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Title Page

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Study Phase: 3

Sponsor Name: Bayer Healthcare LLC.

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Sponsor Signatory

PPD , BS, PharmD

Date

PPD , US Medical Affairs

Bayer Healthcare LLC.

Medical Monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

Protocol Amendment 1 (Version 2.0)

The following sections were amended from Version 1.0 to Version 2.0. Pagination was updated in this table to align with Amendment 2.

Type of Amendment: Substantial

Changes which are considered significant or substantial have been made to the following sections reflected below:

Page Number	Section Number	Paragraph or bullet point/number
17	2.2	Secondary objectives were to compare the efficacy of ABT 50 mg versus placebo on the evolution of prodromal symptoms to aborted lesions, healing of non-primary lesions, duration of episode, duration of symptoms, healing of the aborted primary lesions and intra oral/mucosal non primary lesions, and the incidence of and time to recurrence during 9 months following treatment. **Prodromal symptoms (such as pain, tenderness, itching, tingling or discomfort) are early symptoms that herald the onset of a cold sore outbreak.**
26	5.5	• Withdraw of informed consent by the participant; • **Study intervention kit not available;** • Lack of compliance as determined by the Investigator/designee.
36	8.1.5.1	Participants will record face images and complete 0-10 NRS HL symptom evaluation at 09:00, 14:00 and 19:00 that day ~~with QoL OHIP scoring at the first assessment of the day. All scoring, face images and QoL OHIP will be recorded~~ in the Science 37 Platform. All post-dose time point assessments have an allowable window of ±60 minutes.
40	8.2.2	Removal of a duplicate survey graphic. **Note:** Example for display only and not the licensed version. Specific wording for each question may slightly differ for participants then what is displayed in the protocol. ~~The OHIP-14 is licensed by Mapi Research Trust.~~
49	10.1	**Sponsor's medical expert** for the study Name: PPD, MD Title: PPD, Global Medical Affairs Address: Bayer Healthcare 100 Bayer Boulevard Whippany NJ 07981-0915 USA

Protocol Amendment 2 (Version 3.0)

The following sections were amended from Version 2.0 to Version 3.0.

Type of Amendment: Substantial

Changes which are considered significant or substantial have been made to the following sections reflected below:

Page Number(s)	Section Number(s)	Description, paragraph or bullet point/number
12, 20	1.1, 3.0	Other Objectives • **To evaluate the Global assessment at Day 14.** • To evaluate the ~~adhesion time of Sitavig, the~~ incidence of detachment or swallowing within 6 hours of dosing, and the ~~number of tablets replaced~~ **incidence of replacing the tablet**. Other Endpoints • 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**. Observation period to determine healing will last up to 14 days (CesSymp14). • **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.**
14	1.2	Modification of Study Scheme of Treatment Phase from 8-10 days to 8-13 days. Modification of Day 14 window from ± 1 day to + 2 days.
15	1.3	Modification of Schedule of Activities of Treatment Phase from 8-10 days to 8-13 days. Modification of Day 14 window from ± 1 day to + 2 days. New footnote (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.** Footnotes e, f and g were revised accordingly.

Page Number(s)	Section Number(s)	Description, paragraph or bullet point/number
21	4.1.1.3	Additionally, participants will complete face images, symptom and QoL scores on Days 2 through ~~10~~ **13** with a virtual visit ~~no later than~~ **on** Day 14 **(+2 days)**, Visit 3 using the Science 37 Platform.
35	8.1.3	Randomized participants will start a 6-month Run-in phase during which they will be eligible to start study intervention. **The start date for the Run-in phase is defined as the verified date of receipt of undamaged study intervention by the study participant.**
36	8.1.4	Participants who start to experience prodromal symptoms **before the visible appearance of any signs of HL** must document the start time of symptoms in Science 37 Platform, complete a pre-dose (immediately before dosing) 0-10 NRS cold sore symptom evaluation (pain, burning sensation, itching and swelling) and a face image.
37	8.1.5.5	Header: addition of days 11, 12 and 13.
37, 38	8.1.5.6	Header: modification of Day 14 window from ± 1 day to +2 days. All post-dose time point assessments have an allowable window of ±60 minutes. **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.**
39	8.2.1	Assessed at Screening (pre-dose), Day 1 through the participant's self-reported completion of study intervention (~~up to~~ **on** Day 14 ~~post-dose ±1 day~~).
41	8.2.3	~~A question~~ **Questions** that rate~~s~~ the IMP as a cold sore treatment **and the participant's experience** at the self-reported completion of study intervention (14 days post-dose) using a 5-point Likert scale. New Question ***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**

Page Number(s)	Section Number(s)	Description, paragraph or bullet point/number
49	10.1	**Sponsor's medical expert** for the study Name: PPD, MD Title: PPD, ~~Global~~ **US** Medical Affairs Address: Bayer Healthcare 100 Bayer Boulevard Whippany NJ 07981-0915 USA
51	10.1.4	A copy of the ICF(s) must be provided to the participant. ~~Participants who are rescreened are required to sign a new ICF.~~
54	10.1.10	Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF and/or Science 37 platform by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements **in accordance to the monitoring plan**.

Protocol Amendment 3 (Version 4.0)

The following sections were amended from Version 3.0 to Version 4.0. Pagination was updated in this table to align with Amendment 4.

Type of Amendment: Substantial

Changes which are considered significant or substantial have been made to the following sections reflected below:

Page Number(s)	Section Number(s)	Description, paragraph or bullet point/number
2	Sponsor Signatory	**Sponsor's medical expert** for the study Name: PPD **BS, PharmD** Title: PPD, US Medical Affairs Address: Bayer Healthcare 100 Bayer Boulevard Whippany NJ 07981-0915 USA
16	1.2	Modification of Study Scheme Screening/Randomization Phase Within ~~21~~ **35** days of the start of the Run-in Phase Modification of Study Scheme Day 1 / Day 2 – **Visit 2**** Modification of footnote ** **Visit 2 may occur within 36 hours of Day 1 dosing time**
17	1.3	Schedule of Activities (SoA) Screening/Randomization Phase Within ~~21~~ **35** days of Run-in start Treatment Phase Day 1 - **2** [e]Face images and NRS symptom scores only required if a new outbreak of herpes labialis is ~~determined~~ **suspected** by the investigator.
24	4.1.1.1	Participants will be screened for eligibility up to ~~21~~ **35** days prior to study according to the inclusion/exclusion criteria.
24	4.1.1.3	Participants will be asked to meet with the clinic via the Science 37 Platform within ~~24~~ **36** hours of the start of study intervention (Day 1)
26	5.1	3. Willing to avoid, during the treatment phase, the use of anti-inflammatory **(not including low-dose (81 mg) aspirin),** anti-herpetic, antibiotic and antiviral agents as well as steroids or other natural products that would interfere with the immune system response;

