Document Type:	Statistical Analysis Plan
Official Title:	A Randomized, Multi-Center, Double Blinded, Self-Initiated, Single Treatment Study Comparing Sitavig® (acyclovir) 50 mg Muco-adhesive Buccal Tablet to Placebo in the Treatment of Herpes Labialis in Immunocompetent Adults
NCT Number:	NCT05098938
Document Date:	18 DEC 2023

STATISTICAL ANALYSIS PLAN

TITLE PAGE

A Randomized, Multi-Center, Double Blinded, Self-Initiated, Single Treatment Study Comparing Sitavig® (acyclovir) 50 mg Muco-adhesive Buccal Tablet to Placebo in the Treatment of Herpes Labialis in Immunocompetent Adults

Final Version 1.0: DEC 18, 2023

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DECLARATION

I, the undersigned, declare that I have prepared the statistical analysis plan along with TLF mock shells and that to the best of my knowledge this document is internally consistent with protocol and scientifically rational.

Prepared by:

PPD

12/18/2023

Designation\Role: PPD

Sign & Date (MMM DD, YYYY)

I, the undersigned declare that I have reviewed the statistical analysis plan along with TLF mock shells and that to the best of my knowledge the document is internally consistent with protocol and scientifically rational.

Reviewed by:

PPD

12/18/2023

Designation\Role: PPD

Sign & Date (MMM DD, YYYY)

AUTHORIZATION: I, the undersigned, declare that I have reviewed the statistical analysis plan along with TLF mock shells and that to the best of my knowledge the document accurately reflects the protocol objectives.

Authorized by:

PPD

12/18/2023

PhD

Signing on behalf of PPD

Designation\Role: PPD

Sign & Date (MMM DD, YYYY)

REVISION HISTORY

Version	Date	Author	Reasons

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
BP	Blood Pressure
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DOE	Duration Of Episode
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FU	Follow Up
HL	Herpes Labialis
i.e.,	id est (That Is)
IA	Interim Analysis
IB	Investigator's Brochure
ICH	International Council For Harmonisation
IMP	Investigational Medicinal Product
ITT	Intent To Treat
kg	Kilogram
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
OHIP	Oral Health Impact Profile
PDV	Protocol Deviation
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
RNR	Randomization Number
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, and Listings

Abbreviation or special term	Explanation
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods and data handling procedures to be followed during the final reporting and analyses of data collected for the study protocol 21755.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of SAP has been developed using the protocol (21755 version 5.0 dated SEP 30, 2022) and eCRF (version 4.0 dated FEB 23, 2023).

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2 STUDY DETAILS

2.1 Study Objectives

The primary objective of the study is:

- To compare Duration of Episode (DOE) of cold sores when treated with Sitavig or placebo in subjects experiencing a recurrence of Herpes Labialis (HL).

The secondary objectives of the study are:

- To compare the incidence of aborted lesions between subjects receiving either Sitavig or placebo after experiencing prodromal symptoms of a recurrence of HL.
- To compare the incidence of recurrence of primary HL lesions between subjects receiving either Sitavig or placebo during a 12-month follow-up period.
- To compare the time to recurrence of primary HL lesions between subjects receiving either Sitavig or placebo during a 12-month follow-up period.
- To assess safety and tolerability of the investigational products.

The other objectives of the study are:

- To compare the DOE in subjects who used Sitavig or placebo who initiated study intervention within 1 hour of prodromal symptoms and subjects who initiated study intervention after 1 hour of prodromal symptoms.
- To compare the time to cessation of symptoms in patients experiencing a recurrence of HL in subjects who used Sitavig and placebo.
- To compare the Quality of Life (QoL) in subjects who used Sitavig and placebo.

- To compare the 0-10 Numerical Rating Scale (NRS) HL symptoms by time point in subjects who used Sitavig and placebo.
- To evaluate the Global assessment at Day 14.
- To evaluate the incidence of detachment or swallowing within 6 hours of dosing, and the incidence of replacing the tablet.

2.2 Study Design

This is a randomized, multi-center, subject-initiated, double-blinded, single treatment study comparing acyclovir 50 mg muco-adhesive buccal tablet (Sitavig) to matching placebo in the treatment of HL in immunocompetent adults.

The study consists of a Screening and Randomization Phase, Run-in Phase, Treatment Phase/ Evaluation Phase, and a Follow-Up Phase.

Screening/Randomization Phase:

Subjects will be screened for eligibility up to 35 days prior to study according to the inclusion/exclusion criteria. Eligible subjects will be randomized into one of two study interventions. Subjects will then enter into Run-in Phase, which starts a six-month treatment eligibility window.

Run-in Phase:

The Run-in Phase is a six-month treatment eligibility window that provides the opportunity for subjects to spontaneously start an HL outbreak that would require treatment. Subjects will be in contact with Science 37 using weekly virtual check-ins within the Science 37 Platform. Adverse events and concomitant medications could be recorded. Subjects who do not develop an HL episode within six months will be withdrawn from the study.

