SAMSUNG BIOEPIS

Clinical Study Report (CSR)

Statistical Analysis Plan

An open-label, single group, single-dose clinical study to evaluate the usability of the pre-filled syringe (PFS) of SB11 in subjects with Neovascular Age-Related Macular Degeneration (AMD) or Macular Oedema Secondary to Retinal Vein Occlusion (RVO)

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LIST OF ABBREVIATIONS

The abbreviations should be ordered alphabetically. Use initial capitals for all major words in a title except articles (a, the) and prepositions (for, in, up, by, etc.), unless an article or preposition appears at the beginning or end of the title.

AE	Adverse Event
AMD	Age-Related Macular Degeneration
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CM	Concomitant Medication
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
ENR	Enrolled Set
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
HCP	Healthcare Professional
IE	Intercurrent event
IFU	Instruction for Use
IO	Indirect Ophthalmoscopy
IOP	Intraocular Pressure
IP	Investigational Product
ITV	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PDID	Protocol Deviation Identifier
PFS	pre-filled syringe
PPS	Per-Protocol Set
Pre-AE	Pre-treatment Adverse Event
PT	Preferred Term
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Events
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation

SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of usability evaluation and safety data for Protocol SB11-2001.

It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed. This Statistical Analysis Plan (SAP) is based on the Protocol final version 1.0, dated Jul 05, 2021. The following analyses will be performed for this study.

For clinical study report (CSR), the usability evaluation and safety analyses will be performed after the last subject completes the procedures at Day 7 or the corresponding visit. All study data collected will be analysed and reported for the CSR.

2. STUDY OBJECTIVES, ESTIMANDS AND ENDPOINTS

2.1. Study Objectives

Primary Objective

The primary objective is to assess the ability of Healthcare Professionals (HCPs) to follow the instructions for use (IFU) to prepare and administer SB11 PFS Intravitreal (ITV) injection to subjects.

Secondary Objective

The secondary objective is to evaluate the safety of SB11 PFS in subjects with neovascular AMD or macular oedema secondary to RVO.

2.2. Estimand

Table 1. Objective, Estimands and Endpoints of the Study

Objectives	Estimand	Endpoints
To assess the ability of HCPs to follow the IFU to prepare and administer SB11 PFS ITV injection to subjects	Population: Patients who received Investigational Product (IP) injection during the study period and have at least one usability assessment. Summary measure: - Percentage of successful task completions (for each task) - Percentage of successful task completions on all tasks Intercurrent events (IEs):	Primary endpoint: - Successful task completions

Objectives	Estimand	Endpoints
	Refer to Table 2 on section 8 Strategy: Refer to Table 2 on section 8	

3. SAMPLE SIZE CALCULATION

Approximately 30 subjects are planned to be enrolled. No formal statistical power calculations to determine sample size will be performed for this study as there is no statistical hypotheses available.

4. GENERAL CONSIDERATIONS

This is an open-label, single group, single-dose clinical study to evaluate the usability of the PFS of SB11 in patients with neovascular AMD or macular oedema secondary to RVO. HCPs will prepare and administer ITV injections of SB11 0.5 mg delivered via PFS to subjects (1 injection to each subject) on Day 1 (baseline), and safety follow-up will be assessed until Day 7.

4.1. Analysis Sets

The following sets will be used for the analyses performed in the study.

- Enrolled Set (ENR) consists of all subjects who provide informed consent for this study. "Enrollment" in Electronic Case Report Form (eCRF) does not mean the subject is included in ENR set.
- Full Analysis Set (FAS) consists of all subjects in ENR who are eligible and received IP during the study period and have at least one usability assessment. This is the primary analysis set.
- Per-Protocol Set (PPS) consists of all subjects in FAS who have IP injection without any major protocol deviations (PDs) that have impact on the usability assessment.
- Safety Set (SAF) consists of all subjects in ENR who received at least one IP during the study period.