		4. Female participants of childbearing potential must be using a medically acceptable form of birth control ~~for at least 1 month prior to~~ during screening ~~(3 months on oral contraceptives)~~
26	5.2	13. Known medical history of renal disease, **that in the judgment of the investigator is severe**
28	5.2	21. Participants unwilling to avoid the use of any **antivirals,** oral analgesics, any lip balm or zinc oxide cream, non-steroidal anti-inflammatory drug (including aspirin and probenecid) or topical pain reliever or anesthetic (e.g., benzocaine, lidocaine) as a cold sore treatment during the stud 25. **Use of intramuscular and intra-articular steroids is prohibited;** oral or systemic steroids within 30 days of randomization 26. Prophylactic antiviral treatment during the ~~Follow up Phase up the~~ Screening Phase, Treatment **Phase and in the Follow Up Phase** until ~~to~~ the first new **investigator confirmed** HL outbreak; 29. Participants whose occupations make them unlikely to complete a virtual clinic visit within ~~24~~ **36** hours of study intervention initiation;
28	6.1	During screening ~~and injury assessment, after completion of the pre-treatment baseline procedures/assessments~~ participants who meet the entry criteria ...
29	6.1	Upon successful completion of all screening assessments, **randomization and participant's receipt of study intervention,** participants **then** enter the Run-In Phase
32	6.8	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 participant to apply a second (backup) buccal tablet, **applying two tablets to the gum, or any other situation in which a participant ingests two tablets**
36	8.1.1	The Screening Phase will be up to ~~21~~**35** days.
37	8.1.1	Distribute urine pregnancy test kits (2)**(if applicable)**;
38	8.1.4	**Prior to the start of study intervention, all ~~female~~ WOCBP participants MUST perform a urine pregnancy test,**
40	8.1.6	If the investigator ~~determines~~ **suspects** a HL outbreak has started, the participant will be instructed to record additional 0-10 NRS symptom scores and face images ~~(at the discretion of the investigator)~~ and document the HL outbreak in Science 37 Platform.
44	8.3.1	Vital signs will consist of ~~1~~ **3** pulse and 3 blood pressure measurements

45	8.4.5	If a pregnancy is reported **while the participant is in the treatment phase**, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant's pregnancy.
51	10.1	**Sponsor's medical expert** for the study Name: PPD **, BS, PharmD** Title: PPD , US ~~US~~ Medical Affairs Address: Bayer Healthcare 100 Bayer Boulevard Whippany NJ 07981-0915 USA Phone: PPD E-mail: PPD
53	10.1.4	Additionally, the investigator **or designee** will personally sign and date the form within the Science 37 Platform.
64	10.4	3. Postmenopausal female • A postmenopausal state is defined as no menses for ~~12~~ **24** months without an alternative medical cause.

Protocol Amendment 4 (Version 5.0)

The following sections were amended from Version 4.0 to Version 5.0. Pagination was updated in this table to align with Amendment 4.

Type of Amendment: Substantial

Changes which are considered significant or substantial have been made to the following sections reflected below:

Page Number(s)	Section Number(s)	Description, paragraph or bullet point/number
17	1.1	**Synopsis Number of Participants** CCI [redacted]
25	4.1	CCI [redacted]
29	5.2	Exclusion 32. Positive urine drug screen at Screening; **except for participants with a prescription for a drug belonging to a class (such as amphetamines, benzodiazepines, tricyclic antidepressants, SSRIs, and barbiturates) known by approved labeling or a credible medical information source to potentially interfere with and cause a false positive UDS unless the medication is otherwise exclusionary (e.g., opioids). Participants should deny use of illicit drugs.**

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1. Protocol Summary

1.1 Synopsis

Protocol 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

CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare duration of episode (DOE) of cold sores between Sitavig and placebo in participants experiencing a recurrence of herpes labialis (HL).	• 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 (DurEp14). Duration of episode (DOE) is defined as the time from the initiation of treatment (study intervention initiation) to the healing of primary lesions (loss of crust) for participants who experience a vesicular lesion. For participants whose primary lesions are not vesicular in nature, duration of episode is the time from study intervention initiation to the return to normal skin as determined by the independent blinded reader of the participant's face images using a 6-point Likert scale or to the cessation of symptoms, whichever comes last.

Objectives	Endpoints
Secondary	
• To compare the incidence of aborted lesions between participants receiving Sitavig and placebo after experiencing prodromal symptoms of a recurrence of HL. • To compare the incidence of recurrence of primary HL lesions between participants receiving Sitavig and placebo during a 12-month follow-up period. • To compare the time to recurrence of primary HL lesions between participants receiving Sitavig and placebo during a 12-month follow-up period. • To assess safety and tolerability of the investigational products.	• Incidence of aborted lesions, defined as treated HL lesions that do not progress to the vesicular 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 (Abort14). • Incidence of recurrence of HL lesions during the 12-month follow-up period (IncRec12). Recurrence is determined by assessment from the investigator and documented using numerical rating scale (NRS) symptom scores and face images using the Science 37 Platform. • Time to recurrence of HL lesions, measured in days from resolution of the cold sore treated in the Treatment phase until onset of prodromal symptoms during the follow-up period (TimeRec12). • Safety and tolerability measured by the Incidence of Treatment-Emergent Adverse Events • The percentage of participants who have at least one recurrence during the 12-month follow up period will be calculated.

Other	
• To compare the duration of episode in participants who used Sitavig or placebo who initiated study intervention within 1 hour of prodromal symptoms and participants 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 participants who used Sitavig and placebo. • To compare the quality of life in participants who used Sitavig and placebo. • To compare the 0-10 NRS HL symptoms by time point in participants 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.	• Duration of episode (DOE) will be measured in hours (using the Science 37 Platform), of a single treated HL lesion in participants who initiation study intervention within 1 hour of onset of prodromal symptoms and participants 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. Observation period to determine healing will last up to 14 days (CesSymp14). • 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.

Overall Design: This is a randomized (1:1/acyclovir : placebo), self-initiated, placebo-controlled, double-blind, multi-center parallel study.

Brief Summary:

This is a 14-day clinical trial (Treatment Phase) to test the hypothesis that Sitavig (acyclovir) buccal tablet safely and effectively reduces duration of a herpes labialis cold sore of the lip in immunocompetent adults. Eligible participants who pass screening procedures will be randomized and moved into the Run-in Phase. Participants will be randomly assigned one of two treatment groups - Sitavig (acyclovir) 50 mg buccal tablets or a placebo buccal tablet. The randomization assignment is such that there is a 1 in 2 chance of receiving the placebo treatment. Participants will have a 6 month eligibility window in which they can self-initiate treatment should prodromal symptoms start. At the start of prodromal symptoms, participants will self-

initiate treatment and record face images as well as symptom scores over the next 14 days. Treatment consists of a single application (of the buccal tablet) beginning on Day 1. Face images and symptom scores are captured over the 14 day Treatment Phase.

Study Duration (Treatment Phase): 14 days

Study Duration (Follow up Phase): 12 months

Investigational Medicinal Product (IMP): Sitavig (acyclovir) 50 mg buccal tablet or placebo buccal tablet

Treatment Duration: 1 day

Visit Frequency: After the start of treatment, two visits within the 14 day Treatment Phase. Additional follow up by phone will occur at 3, 6, 9 and 12 months after treatment.

Condition/Disease: Herpes labialis of the lips caused by herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2).

Study Hypothesis: Sitavig (acyclovir) buccal tablet effectively reduces the duration of a cold sore of the lips.

Health Measurement/Observation: Independent blinded lesion evaluation using a 6-point Likert scale and 0-10 NRS symptom scores will occur pre and post treatment.