Treatment Phase/Evaluation Phase:

Once subjects experience prodromal symptoms, they will take face images and self-initiate treatment (study intervention) preferably within one hour and before the visible appearance of any signs of HL lesions according to the product instructions. Subjects will also be completing HL symptom scores (pain, tenderness, itching, tingling and discomfort) as well as QoL scoring using the Oral Health Impact Profile (OHIP) and during the next 10 days within the Science 37 Platform. Subjects will then be under evaluation for healing of the primary lesion(s) up to 14 days.

Subjects will be asked to meet with the clinic via the Science 37 Platform within 36 hours of the start of study intervention (Day 1) and complete face images, symptom and QoL scores using the Science 37 Platform. Additionally, subjects will complete face images, symptom and QoL scores on Days 2 through 13 with a virtual visit on Day 14 (+2 days), Visit 3 using the Science 37 Platform.

Follow-up Phase:

Subjects will automatically transition to the Follow-up Phase after the completion of the Treatment Phase. Subjects will be in contact with the Science 37 using weekly virtual check-ins within the Science 37 Platform with the purpose reporting any adverse events, concomitant medications or new outbreaks of HL. Potential new HL occurrences will be reviewed by the investigator using face images and symptom scores.

The duration of each patient's participation will be up to 20 months.

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A visual presentation of the overall study design is provided in Figure 1.

Study procedures and their timing are summarized in in Table 1.

Figure 1 – Study Scheme

Screening / Randomization Phase		Run-in Phase	Start Study Intervention	Treatment Phase						Follow-Up Phase[a]			
Within 35 days of the start of the Run-in Phase		Start 6-month eligibility window	Day 1	Day 2	Day 3	Day 4-6	Day 7	Day 8-13	Day 14 (+ 2 days)	3 months (± 3 days)	6 months (± 3 days)	9 months (± 3 days)	12 months (± 3 days)
Visit 1 Baseline Face image (no symptoms) Photo and e-diary/App training e-diary/App NRS symptom scores	✱	Weekly virtual check-in Virtual training refresher	**Visit 2**** Pre/post treatment Face images Subject takes IMP at home ◈ e-diary/App NRS symptom scores	**Visit 2** (within 24 hours of treatment start) Face image e-diary/App NRS symptom scores	Face image e-diary/App NRS symptom & QoL scores	Face image e-diary/App NRS symptom scores	Face image e-diary/App NRS symptom & QoL scores	Face image e-diary/App NRS symptom scores	**Visit 3** Face image e-diary/App symptom & QoL scores Global assessment	Phone call e-diary/App Weekly virtual check-in Ad-hoc NRS symptom scores Face image	Phone call e-diary/App Weekly virtual check-in Ad-hoc NRS symptom scores Face image	Phone call e-diary/App Weekly virtual check-in Ad-hoc NRS symptom scores Face image	**End of Study** Phone call e-diary/App Weekly virtual check-in Ad-hoc NRS symptom scores Face image

✱ = participant randomized into one of two blinded study interventions
- Sitavig 50 mg buccal tablet
- Placebo buccal tablet

◈ = participant experiences prodromal symptoms that require study intervention

[a] follow-up dates are established from the Day 1 dosing date

** Visit 2 may occur within 36 hours of Day 1 dosing time

Table 1: Schedule of Activities (SoA)

	Screening & Randomization Phase	Run-in Phase	Treatment Phase							Follow-Up Phase[g]			
Visit Number	1			2					3[d]				
Day or Milestone	Within 35 days of Run-in start	Six-month eligibility window	1	1-2	3	4-6	7	8-13	14 +2d	3 months (call) ±3 days	6 months (call) ±3 days	9 months (call) ±3 days	12 months (call) ±3 days
Virtual visit	X			X					X				
Informed consent	X												
Inclusion/Exclusion criteria	X			X									
Subject demographics	X												
Medical History	X												
Prior/Concomitant Medication	X	X		X						X	X	X	X
History of drug and alcohol use	X												
Urine drug screen	X												
Urine pregnancy test	X		X[a]										
BP and pulse	X			X					X				
Platform (re)training	X	X											
IMP dosing instructions	X												
NRS symptom scores	X		X[b]	X	X	X	X	X	X	X[e]	X[e]	X[e]	X[e]

Face images	X		X[b]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[e]	X[e]	X[e]	X[e]
Randomization[f]													
Virtual weekly check-ins		X								X	X	X	X
Start of prodromal symptoms			X										
IMP administration			X										
IMP compliance check				X					X				
OHIP-14					X		X		X				
Global assessment									X				
IMP kit return									X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
End of Study													X