The number of subjects in the analysis sets will be summarised for FAS. By-subject listing of analysis population details will be provided for the ENR and will include: country, centre, subject identifier, inclusion/exclusion flag for each analysis set, and reason for exclusion from PPS.

4.2. Protocol Deviations

PDs will be pre-defined prior to subject enrollment and documented separately named as Protocol Deviation definition list which includes classification (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, non-compliance with treatment), deviation description, category (major or minor), time point for each PD. Major PDs are defined as those deviations from the study protocol

likely to have an impact on the usability evaluation and/or safety of study treatments. The PD definition list will be included in data review meeting (DRM) minute as an attachment.

PDs and analysis sets will be reviewed and confirmed through the DRM to decide which subjects and/or subject data will be excluded from certain analyses prior to database lock. Decisions regarding the exclusion of subjects and/or subject data from analyses will be made prior to database lock and will be documented and approved.

A summary of the number and percentage of subjects with PD by PD category (major and minor) and PD classification will be presented. Percentages will be based on the number of FAS. By-subject listing of PDs will be provided including subject identifier, visit or date/time, PD classification, PD description, PD severity, relationship with Coronavirus Disease 2019 (COVID-19) and exclusion from specific analysis populations.

4.3. Disposition and Withdrawals

The subject disposition summaries include the following:

- A summary of the number of enrolled subjects, the number and percentage of screen failures and reasons (does not meet eligibility criteria, consent withdrawal, lost to follow up and other) for screen failure, using the ENR.
- A summary of the number of subjects who had IP administration and who completed or discontinued from the study with the reasons (adverse event, consent withdrawal, death, administrative reasons and other) of discontinuation, using the SAF.
- By-subject listing of subject disposition including date of informed consent, date of IP administration, completion or discontinuation date, primary reasons of withdrawal, and reasons for early termination (ET) visit not done, using the ENR.

4.4. Study Day

Study Day will be calculated from the IP dosing date and will be used to show start/end day of assessments and events. Study Day of the IP dosing date will be Day 1.

- If the date of the event is on or after the IP dosing date, then:

  Study Day = (date of event –IP dosing date) + 1

- If the date of the event is prior to the IP dosing date, then:

  Study Day = (date of event –IP dosing date)

4.5. Baseline

Baseline value will be defined as the last available measurement value recorded prior to IP administration.

4.6. Retests, Unscheduled Visits and Early Termination Data and Visit Mapping

In general, the data recorded at the scheduled visit will be presented in the by-visit summaries. Unscheduled/repeated measurements will not be included in the by visit summaries, except for the baseline value.

The ET visit data of vital signs, best corrected visual acuity (BCVA) test, slit lamp examination, intraocular pressure (IOP) and indirect ophthalmoscopy (IO) will be mapped to the next scheduled visit.

Listings will include scheduled, unscheduled, repeated, and ET visit and a visit label of Day X (R0x) will indicate a retested or unscheduled measurement. Those visits will be chronologically presented in the listings.

4.7. Common Calculations

For the purpose of converting days to years or months, 1 year will be equal to 365.25 days and 1 month will be equal to 30.44 days.

For quantitative measurements, change from baseline at Visit X will be calculated as follows:

- Change from baseline at Visit X = Test Value at Visit X – Baseline Value

4.8. Software Version

All report outputs will be conducted using SAS® version 9.4 or higher.

5. STATISTICAL CONSIDERATIONS

5.1. Multicentre Studies

For listings, the term ‘Centre’ will be used to define each investigator site. This study will be conducted by multiple investigators at multiple centres in Poland.

5.2. Missing Data

Missing data will not be imputed generally unless otherwise specified. Handling method of partial and missing dates is described in APPENDIX 1.

5.3. Multiple Comparisons/Multiplicity

Multiple comparison is not needed.

5.4. Statistical Hypotheses

No statistical hypothesis is used.

5.5. Examination of Subgroups

No examination of subgroups is needed.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarised for the FAS.

