Summary of the Clinical Trial Protocol and Statistical Plan

Name of Sponsor/Company:	AiCuris Anti-infective Cures GmbH

Title of the trial: A randomized, double-blind, multi-center, three arm (pritelivir, placebo and Zovirax®) parallel group, comparative trial to assess the efficacy and safety of pritelivir 5% w/w ointment for the treatment of recurrent herpes labialis in adults – LipP 1

Trial center(s): 10 to 14 investigational sites in the US

Planned study period (years): First Subject First Visit: 4th quarter 2016 Last Subject Last Visit: 3rd quarter 2017	**Phase of development:** 2

Objectives: To assess the efficacy, tolerability and safety of pritelivir 5% w/w ointment applied 5 times daily for 4 days for the treatment of recurrent herpes labialis (rHL) in adults

Trial design: This is a randomized, double-blind, multi-center, three arm parallel group, comparative trial to assess the safety and efficacy, ie, proportion of subjects with non-ulcerative lesions, in adult subjects with rHL treated with pritelivir 5% w/w ointment. The statistical superiority will be tested against placebo and a descriptive comparison with Zovirax® Cream will be made. The start of treatment with trial medication will be initiated by the subject within one hour of noticing the first sign or symptom (eg, prodrome) of a recurrence of herpes labialis (HL). Trial medication will be applied to the affected area 5 times daily for 4 days.

Number of subjects (planned): approx. 360 subjects should be enrolled resulting in at least 71 subjects dosed in each treatment arm.

Diagnosis and main criteria for inclusion:

1. Healthy men and women of any ethnic group aged ≥18 years ;
2. Subjects should have experienced ≥4 recurrences of HL in the previous 12-month period;
3. Subjects should have experienced prodromal symptoms in at least 50% of rHL episodes and should have developed ulcerative lesions that have progressed through vesicle, ulcer, and crust stages in at least 50% of the episodes;
4. Willingness not to use any topical application (such as cosmetics, lip balm, sunscreens etc.) other than the trial medication in the area of lesion development from start of prodromal symptoms to healing;
5. Willingness not to use any systemic and topical anti-HSV agent during the trial participation including prescription and over-the-counter products,
6. Willingness not to use any systemic, anti-inflammatory or analgesic agents from start of prodromal symptoms to healing;
7. Willingness to refrain from mechanical disruption (ie, scrubbing, lancing, shaving) of the prodromal area or lesion after start of treatment with trial medication until end of the trial participation;
8. Women of child bearing potential and males must use adequate contraception;
9. Subject must give written informed consent.
10. Subjects with current lesion may be enrolled, but must not to treat the lesion present at randomization with the trial medication; they should be instructed to wait for the next subsequent lesion.

Diagnosis and main criteria for exclusion:

1. Known intolerance to pritelivir or any of the ointment ingredients (ie, butylated hydroxytoluene (BHT), PEG-400, PEG-4000, propylene glycol);
2. Known intolerance to Zovirax® Cream or any of the ingredients (ie, acyclovir, cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, and white petrolatum) or valacyclovir;
3. Any skin conditions that could interfere with the assessment of HL recurrences (eg, eczema, psoriasis, acne);
4. Any other condition which in the opinion of the Investigator would interfere with successful completion of this clinical trial;
5. Pregnant and/or breastfeeding women;
6. Participation in any investigational drug trial within the last 30 days before randomization for this clinical trial;
7. Previous treatment with pritelivir tablets;
8. Previous participation in a HSV vaccination trial (unless having received placebo);
9. Clinically relevant ECG abnormalities (eg, QTc according to Fridericia: QTcF > 450ms for males and QTcF > 470ms for females; PR > 220 ms) at screening;
10. Clinically relevant abnormalities in laboratory indices at screening which in the opinion of the investigator might have an impact on the safety and evaluability of the subject;
11. Known chronic infections which in the opinion of the investigator might have an impact on the safety and evaluability of the subject;
12. Evidence of active malignancy or immunodeficiency disease, or require chronic use of immunosuppressive drugs (eg, systemic steroids) or topical steroids, or chronically use antiviral medication with activity against HSV;
13. HIV positive based on screening labs.

Test product, dose and mode of administration

Pritelivir 5% w/w ointment, 5 times daily, topical application.

Duration of Treatment:

Four days (20 applications).

Reference therapy, dose and mode of administration

Pritelivir placebo ointment, 5 times daily, topical application

Zovirax® Cream, 5 times daily, topical application.

Criteria for evaluation:

Efficacy:

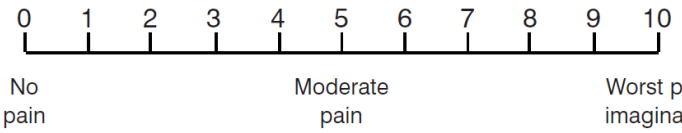
Primary endpoint:

- The percentage of subjects with non-ulcerative lesions in each treatment group.

Secondary endpoints:

- Duration of lesion episode (DOE), defined as time from treatment initiation to the healing of the primary lesion (loss of crust) for subjects who experienced a vesicular lesion. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last;
- Pain rate, defined as number of days with pain at lesion site relative to the total number of days with analyzable pain through daily subject self-assessment;

- Subject-assessed duration of lesion pain, defined as the time from first dose of trial medication until pain is no longer reported by the subject (date and time);
- Subject-assessed severity of lesion pain defined as the average daily NUMERICAL RATING SCALE (NRS) pain score using a single-dimensional scale assessing pain intensity at lesion site, 11 intensities [no pain (0) to worst pain imaginable (10)];



- Maximum lesion area (length x width) for ulcerative lesions during the vesicular, ulcerative and hard crust stages;
- Cumulative lesion area (sum of daily maximum lesion areas);
- Duration of lesion tenderness (unpleasantness upon touching the affected area).