[a] The urine pregnancy test must be performed prior to the start of study intervention and be negative (not pregnant).
[b] NRS symptom scores and face images can be collected at 09:00, 14:00 and 19:00 that day. Depending on the time study intervention starts, NRS symptom scores and face images may or may not be collected for Day 1.
[c] Face images taken at 09:00, 14:00 and 19:00 each day.
[d] The 2-day window pertains to all Visit 3 tasks except the NRS symptom scores, face images, QoL-OHIP and Global assessment which should be collected at their respective nominal times (±60 minutes) on Day 14.
[e] Face image(s) and NRS symptom score(s) required if a new outbreak of herpes labialis is suspected by the investigator.
[f] After successful completion of all screening procedures.
[g] Follow up dates established using the Day 1 dosing date

2.3 Determination of Sample Size

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2.4 Randomization

Subjects will be randomized in a 1:1 ratio to either of the treatment groups (Sitavig or placebo). At Screening, qualified subjects will be assigned a unique number (Randomization Number, [RNR]) in ascending numerical order according to the randomization schedule generated prior to the study by Statistics Department at Bayer.

2.5 Blinding

This is a double-blind study. Thus, neither the investigator nor the subject will know which treatment the subject will receive.

3 DATA ANALYSIS CONSIDERATION

3.1 General Data Considerations

The following conventions will be applied to analyses/data presentation:

All dates will be displayed in DDMMMYYYY format.

The statistical analyses will be performed by Quartesian (now a part of Veranex Solutions), using Statistical Analysis System (SAS) Version 9.3 (or higher). All Tables, Figures, and Listings (TFLs) will be produced in landscape format. In general, all data will be listed by the subject, treatment and visit but not limited to above variables. The number of variables presented in each Listing can vary. Please refer to Mock TFLs.

Data will be summarized by treatment wherever appropriate. The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables. Unscheduled visit data will be presented in Listings, but not in Tables and Figures.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise stated, descriptive statistics will include total number of subjects with non-missing value of a variable/parameter (n), mean, Standard Deviation (SD), minimum, median, and maximum. The number of missing observations will also be presented, if there are any, at a particular visit. In case

of n<2, where n indicates the number of evaluable subjects at a particular time point, only n, minimum and maximum will be displayed.

For categorical variables, data will be summarized using number and percentages. The number (n) indicates the number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects in the respective treatment group (N). The number and percentage of subjects with missing values for a variable/category/event will also be presented, if there are any, for the resulting visits under the "Missing" category.

Unless otherwise stated, all percentages will be expressed to one decimal place. The number and percentage of subjects will always be presented in the form XX (XX.X). Counts of zero in any category will be presented as "0" and if the percentage in any category to be presented is 100, it will be presented as "100".

All statistical testing will be 2-sided at significance level of 0.05 and no multiplicity adjustment will be made.

3.2 Decimal Precision Convention

The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median, Confidence Interval (CI) will be presented to one more decimal place than the original data, whereas the SD and Standard Error (SE) will be presented to two more decimal places than the original data. P-value will be presented with three decimal places. If p-value is closer to 0, then it should be reported as "<0.001" and if it is closer to 1, then it should be reported as ">0.999".

3.3 Handling of Missing Data

For subjects whose HL lesions are healed, however, healing ending date and time are missing, DOE and time to cessation of symptoms will be imputed as 14*24 hours since the observation period to determine healing can last up to 14 days.

To handle missing or partial dates, the following rules will be applied.

3.3.1 For Partial Start Dates

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the first dose date, then impute the month of the dose date.

b. Otherwise, assign "January."

3. If the day is unknown, then:
   a. If the month and year match the month and year of the first dose date, then impute the day of the dose date.
   b. Otherwise, assign "01."

3.3.2 For Partial End Dates

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pre-treatment or on/after treatment, the following strategy will be used:

1. If both start date and stop date are missing, then the most conservative approach is taken, and the AE (or medication) is considered to be treatment emergent (or concomitant medication).
2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken, and the AE (or medication) is considered to be treatment emergent (or concomitant medication).
3. If the start date is missing but the stop date is not missing and is before the day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).
4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication is considered to be concomitant while the AE is defined by start date.

3.4 Study Day

The study day for each assessment/event of a subject will be derived using their first study drug administration date. For the assessments performed on or after first study drug administration date, study day is calculated as

Study Day = *(Date of assessment/event – Date of first study drug administration) + 1*

For the assessments performed prior to first study drug administration, study day is calculated as

Study Day = *(Date of assessment/event – Date of first study drug administration)*

The summary and analysis will be performed considering the different timepoint when the assessment was conducted.

3.5 Statistical Significance & Multiplicity

All analyses will be based on two-tailed testing at significance level (alpha) of 0.05. No multiplicity adjustment will be made for analyzing efficacy endpoints.