CCI [redacted]

Intervention Groups: Participants will be randomized in 1:1 fashion (active or placebo) with a single dose of study intervention.

Data Monitoring/Other Committee: No

1.2 Scheme

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

1.3 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									
Participant demographics	X												
Medical History	X												
Prior/Concomitant Medication	X	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]	X												
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. Introduction

Herpes labialis (HL), also called cold sores of the lip, is an infection primarily caused by herpes simplex virus type 1 (HSV-1) and occasionally herpes simplex virus type 2 (HSV-2). The infection is typically spread between people by direct contact. HL is a rash of the skin and mucous membranes (in particular, the lips) and is characterized by erythema and blisters that are preceded and accompanied by tingling, itching or burning pain [1].

For an infection to manifest, the virus must come in contact with mucosal surfaces or abraded skin. The viral replication takes place at the site of primary infection (epithelial cells), either as an intact virion or the capsid is transported in a retrograde fashion by neurons to the dorsal root ganglia, where, after another round of viral replication, latency is established. After primary infection, the virus recedes via the sensory nerve into the respective ganglion (usually the trigeminal ganglion), where it lies latent throughout the individual's lifetime. Stimuli such as fever, menstruation, sunlight, and upper respiratory infections can reactivate the virus, after which it returns to the epithelial cells via the sensory nerve [2].

HSV1 and HSV2 infections rest in a dormant (inactive) state until the virus is activated. During an active phase of infection, a visible outbreak of sores may be observed. Infrequently, life-threatening infection (e.g., encephalitis) may occur. The more severe the primary infection (as reflected by the size, number, and extent of lesions) the more likely it may be that recurrences may develop when triggered [3,4].

After a period of latency, a proper stimulus may cause reactivation. Reactivation of the virus becomes evident at mucocutaneous sites, appearing as skin vesicles or mucosal ulcers. The blisters in cold sores appear as fluid filled pockets beneath the surface of the skin around the mouth or on the lips. They can break open, ooze, and crust over, lasting for around 7 to 10 days. The severity of the disease varies from person to person and the symptoms can be very painful. There are different products that are used to treat cold sores. There are prescription drugs which are very effective and there are the over the counter (OTC) products as well which can bring relief to the patients [3,4,5].

2.1 Study Rationale

CCI [redacted]

2.2 Background

A randomized, double-blinded, multicentered, placebo-controlled, single-dose trial of early administration of Acyclovir 50-mg mucoadhesive buccal tablets was conducted to evaluate efficacy and safety for the treatment of herpes labialis in immunocompetent patients. This muco-adhesive buccal tablet is designed to allow the rapid and prolonged release of acyclovir in high concentrations directly into the oral cavity at the site of the infection of herpes labialis.

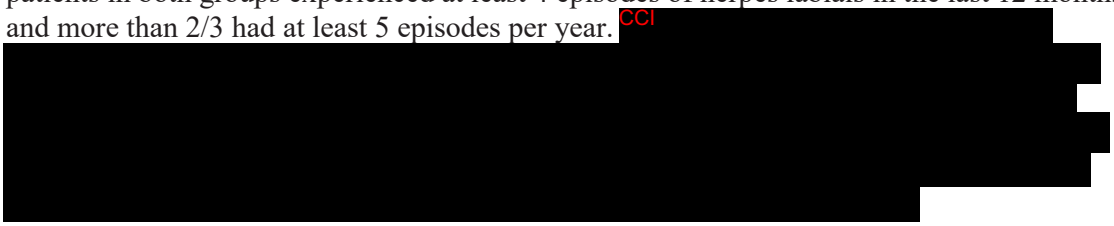
The primary objective of this study was to demonstrate the efficacy of a single mucoadhesive acyclovir buccal tablet (ABT) compared to a single dose of a placebo. The efficacy was measured using the time to healing of the primary vesicular lesion (time-to-event). Secondary objectives were to compare the efficacy of ABT 50 mg versus placebo on the evolution of prodromal symptoms to aborted lesions, healing of non-primary lesions, duration of episode,

duration of symptoms, healing of the aborted primary lesions and intra oral/mucosal non primary lesions, and the incidence of and time to recurrence during 9 months following treatment. Prodromal symptoms (such as pain, tenderness, itching, tingling or discomfort) are early symptoms that herald the onset of a cold sore outbreak.

Local tolerability and general safety were studied. The concentration of acyclovir in the saliva and the adhesion time (incidence of tablets detaching and/or being swallowed within 6 hours after tablet placement) was evaluated as well. Two populations were analyzed in this protocol: the modified intent to treat (mITT) population of everyone who took at least one dose and whose lesion reached the vesicular stage and the intent to treat (ITT) population that took at least one dose of the treatment medication.

After initiating treatment, subjects were under evaluation for up to 14 days or until the primary lesions healed. Subjects were told to fill out a questionnaire and visual analogue scale each evening to record their symptoms. Patients were to return to the clinic within 36 hours of application of the tablet. Evaluation took place on days 1, 3, 5, 7, and 14 (or healing occurred). Additionally, follow-up visits were conducted every 3 months for up to 9 months for recurrence. Adverse effects were to be reported.

The demographic characteristics were similar between treatment and placebo group. All patients in both groups experienced at least 4 episodes of herpes labials in the last 12 months and more than 2/3 had at least 5 episodes per year. CCI



The results of the study showed that time to healing of primary lesion was significantly reduced (p=0.0150) in the ABT 50 mg group compared to the placebo group. The clinical reduction was 0.57 days. The secondary objectives were all improved compared to the placebo group. More patients had aborted lesions, and the duration of non-primary vesicular lesions was reduced. Data showed that ABT 50 mg reduces the occurrence of the vesicular lesions. The duration of the herpes episode and the duration and severity of symptoms were all reduced by the treatment. A notable result in this study was that there were significantly fewer patients in the treatment group who had recurrences of primary lesions than in the placebo group. The difference was even greater in patients who inserted ABT 50 mg correctly within 1 hour of symptoms.

CCI

2.3 Benefit/Risk Assessment

Patients with recurrent HL will be enrolled in this study. The study intervention will be used/applied in accordance with the Prescribing Information for Sitavig [6].

During the study, patients will be closely monitored for evidence of adverse events. Weighing between the potential risks of antiviral medication associated with the study and given the ability to mitigate risks through close monitoring, this study is considered clinically and ethically acceptable.

Relevant emerging safety data, e.g., serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and serious safety-related protocol deviations, will be communicated as soon as possible between the sponsor, all study sites and investigators and trial subjects according to the requirements of the FDA guideline on strategies to identify risks for clinical trials.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of 50 mg acyclovir buccal tablets may be found in the Prescribing Information for Sitavig [6].

The potential impact of COVID-19 on study participants will be evaluated before the start of enrollment and monitored during the study in accordance with FDA guidance [7].

