cytology or SK. It is recommended that the imaging examination be performed at least 24 hrs prior to the procedure.

[b] Examples of preferred terms (CTCAE v5.0) include, but are not limited to, keratitis, eye disorder–other, blurred vision, dry eye, eye pain, flashing lights, photophobia, and watering eyes.

[c] GSK may store samples for up to 3 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of the pathophysiology of belantamab mafodotin – associated keratopathy, the development of related or new treatments, or research methods.

[d] Preferred timing for follow-up slit-lamp examination is 24–48 hours post SK procedure but must be performed within 1 week after SK procedure. Safety follow-up after impression cytology is not required unless the participant is experiencing discomfort or an AE.

[e] The AE/SAE follow-up immediately after the Post–IC or SK procedure can be done by phone, in the 24-48 hours post-procedure.

[f] The participant should be reexamined 2 weeks after the SK procedure if the epithelial defect does not heal completely in the first follow-up. Otherwise, this follow-up is not required.

[g] In the event the cornea has not healed at 2 weeks, additional follow-up should be conducted at the ophthalmologist's discretion until healing is confirmed.

[h] Minimal additional data will be collected to adequately characterize the development of the corneal epithelial changes in participating patients.

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3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Impression cytology or superficial keratectomy procedure population (ICSK) and evaluable impression cytology or superficial keratectomy procedure population (EICSK) are not defined in the protocol amendment 02 (TMF-11824254) but have been added since an enrolled participant may not undergo either impression cytology or superficial keratectomy. These populations have been defined in Section 5.3.

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4. PLANNED ANALYSES

An interim analysis will be performed only if the 5 SK patients target is not met by the planned Final Analysis timeline – final analysis would then be completed once the final recruitment is achieved. If the 5 SK patients target is met by the planned Final Analysis delivery time, then no interim analysis will be performed, and only final analysis will be performed.
Data monitoring committee analyses are not planned.

4.1. FINAL ANALYSIS

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities (Section 3.2) for the last participant in the trial.
A participant is considered to have completed the study if he/she has completed all phases of the study including the

last visit, as specified in the schedule of activities (Section 3.2).
All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this statistical analysis plan, output templates and database lock.

5. Analysis Populations

5.1. All Participants Screened

All participants screened population will contain all participants who signed informed consent.

5.2. All-Treated Population

All-treated population is defined as all participants screened who are enrolled (without screen failure).

5.3. Impression Cytology or Superficial Keratectomy Procedure (ICSK) Population

IC or SK (ICSK) population is defined as participants from all-treated population who had a tissue sample collected using Impression Cytology (IC) or Superficial Keratectomy (SK) procedure, whether or not the specimen is evaluable.

5.4. Evaluable Impression Cytology or Superficial Keratectomy Procedure (EICSK) Population

Evaluable IC or SK (EICSK) population is defined as participants from all-treated population who had an evaluable tissue sample collected using IC or SK procedure. A tissue sample specimen will be determined to be evaluable by the pathologist in the pathology report.

6. General and Statistical Considerations

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date (Day 1) is defined as the day of procedure (impression cytology or superficial keratectomy), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference start date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference start date, then:

Study Day = (date of event – reference date).

In case of partial/missing dates, they will be handled as specified in APPENDIX 1. Imputed dates will not be used to calculate study day of the events and will not be presented in the listings.

6.2. BASELINE

The baseline value will be the latest assessment with a non-missing value done before the IC or SK procedure, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to procedure and used as baseline.

6.3. UNSCHEDULED VISITS

Unscheduled measurements will not be included in tables. Listings will include scheduled and unscheduled visits data.

6.4. STATISTICAL TESTS

No statistical test will be performed.

6.5. MISSING DATA

No imputation of values for missing data will be performed.

6.6. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

Summary statistics will be summarized by visit when appropriate and will consist of values for:

- number of participants, number of missing values, mean, standard deviation, median, lower and upper quartiles, minimum and maximum for quantitative parameters.
- number and percentage of participants for qualitative parameters. Percentages will be presented with one decimal place. Percentages computation will depend on table structure and will be detailed in the table footnotes (See Output templates document).

8. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study.

8.1. DISPOSITION

The number of screened participants, screen failures and reasons of screen failure will be presented on all participants.

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9. DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics will be presented on the all-treated population.
The following demographic data will be reported for this study:

- Age (years) - calculated relative to year of consent
- Sex
- Ethnicity
- Race
- GSK2857916 parent study or patients on commercial prescriptions

Demographic characteristics will be presented in a table by method of tissue collection (impression

cytology/superficial keratectomy/not collected).

Demographic characteristics will also be included in a by-participant listing.

9.1. DERIVATIONS

Age (years) = Year of consent – Year of birth

10. OCULAR HISTORY AND RISK FACTORS

The following ocular history and risk factors will be reported for this study:

- Previous diagnosis of dry eye (Yes/No)
- Previous diagnosis of glaucoma on right/left eye (Yes/No)
- Previous diagnosis of cataract on right/left eye (Yes/No)
- History of cataract surgery on right/left eye (Yes/No)
- History of laser treatment surgery on right/left eye (Yes/No)
- History of other ocular surgery on right/left eye (Yes/No)
- History of serious eye trauma on right/left eye (Yes/No)
- History of ocular disease requiring medical treatment on right/left eye (Yes/No)
- Other (Yes/No)

Ocular history and risk factors will be included in a by-participant listing.

11. OCULAR THERAPY

Ocular therapies will be presented in a by-participant listing only on the all-treated population and coded using MedDRA version 25.0 or above.

Concomitant ocular therapies will be flagged and are therapies which:

- started prior to, on or after the date of informed consent,
- AND ended on or after the date of informed consent or were ongoing at the end of the study.

12. OCULAR MEDICATION

Ocular medication will be presented in a by-participant listing only on the all-treated population and coded using GSK drug dictionary.

Concomitant ocular medications will be flagged and are medications which:

- started prior to, on or after the date of informed consent,
- AND ended on or after the date of inform consent or were ongoing at the end of the study.

13. DISEASE CHARACTERISTICS

The following disease characteristics will be reported for this study:

- Time since initial diagnosis of multiple myeloma – calculated relative to date of screening
- Stage at screening and at initial diagnosis (I/II/III/Unknown)
- Myeloma immunoglobin (IgA/IgD/IgE/IgG/IgM)
- Light chain myeloma at screening (Yes/No) and type.

Disease characteristics will be included in a by-participant listing on the all-treated population.

14. MYELOMA TREATMENT

Prior myeloma treatments will be presented in a by-participant listing only on the all-treated population.

15. EXPOSURE TO BELANTAMAB MAFODOTIN

The following exposure information will be reported for this study:

- Duration of exposure (weeks) derived by: (last date of dose intake – first date of dose intake + 1) / 7.

All exposure information will be included in a by-participant listing on the all-treated population.

16. PRIMARY ENDPOINT

Data collected from "Corneal Tissue Sample" and "Pathology" eCRF pages will be presented on the EICSK population.
Method of tissue collection will be presented in a table on study eye.
"Immunohistochemistry", "Electron microscopy" parts from "Pathology" eCRF page will be presented in tables by method of tissue collection (impression cytology/superficial keratectomy) on study eye.
"Anterior segment slit-lamp photography" and "Pathology comments" parts from "pathology" eCRF page will be presented in a by-participant listing.

All Corneal Tissue Sample and Pathology data will also be included in a by-participant listing on the all-treated population.

17. SECONDARY AND EXPLORATRY ENDPOINTS

17.1. SECONDARY AND EXPLORATORY CLINICAL ENDPOINTS

Data collected from "Corneal symptom grading" eCRF page will be presented in a table by method of tissue collection (impression cytology/superficial keratectomy) and by visit on study eye on the ICSK population.

Data collected from "Ocular corneal examination" eCRF page will be presented in a table by method of tissue collection (impression cytology/superficial keratectomy) and by visit on study eye on the ICSK population.