4 DEFINITIONS AND DERIVATIONS

Run-in Failures: Run-in failures are participants who successfully completed screening and randomized to a blinded study intervention (treatment). Participants start a 6-month eligibility window during the Run-in Phase where they could potentially self-initiate treatment. Participants who are considered a Run-in failure occur because of the following:

- Randomized participants with no prodromal symptoms after 6 months
- Met an exclusion criterion (e.g., medication, pregnancy)
- Adverse event or change in medical history that requires study withdrawal
- Withdraw of informed consent by the participant
- Study intervention kit not available
- Lack of compliance as determined by the Investigator/designee

Baseline: Baseline value is defined as the last non missing assessment prior to first administration of the study drug. If the assessment occurs on the same day as the first study drug administration, then the time of assessment should be compared to the time of first dose administration to derive the baseline value.

Post-baseline: The Post-baseline values are defined as assessments taken after the first administration of study drug/treatment.

Change from Baseline *= (post baseline value – baseline value).*

Duration of Episode (DOE): DOE is defined as the time from the initiation of treatment to the healing of primary lesions (loss of crust) for subjects who experience a vesicular lesion. For subjects whose primary lesions are not vesicular in nature, DOE is the time from study intervention initiation to the return to normal skin as determined by the independent blinded reader of the subject's face images using a 6-point Likert scale or the cessation of symptoms, whichever comes last. For the subjects who do not demonstrate the healing of primary lesions or cessation of symptoms, the data will be censored at 14 days (14*24 hours) regardless of any circumstances. If time (hour) is missing for either treatment initiation or the healing of primary lesion or both, however, both dates are recorded, then DOE is number of days (end date – start date) *24. If only healing ending date and/or time are missing, DOE will be imputed as 14*24 hours. If date of treatment initiation is missing, then DOE will be missing.

DOE (hours) *= (Date and time of healing of primary lesions – Date and time of first treatment administered)*

Vesicular lesion: A lesion will be categorised as vesicular if a subject has face image interpretation Likert scale score of 3 or above.

Healing of primary lesions: A vesicular lesion will be considered as healed if the face image interpretation Likert score drops to either 0 or 1 after progressing to 3 and beyond. For those without a vesicular lesion, healing is defined as a face image interpretation Likert score of 0 or cessation of symptoms i.e., all NRS symptom scores as 0, whichever comes last.

Cessation of symptoms: Cessation of symptoms is defined as the absence of sensations of pain, tenderness tingling, itching or discomfort at the site of the cold sore as measured by NRS. In other words, having the NRS score of 0 for all symptoms such as pain, tingling, tenderness, itching and discomfort is cessation of symptoms.

Time to cessation of symptoms: It is the time (in hours) from the initiation of treatment dose of assigned study intervention to cessation of symptoms. For the subjects who do not demonstrate the cessation of symptoms, the data will be censored at 14 days (14*24 hours) regardless of any circumstances. If hour is missing for either treatment initiation or the endpoint but both dates are recorded, then Time to cessation of symptoms is number of days (end date – start date) multiplied by 24. If either date is missing, then Time to cessation of symptoms is missing.

Time to cessation of symptoms *= (Date and time of cessation of symptoms – Date and time of first treatment administered)*

Time to recurrence of HL lesions: It is the time (in days) from resolution of the cold sore treated in the Treatment phase until appearance of a cold sore during the follow-up period. The time to first recurrence is determined by assessment from the investigator and documented using NRS symptom scores and face images using the Science 37 Platform. For subjects who do not recur during the follow-up period, the data will be censored at the time of last follow-up.

Time to recurrence of HL lesions (Days) *= (Date of first recurrence of HL lesions – Date of healing of primary lesions) + 1*

Treatment Emergent Adverse Event: A TEAE is defined as any new AE that commences on or after the start of the first study drug administration or any pre-existed AE/ condition that worsened in severity following administration of study drug.

End of Treatment Phase: The end of the Treatment Phase for a subject is defined as the date (time) of the last visit in the Treatment Phase.

End of Study: The end of the study is defined as the date of the last follow-up visit (either by documented HL outbreak or at 12 months) of the subject in the study. A subject is considered to have completed the study if he/she has completed all phases of the study up to Follow up Phase.

Aborted Lesion: It is defined as a treated HL lesions that do not progress to the vesicular or crust stage. A lesion that returns to normal skin without forming a vesicle or crust will be counted as an aborted lesion i.e., for this lesion the face image interpretation Likert score will be less than or equal 2 and will never reach a score of 3 or above before healing.

5 PRIMARY, SECONDARY AND EXPLORATORY ENDPOINTS

5.1 Primary Endpoint

The **primary endpoint** of study is:

> Duration of episode (DOE) will be measured in hours (using the Science 37 Platform), of a single treated HL lesion. Observation period to determine healing will last up to 14 days. DOE is defined in detail in section 4.