CCI [redacted]

CCI [redacted]

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare duration of episode (DOE) of cold sores when treated with Sitavig or placebo in participants experiencing a recurrence of herpes labialis (HL).	• 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 (DurEp14). Duration of episode (DOE) is defined as the time from the initiation of treatment (study intervention) initiation to the healing of primary lesions (loss of crust) for participants who experience a vesicular lesion. For participants whose primary lesions are not vesicular in nature, duration of episode is the time from study intervention initiation to the return to normal skin or to the cessation of symptoms, whichever comes last as determined by the independent blinded reader of the participant's face images using a 6-point Likert scale.
Secondary	
• To compare the incidence of aborted lesions between participants 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 participants receiving either Sitavig or placebo during a 12-month follow-up period • To compare the time to recurrence of primary HL lesions between participants receiving either Sitavig or placebo during a 12-month follow-up period. • To assess safety and tolerability of the investigational products.	• 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 (Abort14). • Incidence of recurrence of HL lesions during the 12-month follow-up period (IncRec12). • 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 (TimeRec12). • Safety and tolerability measured by the Incidence of Treatment-Emergent Adverse Events • The percentage of participants who have at least one recurrence during the 12-month follow up period will be calculated. 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.

Objectives	Endpoints
Other	
• To compare the duration of episode in participants who used Sitavig or placebo who initiated study intervention within 1 hour of prodromal symptoms and participants 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 participants who used Sitavig and placebo. • To compare the quality of life in participants who used Sitavig and placebo. • To compare the 0-10 NRS HL symptoms by time point in participants 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.	• Duration of episode (DOE) will be measured in hours (using the Science 37 Platform), of a single treated HL lesion in participants who initiation study intervention within 1 hour of onset of prodromal symptoms and participants 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. Observation period to determine healing will last up to 14 days (CesSymp14). • 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.

4. Study Design

4.1 Overall Design

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

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

CCI [redacted]

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

4.1.1 Study Design Phases

4.1.1.1 Screening/Randomization Phase

Participants will be screened for eligibility up to 35 days prior to study according to the inclusion/exclusion criteria. Participants will be assigned a screening number (SNR) and basic health information will be collected, and the participant will be assessed by the study investigator/designee. Eligible participants will be randomized into one of two study interventions. Participants will enter the Run-in Phase, which starts a six-month treatment eligibility window.

4.1.1.2 Run-in Phase

The Run-in Phase provides the opportunity for participants the time to spontaneously start a HL outbreak that would require treatment. Participants 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. Participants who do not develop an HL episode within six months will be withdrawn from the study.

4.1.1.3 Treatment Phase

Once participants 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. Participants will also be completing HL symptom scores (pain, tenderness, itching, tingling and discomfort) as well as Quality of Life (QoL) scoring using the Oral Health Impact Profile (OHIP) and during the next 10 days within the Science 37 Platform. Participants will then be under evaluation for healing of the primary lesion(s) up to 14 days.

Participants 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, participants 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.

4.1.1.4 Follow-up Phase

Participants will automatically transition to the Follow-up Phase after the completion of the Treatment Phase. Participants 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. For an overview on the trial design and trial procedures see Section 1.2.

CCI [redacted]

CCI [redacted]

4.3 Justification for Dose

Participants who self-initiate study intervention are instructed to apply one (1) 50 mg buccal tablet from the blister package to their upper gum area consistent with the Prescribing Information for Sitavig [6]. The second tablet/dose in the blister is provided as a backup in the event the first buccal tablet cannot be applied as instructed. See Section 6.5 related to applying a second buccal tablet.

4.4 End of Treatment Phase and End of Study Definitions

The end of the Treatment Phase is study is defined as the date of the last visit in the Treatment Phase (Visit 3) of the last participant in the 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 last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study up to Follow up Phase as shown in the Schedule of Activities (Section 1.3).

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions are not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Males or females, 18 years of age or older inclusive;

Type of Participant and Disease Characteristics

2. History of recurrent HL lesions where:
    a. Recurrence is defined as at least 4 episodes in the preceding 12 months;
    b. At least half of the episodes should be vesicular in nature;
    c. At least half of the episodes should be preceded by prodromal symptoms;
    d. Herpes labialis lesions are characterized by their localization on the cutaneous and/or mucosal surfaces of the lips;
3. Willing to avoid, during the treatment phase, the use of anti-inflammatory (not including low-dose (81 mg) aspirin), anti-herpetic, antibiotic and antiviral agents as well as steroids or other natural products that would interfere with the immune system response;
4. Female participants of childbearing potential must be using a medically acceptable form of birth control during screening [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier], abstinence or in same sex relationship and have a negative pregnancy test at Screening and prior to study drug administration. Female participants of non-childbearing potential must be amenorrheic for at least two years or have undergone surgical sterilization (i.e. tubal ligation/occlusion, hysterectomy and/or bilateral oophorectomy);
5. Agreement to abstain from any mechanical disruption of the prodromal area or lesion (i.e. scrubbing, lancing, shaving the area, rubbing with alcohol, application of heat emitting devices used for cold sore treatment, etc.);

Informed Consent and Other

6. Capable of giving signed informed consent as described in Section 10.1.4 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol;
7. Ability to understand and follow study-related instructions;
8. Be willing and able to participate in all scheduled visits, treatment plan, and trial procedures according to the clinical protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participants who did not develop herpes prodromal symptoms within 6 months after randomization in the study;

2. More than 50% of recurrences that aborted spontaneously (without intervention) in the past 12 months;
3. Primary herpes lesion outside the lips (e.g., nose, chin, etc.);
4. Abnormal peri-oral skin condition that might affect the normal course of cold sores (e.g., eczema, psoriasis, etc.);
5. Oral diseases whose prodromal symptoms may mimic those of herpes labialis, including recurrent oral aphthous disease;
6. Oral diseases that might interfere with the evaluation of the efficacy or safety of the treatments, including gingivitis, periodontitis, mucositis, oropharyngeal candidiasis, etc. or upon inspection of the gums and in the judgement of the investigator, are not suitable for study participation;
7. Upper full or partial dentures that in the judgement of the investigator, could interfere with study intervention when applied to the upper gum area;
8. History of infection known to be resistant to acyclovir family agents;
9. Allergy to any acyclovir or its containing agents;
10. Milk allergy or known history of hypersensitivity to one of the components of Sitavig;
11. Self-reported immunocompromised condition, including self-reported Human Immunodeficiency Virus (HIV) positive and previous bone marrow or organ transplant;
12. Self-reported galactose intolerance, lactase enzyme deficiency or glucose galactose malabsorption; this does not include self-reported lactose intolerance;
13. Known medical history of renal disease that in the judgment of the investigator is severe;
14. Evidence or history of clinically significant (in the judgment of the investigator) hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years;
15. Females who are planning to become pregnant, are pregnant or lactating;
16. Participants with a medical disorder, condition, or history of such that could impair the participant's ability to participate or complete this trial in the opinion of the investigator;

Prior/Concomitant Therapy

17. Previous vaccination against herpes simplex;
18. In the opinion of the investigator, concomitant treatment likely to interfere with acyclovir;
19. Use of any drugs (e.g., amikacin, cisplatin) during the study that may interact with acyclovir;
20. Use of any topical cold sore treatment that is not study intervention (e.g., dimethecone, menthol, camphor, benzalkonium chloride, beeswax) or cold sore treatment patch/bandage (e.g., Compeed®) or device during the study;