Continuous variables (age, duration of disease, BCVA in study eye, and IOP in study eye) will be summarised with descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). Qualitative variables (gender, child bearing potential, race, ethnicity, main indication, study eye, and lens status in study eye) will be summarised using frequency and percentages.

By-subject listings of demographics and other baseline characteristics will be provided.

6.1.Demographics Characteristics

- Age (years) - calculated as Year of informed consent – Year of birth
- Gender – Female, Male
- Child bearing potential – Yes, No, Not applicable (Male)
- Race – American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- Ethnicity – Hispanic or Latino, Indian (Indian subcontinent), Chinese, Japanese, Korean, Mixed ethnicity, Other

6.2.Other Baseline Characteristics

- Duration of disease (months) = (Informed consent date – diagnosed date + 1)/30.44
- Main indication – Neovascular AMD, Macular Oedema Secondary to RVO
- BCVA in study eye (Total letter score)
- IOP in study eye (mmHg)
- Study eye – OD (Oculus Dexter – right eye), OS (Oculus Sinister – left eye)
- Lens status in study eye -No cataract, Cataract, Pseudophakia, Pseudophakia with open posterior capsule

7. SURGICAL AND MEDICAL HISTORY

Medical and surgical histories will be coded using Medical Dictionary for Regulatory Activities central coding dictionary (MedDRA version 26.0).

Medical and surgical histories for ocular and non-ocular will be summarised by System Organ Class (SOC), preferred term (PT), respectively, for the FAS.

By-subject listings of medical and surgical histories will be provided for the FAS.

8. USABILITY ASSESSMENT ANALYSES

Since the primary objective is to assess the HCP's successful task completions, target population of clinical question of interest is the population consisting of all subjects who are eligible and received IP injection and have at least one usability assessment (FAS).

In case of the subjects who do not have usability assessment for a specific task, the treatment policy strategy will be applied.

Summaries of the number and timings of IE will be provided for the FAS.

By-subject listing of all IEs will be provided for the FAS.

Table 2 Intercurrent Events and Strategies

IEs	Strategy
Observer did not perform usability assessment for any attempt of a specific task.	Treatment Policy strategy : The collected data will be analysed for usability assessment whether the intercurrent event has occurred or not.

8.1.Primary Usability Assessment Analysis

Analysis of Primary Usability Assessment Endpoint

The primary outcome measure is the HCP's successful task completions as assessed by an independent observer who is trained for usability assessment. HCPs (ophthalmologist and/or assistants) will perform each task in Table 3.

Percentage of successful task completions will be summarised for the FAS.

By-subject listing of individual usability assessment data of observer and self-assessment data of HCP will be provided for the FAS.

Table 3. Usability Task Description

Sequence	Task	Critical Task	Essential Task	Description/Success criteria
1	Open the carton	-	O	Open the carton
2	Remove contents	-	O	Removes sealed blister pack from carton
3	Peel the lid off the blister pack	-	O	Peels the lid off blister pack without damaging the product
4	Carefully remove the PFS from the blister using aseptic technique	-	O	Removes the PFS out of blister pack and does not damage the PFS
5	Remove the syringe cap	-	O	Removes syringe cap without damaging PFS
6	Attach a needle	O	-	Fully attaches a needle to the PFS Luer lock
7	Remove the needle cap	O	-	Pulls the needle cap straight off without damaging the PFS *Note that it is acceptable to remove cap before or after setting dose
8	Set the dose	O	-	Removes air from PFS Sets the required dose by pushing the plunger rod
9	Insert the needle into the injection site	O	-	Inserts the needle into the injection site
10	Press the plunger down to inject the medication	O	-	Presses the plunger down completely
11	Remove the needle from the injection site	-	O	Pulls needle straight out from the injection site
12	Dispose product	O	-	Dispose of the PFS with attached needle according to local regulation

Successful Task Completions

The observer will record if each task is successfully completed by designated HCP(s). Tasks will be considered to be successfully completed if tasks meet success criteria or corrected results are achieved without a use failure (even if the IFU are not followed exactly) for all attempts performed. The information that describes success criteria will be provided to observer separately. If at least one attempt fails to complete a usability task, it will be considered as use failure.