5.2 Secondary Endpoints

Following are the **secondary endpoints** of the study:

- Incidence of aborted lesions, defined as treated HL lesions that do not progress to the vesicular or crust stage. Observation period to determine healing will last up to 14 days.
- Incidence of recurrence of HL lesions during the 12-month follow-up period.
- Time to recurrence of HL lesions, measured in days from resolution of the cold sore treated in the Treatment phase until appearance of a cold sore during the follow-up period.
- The percentage of subjects who have at least one recurrence during the 12-month follow up period.
- Safety and tolerability measured by the incidence of Treatment-Emergent Adverse Events (TEAEs).

5.3 Other Endpoints

Following are the **other endpoints** of the study:

- Duration of episode (DOE) will be measured in hours (using the Science 37 Platform), of a single treated HL lesion in subjects who initiation study intervention within 1 hour of onset of prodromal symptoms and subjects who initiated study intervention more than 1 hour after onset of prodromal symptoms.
- Time to cessation of symptoms, measured in hours from initial application of assigned study intervention. Cessation of symptoms is defined as the absence of sensations of pain, tenderness tingling, itching or discomfort at the site of the cold sore as measured by NRS.
- Quality of life score, as measured by the OHIP-14 questionnaire at 3-, 7- and 14-days post-dose.
- Global assessment of study intervention at Day 14.
- The change from baseline to post-dose in NRS.
- The incidence of detachment or swallowing within 6 hours of dosing and the number (percentage) of subjects with the incidence.
- The percentage of subjects who replace the tablet among those with detachment or swallowing within 6 hours of dosing.

6 ANALYSIS POPULATION AND TREATMENT GROUPS

6.1 Analysis Population

Screened Population: All subjects who signed the Informed Consent Form.

Safety Population: All randomized subjects who take at least one dose of IMP.

Intent-to-treat (ITT) Population: All subjects who are randomized and provide at least one measure of primary efficacy parameters after the first dose of IMP i.e., if there is at least one non-missing assessment of subject's face image using a 6-point Likert scale after study drug initiation.

PP Population: The Per Protocol population will include all subjects in ITT who complete 14-days of evaluations and do not have any major protocol violations. Any exclusion from PP Population will be determined and documented prior to the database lock.

Follow-Up Population: The Follow Up population will be a subgroup of the ITT population who will continue into the 12 month follow up period and will be defined as patients whose lesions were all treated at the end of the Treatment Phase (of 14 Days) of the trial.

The primary efficacy analysis population will be PP population and ITT Population will be secondary. The same analysis on ITT Population will be repeated for the primary and secondary efficacy endpoints to assess the robustness of the results based on PP Population.

6.2 Treatment Groups

In this study there are two treatment groups:

- Sitavig® (acyclovir) 50 mg muco-adhesive buccal tablet (one tablet application on Day 1).
- Placebo muco-adhesive buccal tablet (one tablet application on Day 1).

The treatment groups will be labelled as “Sitavig” and “Placebo” in the TLFs.

7 ANALYSES METHODS AND REPORTING DESCRIPTIONS

7.1 Subject Disposition

Subject disposition for screened population will summarize the number and percentage of subjects screened, screen failure, subjects randomized, subjects in Safety, ITT, PP, and FU populations, who completed the study, and who prematurely discontinued the study along with the reasons for discontinuation and withdrawal from study by treatment groups.

Individual subject data on disposition will be presented in listing.

7.2 Demography and Baseline Characteristics

The demographic and baseline characteristics will include age (years), gender, ethnicity, race, height (cm), weight (kg), and BMI (kg/m2) will be summarized by treatment group for ITT Population. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median and maximum) and for categorical variables, the number and percentage of subjects in each category will be summarized.

Individual subject data listings for demographic and baseline characteristics will be presented.

7.3 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

Medical/Surgical history will be summarized by treatment group with the number and percentage of subjects in each System Organ Class (SOC), Preferred Term (PT), and overall, for the Safety

Population. Subjects will be counted only once at the PT, only once at the SOC, and only once at subject level for the counting of total number of subjects with a medical history term.

Individual subject data listings for medical/surgical history will be presented.

7.4 Prior and Concomitant Medications

Prior medications are those medications that are taken prior to the first dose of study drug i.e., Prior medications have a stop date/time before study treatment starts. Medications stopped on the same day as the start of first study-drug administration will be considered as prior medication only. Concomitant medications are medications taken by subject on/after the start of first study-drug administration. If a medication starts before study entry and continues through the study that will be considered both as prior and concomitant. Prior and concomitant medications will be classified according to the World Health Organization Drug Dictionary (WHODD) version B3SEP2021.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classes and Preferred Term (PT) using number and percentages for Safety Population by treatment groups.

Individual subject data listings will be presented, with separate Listings for prior and concomitant medications.

7.5 Protocol Deviation

Protocol Deviation will be summarized by treatment groups and deviation categories (Major/Minor) using Safety Population.