21. Participants unwilling to avoid the use of any antivirals, oral analgesics, any lip balm or zinc oxide cream, non-steroidal anti-inflammatory drug (including aspirin and probenecid) or topical pain reliever or anesthetic (e.g., benzocaine, lidocaine) as a cold sore treatment during the study;
22. Treatment with topical steroids in the oral area within 4 weeks prior to Investigational Medicinal Product (IMP) administration;
23. Patients undergoing any cancer treatment (e.g., chemotherapy);
24. Immunomodulator medications (immuno-suppressive or immuno-stimulation) within 30 days of randomization;
25. Oral or systemic steroids (intravascular, intramuscular or intra-articular, not including inhaled) within 30 days of randomization;
26. Prophylactic antiviral treatment during the Screening Phase, Treatment Phase and in the Follow Up phase until the first new investigator confirmed HL outbreak;

Other Exclusions

27. Participants unwilling to avoid the use of cosmetics on facial area at the start of prodromal symptoms and throughout the Treatment Phase of the study;
28. Facial hair that obscures complete visualization of the cold sore;
29. Participants whose occupations make them unlikely to complete a virtual clinic visit within 36 hours of study intervention initiation;
30. Participation in another therapeutic trial evaluating new drugs or which could interfere with the evolution of HL lesions or evaluation of the drug in the study within the preceding 30 days;
31. Alcoholism or drug abuse within 2 years prior to the Screening Visit or routine consumption of 3 or more alcohol containing beverages per day; Alcohol containing beverages are defined as one beer (5%), one glass of wine (11%) and one shot (40%) hard liquor;
32. Positive urine drug screen at Screening; except for participants with a prescription for a drug belonging to a class (such as amphetamines, benzodiazepines, tricyclic antidepressants, SSRIs, and barbiturates) known by approved labeling or a credible medical information source to potentially interfere with and cause a false positive UDS unless the medication is otherwise exclusionary (e.g., opioids). Participants should deny use of illicit drugs.
33. Inability to properly understand protocol requirements, to follow the study procedures, to fully use the Science 37 Platform or to start the self-initiation of study intervention;
34. Member or first-degree relative of study staff or the Sponsor directly involved in the study;
35. Unwilling or unable to comply with all requirements outlined in the protocol;

Prior/Concurrent Clinical Study Experience

36. Previous enrollment in this study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be rescreened.

Screen failures will be documented within the Science 37 Platform.

5.5 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. CCI

All Run-in failures and the reason for the failure will be documented in the Science 37 Platform and stored in the clinical database.

5.6 Criteria for Temporarily Delaying Study Intervention Administration

Not applicable

6. Study Intervention(s) and Concomitant Therapy

The study center/pharmacy will dispense a blinded treatment after successfully completing screening and baseline assessments. The blisters of investigational medicinal product (IMP) for each treatment will be dispensed using a computer generated randomization schedule.

6.1 Study Intervention Administered

During screening participants who meet the entry criteria will be sequentially assigned to a unique number in ascending order (randomization number, RNR) according to the

randomization schedule prepared prior to the study. A separate kit number (and corresponding kit) will be assigned by the interactive (x-voice/web) response system (IXRS) that correlates to the blinded study intervention assigned when the subject was randomized.

Participants will be numbered according to the following scheme:

14001XXXXX

14 = country code (USA)

001 = site number (for site 1)

XXXXX = RNR (starting with 10001)

Whereas the "Xs" will be replaced with a five digit sequentially assigned number as each subject enters the study (e.g., first subject number at Site 1 of the study will be 1400110001).

Once a number has been assigned to a participant, it cannot be reassigned to another participant.

Participants who do not meet all of the eligibility criteria will not be randomized. Upon successful completion of all screening assessments, randomization and participant's receipt of study intervention, participants then enter the Run-In Phase in which they are eligible to start study intervention. At the first sign of prodromal symptoms, participants may self-initiate study intervention which automatically moves them into the Treatment Phase and one of two blinded study interventions:

- 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).

Participants will apply one (1) muco-adhesive buccal tablet to the upper gum of the mouth on the same side of the mouth where the prodromal symptoms started. Any dosing-related deviations outside of the allowable window (e.g., >1 hour after the start of prodromal symptoms, second tablet administered) will be documented in the Science 37 Platform (see Section 6.5).

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the study protocol.

6.2 Identity of Study Interventions

Table 1 – Study Interventions

Intervention	Test	Reference
UI Number	1614773	1614773-003
Type	Drug	Placebo
Dose Formulation	acyclovir hypromellose milk protein concentrate sodium lauryl sulfate magnesium stearate microcrystalline cellulose povidone colloidal silicon dioxide	hypromellose milk protein concentrate sodium lauryl sulfate magnesium stearate microcrystalline cellulose povidone colloidal silicon dioxide
Dose Strength	1 tablet	1 tablet
Dosage	50 mg	Not applicable
Route of Administration	Oral (upper gum area)	Oral (upper gum area)
Packaging and Labeling	Study Intervention will be provided in a blister. Each blister will be labeled as required per FDA requirements	Study Intervention will be provided in a blister. Each blister will be labeled as required per FDA requirements
Batch Number	available in the study file	available in the study file
Manufacturer	Farméa 10 rue Bouché Thomas ZAC d'orgemont 49 000 Angers - France	Farméa 10 rue Bouché Thomas ZAC d'orgemont 49 000 Angers - France

All study drugs will be manufactured and labeled according to Good Manufacturing Practice (GMP) and applicable local laws. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all investigational products as well as the labels will be maintained in the clinical supply file.

The source of test and reference products will be documented in the clinical supply file.

6.3 Preparation/Handling/Storage/Accountability

Only participants randomized in the study may receive study intervention and only authorized staff may supply study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized staff.

The investigator's delegated staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

6.4 Measures to Minimize Bias: Randomization and Blinding

Study using Pre-Coded Randomization provided to the site	At Screening, qualified participants will be assigned a unique number (randomization number, [RNR]) in ascending numerical order. The randomization number encodes the participant's treatment assignment to one of the two arms of the study, according to the randomization schedule generated prior to the study by the Statistics Department at Bayer. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study. The treatment kit number will be pre-printed on the study intervention (treatment) kit package.
Blind Break	The IXRS will allow the investigator to see (unblind) the study intervention assignment for each participant should it be medically necessary (as it relates to a SAE). Participants who are unblinded during the Treatment Phase of the study will not be included in the Treatment Phase analysis. Participants who are unblinded during the Follow-up Phase will not be included in the Follow-up analysis. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records to verify that randomization/dispensing has been done accurately. If necessary, Bayer Pharmacovigilance may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.5 Study Intervention Compliance

Participants will be following the dosing instructions provided for applying a single buccal tablet to the upper gum on the same side of the mouth as the HL symptoms. Participants will record the date/time of dosing using the Science 37 Platform. Any deviations from the dosing instructions (e.g., greater than 1 hour after prodromal symptoms, applying a second tablet) will be recorded in the electronic case report form (eCRF) and/or Science 37 Platform.

For participants who self-administer a second tablet at the time of dosing (Day 1), the reason for applying a second tablet must be recorded in the eCRF and/or Science 37 Platform. Possible reasons are:

- Accidentally swallowed (see Section 6.8 related to an overdose);
- Tablet did not stick to gum when applied, not swallowed;
- Accidentally chewed, not swallowed;
- Lost/dropped first tablet, not used;
- First tablet was damaged, not used;
- Other (explanation not previously stated).