Use Failure

If any use failure of HCP(s) is observed by the observer, the observer will ask HCP(s) the reason why she/he commit use failure(s) on each task in the follow-up session.

If use failures of HCP(s) which can result in unacceptable clinical impact or harm to the subject are observed, the observer will correct and/or instruct the HCP(s). Unacceptable clinical impact or harm includes, but not limited to, significant overdose and condition that can result in increased IOP or infection.

Percentage of Successful Task Completions

Percentage of successful task completions (%) = (the number of subjects in whom HCP successfully completed each task in every attempt / the number of subjects with available usability assessment results for each task) x 100

Percentage of Successful Completion on All Tasks

Percentage of successful completion on all tasks (%) = (the number of subjects in whom HCP successfully completed all tasks in every attempt / the number of subjects in analysis set with available usability assessment results for every task) x 100

Sensitivity Analysis of Primary Usability Assessment Endpoint

No sensitive analysis of primary endpoint will be performed.

Supportive Analysis of Primary Usability Assessment Endpoint

The analysis of primary usability assessment (i.e., calculating the percentage of successful task completions and the percentage of successful completion on all tasks) will be repeated for the PPS as a supportive analysis.

8.2. Secondary Usability Assessment Analysis

Analysis of Secondary Usability Assessment Endpoint

The secondary outcome measure is the HCP's successful completion on critical task and essential task as assessed by an independent observer who is trained for usability assessment. HCPs (ophthalmologist and/or assistants) will perform each task as Table 3. Percentage of successful completion on critical task and essential task will be summarised for the FAS and PPS, respectively. Success type and use failure reason for performed HCP (ophthalmologist and/or assistants) will be summarised. If there are several success types or use failure reasons, the result from the first success or use failure with observer's assessment will be used for summary. If both ophthalmologist and assistant performed for same task, HCP from first attempt with observer's assessment will be used for summary.

8.3. Successful Completion on Critical Tasks

Successful Task Completions

The observer will record if each critical task is successfully completed by designated HCP(s). Critical tasks will be considered to be successfully completed if tasks meet success criteria or corrected results are achieved without a use failure (even if the IFU are not followed exactly) for all attempts performed. The information that describes success criteria will be provided to observer separately. If at least one attempt fails to complete a critical usability task successfully, it will be considered as use failure.

Use Failure

If any use failure of HCP(s) is observed by the observer, the observer will ask HCP(s) the reason why she/he commit use failure(s) on each critical task in the follow-up session.

If use failures of HCP(s) which can result in unacceptable clinical impact or harm to the subject are observed, the observer will correct and/or instruct the HCP(s). Unacceptable clinical impact or hard includes, but not limited to, significant overdose and condition that can result in increased IOP or infection.

Percentage of Successful Completion on Critical Task

Percentage of successful completion on critical task (%) = (the number of subjects in whom HCP successfully completed each critical task in every attempt / the number of subjects with available usability assessment results for each critical task) x 100

Percentage of Successful Completion on All Critical Task

Percentage of successful completion on all critical tasks (%) = (the number of subjects in whom HCP successfully completed all critical tasks in every attempt / the number of subjects in analysis set with available usability assessment results for every critical task) x 100

8.4. Successful Completion on Essential Tasks

Successful Task Completions

The observer will record if each essential task is successfully completed by designated HCP(s). Essential tasks will be considered to be successfully completed if tasks meet success criteria or corrected results are achieved without a use failure (even if the IFU are not followed exactly) for all attempts performed. The information that describes success criteria will be provided to observer separately. If at least one attempt fails to complete an essential usability task successfully, it is not considered as use failure.

Use Failure

If any use failure of HCP(s) is observed by the observer, the observer will ask HCP(s) the reason why she/he commit use failure(s) on each essential task in the follow-up session.