Individual subject data listings for protocol deviations will be presented.

7.6 Study Drug Exposure and Overdose

For this study, any dose of study intervention greater than one (1) tablet being ingested will be considered an overdose. This includes tablets that were accidently swallowed requiring the subject to apply a second (backup) buccal tablet, applying two tablets to the gum, or any other situation in which a subject ingests two tablets.

Overdose for ITT and PP populations will summarize the number and percentage of subjects who self-administer a second tablet along with the reason for taking second tablet by treatment groups.

Individual subject data for overdose will be presented in Listing. Also, a listing will be presented all other overdoses where all other overdoses are defined as any reason other than these Accidentally

swallowed, Tablet did not stick to gum when applied and not swallowed Accidentally chewed will be considered as all other overdoses.

7.7 Efficacy Analysis

7.7.1 Analysis of Primary Efficacy Endpoint

The primary efficacy variable is DOE, which will be measured in hours (using the Science 37 Platform), of a single treated HL lesion. Observation period to determine healing will last up to 14 days. DOE is defined in detail in section 4.

DOE will be analyzed using Kaplan-Meier method for treatment groups (Sitavig and Placebo). Median, associated 95% CIs and survival probabilities will be estimated using Kaplan-Meier (KM) Method. DOE curves between the two treatment groups will be compared with a log-rank test and the corresponding hazard ratio (with 95% CI) will be estimated using Cox proportional hazard method.

The analysis of primary efficacy endpoint will be performed on both ITT and PP population, with PP population being the primary efficacy population and ITT population being secondary. Individual subject data for DOE will be presented in Listing.

7.7.2 Analysis of Secondary Efficacy Endpoints

- **Incidence of aborted lesions**, defined as treated HL lesions that do not progress to the vesicular or crust stage. A lesion that returns to normal skin without forming a vesicle or crust will be counted as an aborted lesion. Observation period to determine healing will last up to 14 days. The incidence(events) of aborted lesions will be reported by treatment groups and proportions of subjects with at least one Incidence of Aborted Lesions will be compared between the two treatment groups using the Chi square or Fisher's Exact test for categorical data for both ITT and PP populations. Individual subject data for aborted lesions will be presented in Listing.

- **Incidence of recurrence of HL lesions** during the 12-month follow-up period will be reported by treatment groups for FU population. Recurrence is determined by assessment from the investigator and documented using NRS symptom scores and face images using the Science 37 Platform.

  The percentage of subjects with at least one recurrence of HL lesions during the 12-month follow-up period will be compared between the two treatment groups using the Chi square or Fisher's Exact test for homogeneity of proportions for categorical data using FU population.

Individual subject data for recurrence of HL lesions will be presented in Listing.

- **Time to recurrence of HL lesions**, measured in days from resolution of the cold sore treated in the Treatment phase until appearance of a cold sore during the follow-up period. For subjects who do not recur during the follow-up period, the data will be censored at the time of last follow-up. Time to recurrence of HL lesions will be analyzed similarly to the analysis of primary endpoint using KM method for FU population. Individual subject data Listing for time to recurrence of HL lesions will be presented.

7.7.3 Analysis of Other Efficacy Endpoints

The analysis of other endpoints will be performed on ITT population.

- **Duration of episode (DOE)** will be measured in hours (using the Science 37 Platform), of a single treated HL lesion in subjects who initiate study intervention within 1 hour of onset of prodromal symptoms and subjects who initiated study intervention more than 1 hour after onset of prodromal symptoms. DOE will be analyzed similarly to the analysis of primary efficacy endpoint using KM method. Individual subject data Listing for DOE will be presented.
- **Time to cessation of symptoms**, measured in hours from the initiation of first dose of study drug. Cessation of symptoms is defined as the absence of sensations of pain, tingling, or burning at the site of the cold sore. Observation period to determine healing will last up to 14 days. Time to cessation of symptoms will be analyzed similarly to the analysis of primary efficacy endpoint using KM method. Individual subject data listing for Time to cessation of symptoms will be presented.
- **Quality of life score**, as measured by the OHIP-14 questionnaire at 3-, 7- and 14-days post-dose will be analysed using Cochran-Mantel-Haenszel (CMH) method with a modified ridit score. The number and percentage of subjects will be summarized for each question/item in OHIP-14 questionnaire by scheduled visits and treatment groups. The actual values of OHIP-14 weighted score for subscale category questions will be summarized by scheduled visits and treatment groups. The post-dose values will be compared between the Sitavig and placebo groups using two sample t-test assuming the normality of data and if the data is non-normal then Wilcoxon Rank-Sum test (also known as the Mann-Whitney U test) will be used. Please refer the Section 9.2 in this SAP for weight factors associated with subscale category questions. Individual subject data listing for OHIP-14 will be presented.
- **Global assessment of treatment efficacy** at Day 14 using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent) will be analysed using CMH method with a modified ridit score. The number and percentage of subjects will be summarized for Global assessment of treatment efficacy. Individual subject data listing for Global evaluation will be presented.