6.6 Dose Modification

Not applicable

6.7 Continued Access to Study Intervention after the Treatment Phase

No study intervention will be available for the Follow-up Phase. Study participants will follow their own standard of care for the treatment of a new HL occurrence during the 12 month Follow-up Phase. Study participants cannot receive prophylactic antiviral treatment for HL until a new outbreak occurs. Following a new outbreak determined by the investigator, participants can start prophylactic treatment for HL as advised by a healthcare professional.

6.8 Treatment of 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 participant to apply a second (backup) buccal tablet, applying two tablets to the gum, or any other situation in which a participant ingests two tablets.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Principal Investigator (or delegate) immediately;
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether any symptomatic or supportive care is needed;

- Document the quantity of the excess dose, date/time of the overdose and reason for using the backup tablet (see Section 6.5) in the eCRF and/or Science 37 Platform.

6.9 Concomitant Therapy

Any medication (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Rescue Medicine

No rescue medication will be provided for this study.

7. Discontinuation of Study Intervention and Participant

7.1 Discontinuation of Study Intervention

Not applicable

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost during the Treatment Phase

A participant will be considered lost if he or she repeatedly fails to return/present for scheduled visits within the Science 37 Platform and is unable to be contacted by Science 37.

The following actions must be taken if a participant fails to present for a required study visit:

- Science 37 must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented within the Science 37 Platform.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4 Lost during the Follow-up Phase

A participant will be considered lost if he or she repeatedly fails to present for scheduled visits within Science 37 Platform and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to present for a required study visit:

- The site must attempt to contact the participant to ascertain whether or not the participant wishes to and/or should continue in the study;
- The site must make at least 2 attempts to contact the participant and document the attempted contacts in the source documentation;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

8.1 General Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA Section 1.3 is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Science 37 Platform report will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3)

8.1.1 Screening Phase Day 1 (Visit 1)

Note: Visits stated in the assessment periods and their subsequent tasks/procedures will occur as a virtual visit including the assessment of adverse events. This includes the shipment of supplies to the participant's home required to complete the necessary testing before and after the start of study intervention.

At the Screening visit, the Principal Investigator or appropriate designee will discuss with each participant the nature of the study, its requirements and its restrictions. Written Informed consent will be obtained within the Science 37 Platform prior to performance of any protocol-specific procedures.

The Screening Phase will be up to 35 days. The following will be determined during the Screening Visit:

- Assignment of a unique SNR;
- Signed Informed Consent Form (ICF);
- Review inclusion and exclusion criteria;
- Participant demographics;
- Medical history (herpes labialis is based on the participant's self-reported history)
- Medication history of all prescription and over-the-counter drugs (including topicals, herbal products, vitamins and nutritional supplements), use of topical heat or cold, and other products of topical application and investigational drugs, taken within 30 days prior to screening;
- History of drug and alcohol use;
- Sitting blood pressure (BP) and pulse after sitting for at least 5 minutes;
- Self-reported height and weight, (for a Body Mass Index [BMI] calculation);
- Menstrual cycle information;
- Urine pregnancy test (if applicable);
- Urine tests for illicit drugs;
- Distribute urine pregnancy test kits (2 if applicable);
- Discuss the procedure to report adverse events;
- Science 37 Platform training;
- Baseline face image;
- Study intervention kit with dosing instructions (randomized participants only).

The Principal Investigator or his/her designee must review all screening results before proceeding to the Run-in phase of the study. Eligible participants will receive their allotted study intervention kit as per randomization, pregnancy test kits and be trained on how to use the Science 37 Platform, study intervention and pregnancy kits prior to starting the Run-in phase.

Participants will use their own device (e.g., smartphone) provided it is compatible with study requirements.

8.1.2 Randomization

After confirmation that participants meet the inclusion and no exclusion criteria at Screening, qualified participants will be randomized to either Sitavig or placebo (as a blinded study intervention), participants will receive blinded intervention via courier service to their home and will be instructed to use the product upon first experience of prodromal symptoms according to the product directions. Instructions on how to use Science 37 Platform will be provided for participants to record their face images, 0-10 NRS cold sore symptoms, QoL-OHIP, and global evaluation as well as any adverse events.

8.1.3 Run-in Phase

Randomized participants will start a 6-month Run-in phase during which they will be eligible to start study intervention. The start date for the Run-in phase is defined as the verified date of receipt of undamaged study intervention by the study participant. Participants must develop prodromal symptoms within 6 months of the start of the Run-in phase. Participants will be required to perform weekly "check-ins" within Science 37 Platform during the Run-in phase to verify their willingness to participate and if they have had any adverse events not already recorded. Any participant experiencing prodromal symptoms can immediately start study intervention and proceed to the Treatment/evaluation phase. Participants will be instructed to contact the Science 37 study team within 36 hours of study intervention initiation.

Participants who do not experience any prodromal symptoms after 6 months are withdrawn from the study.

8.1.4 Treatment/Evaluation Phase (Day 1)

Participants who start to experience prodromal symptoms before the visible appearance of any signs of HL must document the start time of symptoms in Science 37 Platform, complete a pre-dose (immediately before dosing) 0-10 NRS cold sore symptom evaluation (pain, burning sensation, itching and swelling) and a face image. **Prior to the start of study intervention, all WOCBP participants MUST perform a urine pregnancy test, and verify that the results are negative (not pregnant), and record in the Science 37 Platform**. After verification of a negative pregnancy test result, the participant may self-initiate study intervention.

Any participant who has a positive pregnancy test or is not sure of the results must contact the Science 37 study team immediately. Participants with a verified positive pregnancy test must not self-administer study intervention and will be withdrawn from the study.

Participants must always record pre-dose NRS and a face image irrespective of the start time of prodromal symptoms in the **Science 37 Platform.** After the completion of all pre-dose procedures, participants will be instructed to self-administer one (1) tablet. Should the buccal tablet adhere to the upper gum correctly, a second dose/tablet is NOT applied. A second tablet in the treatment kit is provided and labeled "BACKUP". The backup tablet should only be used if an issue occurs applying the first tablet (see Section 6.5).

After dosing, participants will complete the 0-10 NRS cold sore symptom evaluation, and face images at 09:00, 14:00 and 19:00 that day within Science 37 Platform. Depending on time of day study intervention is started, some Day 1 assessments and face images may not be collected if the time (minus the 60 minute window) occurs before the time of dosing. If dosing is started after 19:00, then post-dose NRS and face images will be collected starting the next day at 09:00. All post-dose time point assessments (NRS and face images) have an allowable window of ±60 minutes.

8.1.5 Treatment/Evaluation Phase (Days 1 through 14)

8.1.5.1 Day 1-2 (Visit 2)

Within 36 hours after the start of study intervention, participants will present for Visit 2. Visit 2 can be performed on Day 1 or Day 2. The following procedures will be done for this visit:

- Review inclusion/exclusion criteria
- Review concomitant medications;
- Sitting BP and pulse after at least 5 minutes in a sitting position;
- Review Science 37 Platform data for completeness;
- Review study intervention kit (drug accountability);
- Review used/unused pregnancy test kits for signs of use;
- Adverse Event assessment.