If use failures of HCP(s) which can result in unacceptable clinical impact or harm to the subject are observed, the observer will correct and/or instruct the HCP(s). Unacceptable clinical impact or hard includes, but not limited to, significant overdose and condition that can result in increased IOP or infection.

Percentage of Successful Completion on Essential Task

Percentage of successful completion on essential task (%) = (the number of subjects in whom HCP successfully completed each essential task in every attempt / the number of subjects in analysis set with available usability assessment results for each essential task) x 100

Percentage of Successful Completion on All Essential Task

Percentage of successful completion on all essential tasks (%) = (the number of subjects in whom HCP successfully completed all essential tasks / the number of subjects in analysis set with available usability assessment results for every essential task) x 100

8.5. Exploratory Efficacy Analysis

No exploratory efficacy analysis will be performed.

8.6. Pharmacokinetic Analysis

No pharmacokinetic analysis will be performed.

8.7. Serum Concentration

Not applicable.

8.8. Pharmacokinetic Parameters

Not applicable.

9. SAFETY ANALYSIS

Safety analysis will be conducted for the SAF.

9.1. Study Medication Exposure

IP administration will be listed by subject with treatment, dosing details such as date and time of dosing and injected eye for the SAF.

9.2. Prior/Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary Global Mar 2023. Any medications until EOS (End of Study)/ET visit will be included for the analyses.

A summary of prior and concomitant medication giving the number and percentage of subjects will be provided by Anatomical Therapeutic Chemistry (ATC) Drug Class and/or PT.

By-subject listing of prior and concomitant medication will be provided for the SAF.

9.3. Prohibited Medications

Prohibited medications will be coded using the WHODrug dictionary Global Mar 2023. Any medications until EOS/ET visit will be included for the analyses.

Prohibited medications will be defined as any medications which are detected as PDs by PD identifier (PDID) ‘M01’, ‘M02’, ‘M03’, ‘M04’, ‘M05’, ‘M06’, ‘M07’, ‘E07’, ‘E08’, ‘E09’, ‘E10’, ‘E11’, ‘E12’, ‘E13’, and ‘E14’ defined in the approved PD definition list and confirmed by medical review as prohibited medication. The prohibited medications will be confirmed by medical reviewer during PD review, and the final confirmed prohibited medications will be reported as PDs.

A summary of prohibited medications giving the number and percentage of subjects and the number of events will be provided by ATC Drug Class and/or PT in a manner similar to concomitant medication analysis.

By-subject listing of prohibited medication will be provided for the SAF.

9.4. Laboratory Evaluations

Not applicable.

9.5. Vital Signs

Vital sign assessment consists of systolic and diastolic blood pressure (mmHg), pulse rate (bpm), and body temperature (°C).

The observed values and change from baseline will be summarised using n, mean, SD, median, minimum and maximum by visit.

By-subject listing of all vital sign parameters will be provided for the SAF.

9.6. Immunogenicity Analysis

Not applicable.

9.7. Other Observations Related to Safety

Following observations will be provided:

- Physical examination (listing only)
- Pregnancy test (listing only)
- Ophthalmic examinations: Several ophthalmic examinations will be performed and summarised as described in below.

BCVA Examinations

BCVA will be assessed in both the study eye and fellow eye at Screening and prior to ITV injection at Day 1. BCVA in study eye will also be assessed during visit at Day 7 (EOS visit) or ET visit.

For the total letter score of BCVA in study eye, a summary of actual value and change from baseline by visit will be provided.

By-subject listings of results in full BCVA examination for both eyes will be provided for the SAF.

Full Ophthalmic Examinations

The full ophthalmic examinations will consist of slit lamp examination in both eyes, IOP measurements and IO in study eye only.

For slit lamp examination in study eye, incidence of anterior chamber flare, anterior chamber cells, vitreous cells, and abnormal findings by visit will be provided.

For IOP measurements, a summary of actual value and change from baseline will be provided by visit. Baseline will be pre-injection value.