- **The change from baseline to post-dose in NRS**. The actual and the change from baseline values of NRS score for each symptom/question will be summarized by scheduled visits and treatment groups. The change from baseline to post-dose values will be compared between the Sitavig and placebo groups using two sample t-test assuming the normality of data and if the data is non-normal then Wilcoxon Rank-Sum test (also known as the Mann-Whitney U test) will be used. Individual subject data Listing for NRS scores will be presented.
- **The incidence of detachment or swallowing within 6 hours of dosing** will be reported by treatment groups. The percentage of subjects with detachment or swallowing within 6 hours of dosing will be compared between the two treatment groups using the Chi square or Fisher's Exact test for homogeneity of proportions for categorical data. Individual subject data Listing for incidence of detachment or swallowing within 6 hours of dosing will be presented.
- **The percentage of subjects who replace the tablet** among those with detachment or swallowing within 6 hours of dosing will be analysed using the Chi square or Fisher's Exact test for homogeneity of proportions for categorical data. Individual subject data Listing of subjects who replace the tablet among those with detachment or swallowing within 6 hours of dosing will be presented.

7.8 Safety Analysis

The analysis of safety data will include assessments of Adverse Events (AEs) and Vital Signs on the Safety population.

7.8.1 Adverse Events

AEs will be coded using MedDRA version 24.1. A subject experiencing the same AE more than once will be counted only once for that preferred term, assuming the worse severity and worse relatedness to study drug. If severity is missing then the worst severity should be considered and if relationship is missing, then the worst relationship should be considered.

The AEs will be summarized overall for with the number and percentage of subjects in the following categories:

- Number of Subjects with AEs
- Number of Subjects with Serious AEs
- Number of Subjects with TEAEs
- Number of Subjects with Serious TEAEs
- Number of Subjects with Treatment related TEAEs
- Number of Subjects with Treatment related Serious TEAEs
- Number of Subjects with TEAEs Leading to Study Discontinuation
- Severity Grades
- Relationship with Study Drug
- Action Taken

- Outcome of AE

A summary of TEAEs, including the number of events reported, the number and percentage of subjects with event, will be presented by SOC and PT in the following categories.

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by SOC, PT and Severity
- Summary of TEAEs by SOC, PT and Relationship with Study Drug
- Summary of TEAEs leading to study withdrawal by SOC and PT
- Summary of Serious TEAEs by SOC and PT
- Summary of TEAEs leading to death

Separate individual subject data listings for AEs, TEAEs, death due to TEAEs, TEAEs relationship with study drug, and TEAEs leading to study withdrawal will be presented.

7.8.2 Vital Signs

The Vital Signs parameters include Systolic and Diastolic Blood Pressure (mm hg), and heart rate (bpm). Descriptive statistics (n, Mean, SD, Median, Minimum and Maximum) of the observed (Reading Averages) and the change from baseline values will be summarized by treatment group at each scheduled visit.

Individual subject data for vital signs parameters will be presented in Listing.

7.9 PK/PD Analysis

No PK/PD analyses will be conducted in this trial

7.10 Pooled Analyses

No pooled analyses will be conducted in this trial

7.11 Subgroup Analyses

No Subgroup analyses will be conducted in this trial

7.12 Interim Analysis

No Interim analyses will be conducted in this trial

7.13 Changes to Analyses Specified in Protocol

In protocol section 9.4.3, it is mentioned that the "*Incidence of recurrence of HL lesions during the 12-month follow-up period (IncRec12) will be analyzed using Chi-square test.*" However, no analysis is being performed on the incidence of recurrence of HL lesions and simply the total number of incidences/events will be reported.

8 REFERENCE

- *Bayer Healthcare LLC, protocol 21755 version 5.0 dated SEP 30, 2022, and eCRF version 4.0 dated FEB 23, 2023.*
- *FDA Guidance for Industry: E3 Structure and Content of Clinical Study Reports. July 1996. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e3-structure-and-content-clinical-study-reports.*
- *FDA Guidance for Industry: E9 Statistical Principles for Clinical Trials. September 1998. Available online:* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials.
- *Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol. 1997 Aug;25(4):284-90. doi: 10.1111/j.1600-0528.1997.tb00941.x. PMID: 9332805.*

9 APPENDIX

9.1 Numerical Rating Scale (0-10)

Assessed at Screening (pre-dose), Day 1 through the subject's self-reported completion of study intervention (on Day 14). Subjects will complete a NRS 0-10 symptoms scales for pain, tenderness, itching, tingling and discomfort for each time point. All post-dose time point assessments have an allowable window of ± 60 minutes.