Participants will record face images and complete 0-10 NRS HL symptom evaluation at 09:00, 14:00 and 19:00 that day in the Science 37 Platform. All post-dose time point assessments have an allowable window of ±60 minutes.

8.1.5.2 Day 3

The following procedures will be done by the participant:

- Face images at 09:00, 14:00 and 19:00 that day;
- 0-10 NRS cold sore symptom evaluation at 09:00, 14:00 and 19:00 that day;
- QoL-OHIP at 09:00 that day;

All post-dose time point assessments have an allowable window of ±60 minutes.

8.1.5.3 Days 4, 5 and 6

The following procedures will be done by the participant for each day:

- Face images at 09:00, 14:00 and 19:00 each day;
- 0-10 NRS cold sore symptom evaluation at 09:00, 14:00 and 19:00 each day.

All post-dose time point assessments have an allowable window of ±60 minutes.

8.1.5.4 Day 7

The following procedures will be done by the participant:

- Face images at 09:00, 14:00 and 19:00 that day;
- 0-10 NRS cold sore symptom evaluation at 09:00, 14:00 and 19:00 that day;
- QoL-OHIP at 09:00 that day.

All post-dose time point assessments have an allowable window of ±60 minutes.

8.1.5.5 Days 8, 9, 10, 11, 12 and 13

The following procedures will be done by the participant:

- Face images at 09:00, 14:00 and 19:00 each day;
- 0-10 NRS cold sore symptom evaluation at 09:00, 14:00 and 19:00 each day;

All post-dose time point assessments have an allowable window of ±60 minutes.

8.1.5.6 Day 14 +2 days (Visit 3)

Participants will asked to meet with the clinic via the Science 37 Platform for Visit 3. The following procedures will be done for this visit:

- Review concomitant medications;
- Sitting BP and pulse after sitting for at least 5 minutes;
- Face images at 09:00, 14:00 and 19:00 that day;
- 0-10 NRS cold sore symptom evaluation at 09:00, 14:00 and 19:00 that day;
- QoL-OHIP at 09:00 that day;
- Global Evaluation of study intervention at 19:00 that day;
- Initiate the return of IMP kit;
- Review the Science 37 Platform data for completeness;
- Adverse Event assessment.

All post-dose time point assessments have an allowable window of ±60 minutes. 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.

8.1.6 Follow up Phase

During the follow-up phase, participants will be asked to continue in the study till either a documented HL outbreak has occurred or for 12 months, whichever comes first. Participants will be contacted by phone at 3, 6, 9 and 12 months after the start of study intervention to assess any concomitant medications or adverse events. Date of the follow up visit will be determined from the date established on Day 1.

Additionally, participants may at any time during the follow phase record a new episode/outbreak of HL. Should a potential HL outbreak occur, the participant will contact Science 37 study team the study center to determine if the outbreak is related to HL. If the investigator suspects a HL outbreak has started, the participant will be instructed to record additional 0-10 NRS symptom score(s) and face image(s) and document the HL outbreak in Science 37 Platform. Participants with a documented HL outbreak are considered completed (see Section 4.4). Should no HL outbreak occur, participants will complete the study at the end of the 12 month Follow-up Phase.

8.2 Efficacy Assessments

8.2.1 Numerical Rating Scale (0-10)

Assessed at Screening (pre-dose), Day 1 through the participant's self-reported completion of study intervention (on Day 14). Participants 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 tenderness										Worst possible tenderness

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

0	1	2	3	4	5	6	7	8	9	10
No itching										Worst possible itching

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

0	1	2	3	4	5	6	7	8	9	10
No tingling										Worst possible tingling

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

0	1	2	3	4	5	6	7	8	9	10
No discomfort										Worst possible discomfort

8.2.2 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 [9].

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?	○	○	○	○	○	○

Note: Example for display only and not the licensed version. Specific wording for each question may slightly differ for participants then what is displayed in the protocol.

8.2.3 Global Evaluation

Questions that rate the IMP as a cold sore treatment and the participant'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

8.2.4 Face Image Interpretation

Participants 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

8.3 Safety Assessments

All safety assessments are detailed in Sections 8.3.1 and 8.3.2. Planned visits for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Vital Signs

Blood pressure and pulse will be assessed with an automated device.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a sitting position for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will consist of 3 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded [10].

8.3.2 Pregnancy Testing

Female participants of childbearing potential will undergo urine pregnancy testing at Screening and Day 1 (prior to dosing).

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3. The definition of unsolicited and solicited AEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF)] at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to Bayer Pharmacovigilance within one business day of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

A subject's participation is to be terminated immediately if a pregnancy is supposed (i.e. in case her pregnancy test becomes positive). The investigator must report to the sponsor any pregnancy occurring in a female subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

If a pregnancy is reported while participant is in the Treatment phase, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant's pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE (see Section 10.3.4). Send the completed pregnancy forms to:

cc-consreldept@bayer.com
(USA)

8.5 Pharmacokinetics

PK and pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics or Pharmacogenomics

Genetics are not evaluated in this study.

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 Immunogenicity Assessments

Not Applicable

8.9 Health Economics

Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

Statistical analysis will be performed using statistical analysis software (SAS) and the version used will be specified in the Statistical Analysis Plan (SAP) and placed on file. The SAP will contain a more comprehensive explanation than described below of the methodology used in the statistical analyses. The SAP will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

9.1 Statistical Hypotheses

The primary efficacy endpoint is the duration of episode (DOE). The treatment comparison between Sitavig and placebo will be made as 2-sided at the significance level of 0.05. No multiplicity adjustment will be made.

9.2 Sample Size Determination

CCI [redacted]

9.3 Analysis Set

For the purposes of analysis, the following analysis sets are defined:

Table 2 – Analysis Populations

Participant Analysis Set	Description
Safety	All randomized subjects who take at least one dose of IMP. Safety analyses will be conducted on the safety population.
Intent To Treat (ITT)	All subjects who are randomized and provide at least one measure of primary efficacy parameters after the 1st dose of IMP.
Per Protocol (PP)	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. 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.

9.4 Statistical Analyses

9.4.1 General Considerations

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

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

9.4.2 Primary Endpoint

The primary efficacy variable 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 (DurEp14).

Duration of episode (DOE) is defined as the time from the initiation of treatment (study intervention) to the healing of primary lesions (loss of crust) for participants who experience a vesicular lesion. For participants whose primary lesions are not vesicular in nature, duration of episode is the time from study intervention initiation to the return to normal skin as determined by the independent blinded reader of the participant'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) or time of loss of follow-up, whichever happens earlier.

Duration of episode (DOE) will be estimated and plotted using Kaplan-Meier method and analyzed using log-rank test.

9.4.3 Secondary 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 (Abort14). The incidence of aborted lesions will be analyzed using Chi-square test.
- Incidence of recurrence of HL lesions during the 12-month follow-up period (IncRec12) will be analyzed using Chi-square test.
- 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 (TimeRec12). The time to 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 will be analyzed similarly to the primary endpoint.

- Safety and tolerability measured by the Incidence of Treatment-Emergent Adverse Events
- The percentage of participants who have at least one recurrence during the 12-month follow up period will be analyzed using Chi-square test.