Safety:

- An overall summary of adverse events (AEs) will be provided including the number and percentage of subjects with any AE, treatment emergent AE (TEAE), related TEAE, serious AE, severe AE, and TEAE leading to early termination;
- TEAEs by system organ class (SOC), preferred term (PT), and treatment group. Summarization by maximum severity will also be presented;
- Safety laboratory parameters;
- Safety signals such as hematological changes, lymphadenopathy, CRP increase, cutaneous adverse events and changes in (a)PTT;
- Vital signs (systolic and diastolic blood pressure, pulse rate) by visit and treatment group;
- Standard 12-lead electrocardiogram (ECG) by visit and treatment group;
- Physical examination by visit and treatment group.

Compliance:

- The percentage compliance will be calculated as the number of doses applied documented in the diary divided by 20 times 100.

Pharmacokinetics:

- C_{max}, T_{max}, AUC, if feasible

Methodology:

Efficacy measurements:

After self-initiation of treatment with trial medication subjects will be assessed daily for the following parameters by the Investigator until healing:

1. Lesion stage:
   - prodrome (symptoms including itching, pain, tingling, but no physical evidence of disease by inspection or by palpation in the application area),
   - erythema
   - papule (any elevation of skin without fluid in the application area)/edema,
   - vesicle (blister, fluid filled or collapsed, in the application area),
   - ulcer/soft crust,
   - hard crust,
   - residual abnormalities (residual erythema/scaling),
   - normal appearing skin.

2. Maximum lesion area (length x width) in mm^2

Subject diary documentation:

Subjects will document the following in their diary:

1. Time of each application of trial treatment,
2. Pain intensity, changes in pain intensity, and cessation of pain at each application of trial treatment (at the first and last daily application as a minimum),
3. Pain intensity, changes in pain intensity, and cessation of pain in the morning and evening on days after stop of application of trial treatment until pain disappeared,
4. Lesion stage at each application of trial treatment,
5. Lesion stage in the morning and evening on days after stop of application of trial treatment until lesion healing,
6. Lesion tenderness at each application of trial treatment, and,
7. Lesion tenderness in the morning and evening on days after stop of application of trial treatment until lesion tenderness disappeared.

Subject diaries will be reviewed by the investigational site staff at each visit.

Safety measurements:

The following safety measures will be performed at screening and at Visit 5 (Day 5/6) and at the End of Trial Visit (Day 12±1) after initiation of treatment:

1. Safety laboratory parameters, ie, serum chemistry, hematology, coagulation and urinalysis
2. Vital signs, ie, systolic and diastolic blood pressure, pulse rate
3. Standard 12-lead electrocardiogram (ECG) according to Einthoven, Goldberger and Wilson
4. Physical examination including the assessment of the skin, head, eyes, ears, nose, neck, lymph nodes, throat, and extremities, and the following body systems: musculoskeletal, cardiovascular, respiratory, gastrointestinal and neurological.

Any other clinically relevant findings will be recorded.

Blood sampling for pharmacokinetics:

Blood sampling for pharmacokinetic analysis (one per day, in total seven samples) will be performed at randomization, daily at Visit 1 to Visit 5, and at the End of Trial Visit (Day 12±1).

The time of PK blood sampling will be documented.

Statistical methods:

Sample size calculation:

The primary endpoint will be the percentage of subjects with non-ulcerative lesions in each treatment group.

The percentage of subjects with non-ulcerative lesions if left untreated with HL is estimated as 26%. The percentage of subjects with non-ulcerative lesions is assumed to be 50% when applying pritelivir 5% w/w ointment as compared to placebo. The following table shows the total number of subjects with recurrences needed to show superiority of pritelivir compared with placebo with 80% power and assuming a type I error rate of 5%.

Proportion of subjects with non-ulcerative lesions:		**Total number of evaluable recurrences needed 1:1:1 randomization**			**Total evaluable recurrences needed**	**Total number of subjects needed (including 40% who do not develop a recurrence)**
Placebo	**Pritelivir**	**Pritelivir**	**Placebo**	**Zovirax®**		
26%	50%	71	71	71	213	360

It is assumed that 71 recurrences in each arm are sufficient to allow for a descriptive comparison of pritelivir with Zovirax®.

In order to obtain 213 evaluable HL recurrences, 360 subjects need to be randomized in a 1:1:1 randomization scheme to cover the rate of approx. 40% of subjects which do not develop a recurrence or drop out.

Primary efficacy analysis:

The primary efficacy analysis will be performed in the ITT (Intend to Treat Set) and the PPS (Per-Protocol Set).

ITT includes the results from all randomized subjects who applied the trial medication at least once and had at least one lesion status assessment done/reported after start of treatment.

PPS is a subset of the ITT excluding subjects with major protocol violations.

Secondary efficacy analyses

The secondary efficacy analyses will be performed in the ITT and the PPS.

Safety

All safety and tolerability parameters will be listed. All safety analyses will be performed in the Safety Set (= all randomized subjects who applied at least one dose of trial medication).