My cold sore pain at this time is …

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst Possible pain

*The **tenderness** of my cold sore at this time is …*

0	1	2	3	4	5	6	7	8	9	10

No pain Worst Possible pain

*The **itching** of my cold sore at this time is …*

0	1	2	3	4	5	6	7	8	9	10

No pain Worst Possible pain

*The **tingling** of my cold sore at this time is …*

0	1	2	3	4	5	6	7	8	9	10

No pain Worst Possible pain

*The **discomfort** of my cold sore at this time is …*

0	1	2	3	4	5	6	7	8	9	10

No pain Worst Possible pain

9.2 Oral Health Impact Profile (OHIP)

Developed from the OHIP-49 questionnaire, the OHIP-14 is a 14-part quality of life (QoL) questionnaire about the social impact of oral disease. The OHIP-14 consists of a set of questions measuring the functional limitation, clinical pain, psychological discomfort, clinical disability, psychological disability, social disability and handicap of persons that could arise as a result of problems with the teeth or mouth. Questions are answered using a 6-point Likert scale

Directions: **This questionnaire asks how trouble with your teeth or mouth may have caused problems in your daily life. Completely fill in the ONE circle for each statement that best describes how often you have had each of the problems TODAY.**

	Very Often	Fairly Often	Occas-ionally	Hardly ever	Never	Don't know
1. Have you had trouble pronouncing any words because of problems with your teeth or mouth?	○	○	○	○	○	○
2. Have you felt that your sense of taste has worsened because of problems with your teeth or mouth?	○	○	○	○	○	○
3. Have you had painful aching in your mouth?	○	○	○	○	○	○
4. Have you found it uncomfortable to eat any foods because of problems with your teeth or mouth?	○	○	○	○	○	○
5. Have you been self conscious because of your teeth or mouth?	○	○	○	○	○	○
6. Have you felt tense because of problems with your teeth or mouth?	○	○	○	○	○	○
7. Has your diet been unsatisfactory because of problems with your teeth or mouth?	○	○	○	○	○	○
8. Have you had to interrupt meals because of problems with your teeth or mouth?	○	○	○	○	○	○
9. Have you found it difficult to relax because of problems with your teeth or mouth?	○	○	○	○	○	○
10. Have you been a bit embarrassed because of problems with your teeth or mouth?	○	○	○	○	○	○
11. Have you been a bit irritable with other people because of problems with your teeth or mouth?	○	○	○	○	○	○
12. Have you had difficulty doing your usual jobs because of problems with your teeth or mouth?	○	○	○	○	○	○
13. Have you felt that life in general was less satisfying because of problems with your teeth or mouth?	○	○	○	○	○	○
14. Have you been totally unable to function because of problems with your teeth or mouth?	○	○	○	○	○	○

OHIP-14 Questionnaire	Subscale Category	Weight
1. Have you had trouble pronouncing words because of problems with your mouth?	Functional limitation	0.51
2. Have you felt that your sense of taste has worsened because of problems with your mouth?	Functional limitation	0.49
3. Have you had painful aching in your mouth?	Physical pain	0.34
4. Have you found it uncomfortable to eat any foods because of problems with your mouth?	Physical pain	0.66
5. Have you been self-conscious because of your mouth?	Psychological discomfort	0.45

6. Have you felt tense because of problems with your mouth?	Psychological discomfort	0.55
7. Has your diet been unsatisfactory because of problems with your mouth?	Physical disability	0.52
8. Have you had to interrupt meals because of problems with your mouth?	Physical disability	0.48
9. Have you found it difficult to relax because of problems with your mouth?	Psychological disability	0.60
10. Have you been a bit embarrassed because of problems with your mouth?	Psychological disability	0.40
11. Have you been a bit irritable with other people because of problems with your mouth?	Social disability	0.62
12. Have you had difficulty doing your usual jobs because of problems with your mouth?	Social disability	0.38
13. Have you felt that life in general was less satisfying because of problems with your mouth?	Handicap	0.59
14. Have you been totally unable to function because of problems with your mouth?	Handicap	0.41

9.3 Global Evaluation

Questions that rate the IMP as a cold sore treatment and the subject's experience at the self-reported completion of study intervention (14 days post-dose) using a 5-point Likert scale.

Overall, I would rate the effectiveness of my study medication in relieving my cold sore as…

- 0 = poor
- 1 = fair
- 2 = good
- 3 = very good
- 4 = excellent

Overall, I would rate the experience (ease, comfort, convenience of use etc.) of the study medication as…

- 0 = poor

- 1 = fair
- 2 = good
- 3 = very good
- 4 = excellent

9.4 Face Image Interpretation

Subjects face images pre- and post-study intervention will be evaluated by an independent reader blinded to the study intervention administered. Lesion interpretation will be done using a 6-point Likert scale.

- 0 = Normal lip
- 1 = Erythema
- 2 = Papule
- 3 = Vesicle
- 4 = Ulcer
- 5 = Crust