For IO, incidence of the vitreous inflammation in study eye will be provided by visit.

By-subject listings of results in full ophthalmic examinations will be provided.

Optical Coherence Tomography

The optical coherence tomography (OCT) will be performed on the study eye at Screening, prior to ITV injection at Day 1 and Day 7 (EOS visit) or ET visit.

By-subject listings of results in OCT will be provided.

10. ADVERSE EVENTS

All outputs for adverse events (AEs) will be based on the SAF. All reported terms for AEs will be coded using MedDRA version 26.0.

Pre-treatment adverse events (Pre-AEs) will be defined as any AEs with an onset date before the date of IP administration.

Treatment-Emergent adverse events (TEAEs) will be defined as any AEs with an onset date on or after the date of IP administration. If pre-AEs increase in severity after IP administration, they will be considered as TEAEs.

See APPENDIX 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as a treatment-emergent or not, the AE will be classified by the worst case, i.e., treatment-emergent.

By-subject listing for all AEs will be provided.

In the listing, COVID-19 flag will be populated for AE for COVID-19 using below rule.

- AEs for COVID-19: includes AEs, where the verbatim term contains key text "Asymptomatic COVID-19" or "COVID-19 *disease or sign/symptom*" or "Suspected COVID-19 *disease or sign/symptom*". AEs related to COVID-19 vaccine, where the verbatim term contains "sign/symptom/disease related to COVID-19 vaccine" will not be included. The Italic text will be replaced with actual disease, or sign/symptom.

10.1. Summary of All Adverse Events

All AEs will be summarised by number, percentage of subjects and number of events. The following categories will be presented in the summary of AEs in the SAF.

- No AEs/AEs
- Pre-AEs
- TEAEs by severity (Mild/Moderate/Severe)
- TEAEs by causality (Drug/ITV injection) (Related/Not related)
- Ocular TEAEs in study eye by severity and causality
- Ocular TEAEs in fellow eye by severity and causality
- Non-ocular TEAEs by severity and causality
- TEAEs of special interest by category
- TEAEs leading to study discontinuation
- Serious adverse events (SAEs) by causality
- Ocular serious TEAEs in the study eye

- Ocular serious TEAEs in the fellow eye
- Non-ocular serious TEAEs
- TEAEs leading to death

10.2. TEAEs

The TEAEs will be presented by SOC and PT using number and percentage of subjects and number of events. The following categories will be presented in the summary of TEAEs in the SAF.

- Incidence of all TEAEs
- Incidence of ocular TEAEs in the study eye and fellow eye
- Incidence of non-ocular TEAEs

10.3. TEAEs by Severity

The TEAEs will be presented by SOC, PT and severity using number and percentage of subjects and number of events. Severity will be reported as mild, moderate or severe. TEAEs with missing severity will be considered as the worst-case severity (i.e., severe). If a subject reports TEAEs with different severity within the same SOC/PT, the subject with the worst-case severity (i.e., severe) will be counted in the corresponding severity summaries.

10.4. TEAEs by Causality (Relationship to drug or ITV injection)

The TEAEs will be presented by SOC, PT and causality (Drug/ITV injection) using number and percentage of subjects and number of events. Relationship will be reported as related or not related. TEAEs with missing relationship will be considered as the worst-case causal relationship (i.e., related). If a subject reports TEAEs with different causal relationship within the same SOC/PT, the subject with the worst-case causal relationship (i.e., related) will be counted in the corresponding relationship summaries.

10.5. SAEs

Incidence of SAEs will be summarised by SOC and PT and listed.

10.6. TEAEs Leading to Death

If any subjects die during the study as recorded on the Adverse Event page of the eCRF, the incidence of TEAEs leading to death will be presented by SOC and PT and listed.

10.7. TEAEs Leading to Study Discontinuation

Incidence of TEAEs leading to study discontinuation will be summarised by SOC and PT and listed.