9.4.4 Other Endpoints

- Duration of episode (DOE) will be measured in hours (using the Science 37 Platform), of a single treated HL lesion in participants who initiation study intervention within 1 hour of onset of prodromal symptoms and participants who initiated study intervention more than 1 hour after onset of prodromal symptoms.
- Time to cessation of symptoms, measured in hours from the 1st dose of assigned study intervention. 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 (CesSymp14).
- Quality of life score, as measured by the OHIP-14 questionnaire at 3, 7 and 14 days post-dose will be analyzed using CMH method with a modified ridit score.
- 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 analyzed using CMH method with a modified ridit score.

9.4.5 Safety Analysis

Safety will be measured by adverse events (AEs) and vital signs. Only descriptive analyses will be conducted on the Safety Population. No imputation will be made for missing safety data. Quantitative data for safety variables will be described by summary statistics for the original data as well as for the differences to baseline when it is appropriate. Frequency tables will be provided for qualitative data. No statistical test will be planned regarding the safety analyses.

Only treatment-emergent AEs will be included in the summary analysis, i.e., AEs that begin or worsen after the first application of Investigational Medicinal Product (IMP). The number and percent of subjects who experience any event and the number of events overall, by System Organ Class, and by Preferred Term will be displayed by treatment group. Tables will also be produced by severity and relationship to IMP. Seriousness, severity, relationship to IMP duration, and outcome will also be listed.

Listings of individual data will be presented.

9.5 Treatment Phase Analysis

The statistical analysis will be performed upon completion of all study participants who complete the Treatment Phase (up to Day 14). The additional analysis of treatment follow-up will be conducted upon completion of follow-up phase (up to 12 months). The SAP will provide further details about those planned analyses.

9.6 Interim Analysis

No interim analysis is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Investigator(s) and other study personnel

Sponsor's medical expert for the study

Name: PPD, BS, PharmD
Title: PPD, US Medical Affairs
Address: Bayer Healthcare
100 Bayer Boulevard
Whippany NJ 07981-0915 USA

Phone: PPD
Email: PPD

Principal investigator for the study

Name: Jonathan Cotliar, MD
Title: Physician
Address: Science 37
PPD
Phone: PPD
Email: PPD

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Funding

This study will be funded by the sponsor.

10.1.4 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent within Science 37 Platform that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. Each participant will be informed about the following aspects of premature withdrawal:

- Each participant has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The participant's consent covers assessments as specified in the visit description described in Section 8.1.5.6 to be conducted after withdrawal of consent.
- The participant's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Participant-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The participant has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the participant's oral objection may be documented in the participant's source data.

Each participant will have ample time and opportunity to ask questions.

Only if the participant agrees to sign the informed consent form within the Science 37 Platform and has done so, may he/she enter the study. Additionally, the investigator, or designee, will personally sign and date the form within the Science 37 Platform. The participant will be able to download a PDF version of the fully executed ICF from the Science 37 Platform.

Documentation of Informed Consent will be recorded within the Science 37 Platform which includes a statement that informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be consented to the most current version of the ICF(s) during their participation in the study.

The informed consent form and any other written information provided to participants will be revised whenever important new information becomes available that may be relevant to the participant's consent, or there is an amendment to the protocol that necessitates a change to the content of the participant information and / or the written informed consent form. The investigator will inform the participant of changes in a timely manner and will ask the participant to confirm his/her participation in the study by signing the revised informed consent form within the Science 37 Platform. Any revised written informed consent form and written information must receive the IRB`s approval / favorable opinion in advance of use.

A copy of the ICF(s) must be provided to the participant.

10.1.5 Data Protection and Confidentiality

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Participant names will not be supplied to the sponsor. Only the participant numbers (SNR, RNR and treatment kit) will be recorded on the eCRF and/or Science 37 Platform, and if the participant name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the participants will be informed in writing that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the participant's identity will remain confidential.

The investigator will maintain a list to enable participants to be identified.

10.1.6 Compensation for Health Damage of Participants/Insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

10.1.7 Committees Structure

Not applicable

10.1.8 Dissemination of Clinical Study Data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov as applicable to local regulations.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

10.1.9 Data Quality Assurance

Participant data necessary for analysis and reporting will be provided to the Sponsor in CDISC (Clinical Data Interchange Standards Consortium) standards.

Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on the eCRF and/or Science 37 platform as well as for data from other sources (e.g., laboratory). Guidance on completion of eCRFs will be provided (when applicable).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

Reasons for missing data, especially inability to perform a test, must be documented.

All participant data relating to the study will be recorded on an eCRF and/or Science 37 platform unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF and/or Science 37 platform. The investigator must maintain accurate documentation (source data) within the Science 37 Platform that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan or applicable monitoring SOP.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF and/or Science 37 platform by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 20 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.10 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed within the Science 37 Platform.

Data reported on the eCRF and/or Science 37 platform that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records (if applicable).

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF and/or Science 37 platform.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF and/or Science 37 platform by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements in accordance to the monitoring plan.

10.1.11 Missing Data

Reasons for missing data, especially inability to perform a test, must be documented.

10.1.12 Audit and Inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

10.1.13 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Participant files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership). The investigator site file is not to be destroyed without the sponsor's approval. The contract with the investigator/institution will contain all regulations relevant for the study center.

10.1.14 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first subject screened and is considered the first act of recruitment and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.15 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

Not applicable

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local at the application site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2 Definition of SAE

An SAE is defined as any AE that, at any dose:	
a.	**Results in death**
b.	**Is life-threatening** • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c.	**Requires inpatient hospitalization or prolongation of existing hospitalization** • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. • Invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment.
d.	**Results in persistent or significant disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**
f.	**Other situations:** • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Action taken with study treatment (i.e. investigational product withdrawn, interrupted, changed, unknown), any remedial drugs therapy and the outcome of the AE is recorded. Outcomes may be:
    - Recovered/resolved
    - Recovering/resolving
    - Recovered/resolved with sequelae
    - Not recovered/not resolved
    - Fatal
    - Unknown

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer Pharmacovigilance via Paper Data Collection Tool
• Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to Bayer Pharmacovigilance. • In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting: cc-consreldept@bayer.com (USA)

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 24 months without an alternative medical cause.
- Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant during the Treatment phase. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Abbreviations

ABT	acyclovir buccal tablet
AE	adverse event
BAY no.	BAY number is the main identifier for compounds within the Bayer HealthCare Organization
BMI	body mass index: weight [kg] / (height [m])²
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	consolidated standards of reporting trials
CRO	contract research organization
DOE	duration of episode
eCRF	electronic case report form
e.g.	exempli gratia (for example)
FDA	Food and Drug Administration
GCP	good clinical practice
GMP	good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	herpes labialis
HRT	hormonal replacement therapy
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
i.e.	id est (that is)
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent to treat
IXRS	interactive (x-voice/web) response system
kg	kilogram
MedDRA	medical dictionary for regulatory activities
mITT	modified intent to treat
NRS	numerical rating scale
OHIP	oral health impact profile
OTC	over-the-counter
PP	per protocol
QA	quality assurance

QoL	quality of life
RNR	randomization number
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SNR	screening number
SoA	Schedule of Activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
UI	unique identifier (drug formula)
USA	United States of America
WOCBP	woman of childbearing potential

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