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Safety follow up visit is required for participants with superficial keratectomy procedure but not required for participants with impression cytology unless the participant is experiencing discomfort or an AE. At this visit, the table will present participants with superficial keratectomy procedure and participants with impression cytology who have had at least one safety follow-up visit.

For by-visit tables, if two safety follow-up visits have been done, the latest non-missing value will be considered

only.

All secondary and exploratory clinical data will also be included in a by-participant listing on the all-treated population. Unscheduled visits will be displayed in these listings.

17.2. SECONDARY SAFETY ENDPOINTS

17.2.1. ADVERSE EVENTS

Adverse Events (AEs) related to the IC or SK procedure only will be collected from the start of intervention until the last follow-up visit at the time points specified in the schedule of activities (Section 3.2).

All Serious Adverse Events (SAEs) related to the IC or SK procedure only will be collected from the start of intervention until the last follow-up visit at the time points specified in the schedule of activities (Section 3.2). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests) will be recorded from the time a participant consents to participate in the study.

AEs and SAEs will be presented on the ICSK population and coded using MedDRA version 23.0 or above.

An overall summary table of number of participants within each of the categories described below, will be provided by method of tissue collection (impression cytology/superficial keratectomy) summarizing:

- Participants with at least one AE related to the IC or SK procedure.
- Participants with at least one SAE related to the study participation or to the IC or SK procedure.
- Participants with at least one SAE leading to study discontinuation
- Participants with AE leading to death.

AEs and SAEs will be presented in tables by PT and sorted by decreasing frequencies on total, and broken down by maximum grade. AEs will be graded according to the NCI Common Terminology Criteria of Adverse Events (NCI CTCAE) Version 5.0.
Participants will be counted only once for each PT even if they have multiple records of the same PT. If a participant reports an AE more than once within that PT, the AE with the worst-case grade will be used in the corresponding grade summaries.

AEs leading to Death are those events which are recorded on the Adverse Events page of the parent study eCRF as at least one of the following criteria:

- AE Term: "Death"
- Outcome: "Death related to adverse event"
- Seriousness: Results in death
- Toxicity grade (CTCAE): Grade 5

AEs leading to death will be presented in a by-participant listing on the all-treated population.

All secondary safety data will also be included in a by-participant listing on the all-treated population.

17.2.2. VITAL SIGNS

Data collected from "Vital signs" eCRF page will be presented in a by-participant listing only on the all-treated population.

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[redacted]

17.3.3. BIOMARKERS

Biomarker measurements will be presented on the PD Biomarker population for:

- Soluble BCMA

All biomarker data will be included in a by-participant listing on the PD Biomarker population.

APPENDIX 1. PARTIAL DATE CONVENTIONS

Algorithm for Prior / Concomitant Ocular Therapy/Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < informed consent date, assign as prior If stop date >= informed consent date and start date <= end of study, assign as concomitant If stop date >= informed consent date and start date > end of study, assign as post study

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < informed consent date, assign as prior If stop date >= informed consent date and start date <= end of study, assign as concomitant If stop date >= informed consent date and start date > end of study, assign as post study
	Missing	If stop date is missing could never be assumed a prior study If start date <= end of study, assign as concomitant If start date > end of study, assign as post study
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < informed consent date, assign as prior If stop date >= informed consent date and start date <= end of study, assign as concomitant If stop date >= informed consent start date and start date > end of study, assign as post study
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < informed consent date, assign as prior If stop date >= informed consent date and start date <= end of study, assign as concomitant If stop date >= informed consent date and start date > end of study, assign as post study

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of study, assign as concomitant If start date > end of study, assign as post study
Missing	Known	If stop date < informed consent date, assign as prior If stop date >= informed consent date, assign as concomitant Cannot be assigned as 'post study'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < informed consent date, assign as prior If stop date >= informed consent date, assign as concomitant Cannot be assigned as 'post study'
	Missing	Assign as concomitant

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	12 Oct 2022 21:15:44 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	12 Oct 2022 21:16:41 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	12 Oct 2022 23:39:03 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	13 Oct 2022 08:18:48 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	13 Oct 2022 09:47:44 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	13 Oct 2022 13:39:21 UTC