10.8. TEAEs of Special Interest

Incidence of TEAEs of special interest will be summarised by category of special interest, SOC and PT and listed.

10.9. TEAEs for Intraocular Pressure in Study Eye

All TEAEs for IOP in study eye will be presented by SOC and PT. (Defined in APPENDIX 2)

10.10. TEAEs for Intraocular Inflammation in Study Eye

All TEAEs for intraocular inflammation in study eye will be presented by SOC and PT. (Defined in APPENDIX 3)

10.11. Other AEs

Other AEs are all TEAEs excluding serious AEs. All other AEs will be presented by SOC and PT.

11. REFERENCES

1. ICH E9 Statistical Principles for Clinical Trials
2. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
3. ICH E3 Structure and Content of Clinical Study Reports

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. However, in general, when calculating relative days, partial dates with missing day only will be assumed to be 15th of the month, and partial dates with both missing day and month will be assumed to be June 30. Otherwise, the following rules in the given table will be applied for each case.

If complete (imputed) end date is available and the imputed start date is greater than the (imputed) end date, then imputed start date should be set to the (imputed) end date.

11.1. Algorithm for Adverse Events and Medications

When the start date is missing,

	Case	Imputed Value
Missing Day	year and month = year and month of IP dosing date	IP dosing date
	year and month <> year and month of IP dosing date	the 1st of the month
Missing Day and Month	year = year of IP dosing date	IP dosing date
	year <> year of IP dosing date	1st of January
Completely Missing	N/A	

If complete (imputed) end date is available and the imputed start date is greater than the (imputed) end date, then imputed start date should be set to the (imputed) end date.

When the end date is missing,

	Case	Imputed Value
Missing Day	year and month < year and month of last follow-up date	last day of the month
	year and month = year and month of last follow-up date	last follow-up date
Missing Day and Month	year < year of last follow-up date	31st of December
	year = year of last follow-up date	last follow-up date
Completely Missing	N/A	

For the end date imputation, the last follow-up date is defined as the last available visit date, i.e., including safety follow-up visit date and/or unscheduled visit date after the EOS visit, the last start/end date of AE or concomitant medication (CM), and the date of death.

11.2. Algorithm for Treatment-Emergent

After imputation for partial dates is implemented, whether AE is TEAE will be decided.

When start date is present,

- If known/imputed start date ≥ the date of dose of IP, then AE is considered as TEAE

When start date is completely missing but end date is present

- If known/imputed end date ≥ the date of dose of IP, then AE is considered as TEAE

When both start date and end date are completely missing

- AE is considered as TEAE

11.3. Algorithm for Concomitant

After imputation for partial dates is implemented, whether medication is concomitant will be decided.

When both start date and end date are present

- If known/imputed end date ≥ the date of first dose of IP and known/imputed start date ≤ the date of EOS/ET visit, then medication is considered as concomitant

When start date is present and end date is completely missing

- If known/imputed start date ≤ the date of EOS/ET visit, then medication is considered as concomitant

When start date is completely missing but end date is present

- If known/imputed end date ≥ the date of first dose of IP, then medication is considered as concomitant

When both start date and end date are completely missing

- Medication is considered as concomitant

APPENDIX 2. CODE FOR INTRAOCULAR PRESSURE ADVERSE EVENT

Intraocular pressure AE_MedDI

APPENDIX 3. CODE FOR INTRAOCULAR INFLAMMATION ADVERSE EVENT

Intraocular inflammation AE_M

STATISTICAL ANALYSIS PLAN SIGNATURE PAGES

SIGNATURE PAGE

Declaration of the authors

Protocol Title: Applicable to this Statistical Analysis Plan: An open-label, single group, single-dose clinical study to evaluate the usability of the pre-filled syringe (PFS) of SB11 in subjects with Neovascular Age-Related Macular Degeneration (AMD) or Macular Oedema Secondary to Retinal Vein Occlusion (RVO)

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(Mmm dd, yyyy)

*Note: The signature will be replaced with E-signature on the first page of this document.