Protocol

Statistical Analysis Plan

EpiCeram for skin protection in healthcare workers using personal protective equipment

NCT04793711

March 1, 2021

EpiCeram for skin protection in healthcare workers using personal protective equipment.

Protocol: PPE-01

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Date: November 5, 2020 Version: 1

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Guideline Signature and Financial Disclosure

This guideline has been written by Primus Pharmaceuticals, Inc.

Director of Clinical Development, Robert M. Levy, M.D.

Robert M. Levy, M.D. March 1, 2021

Director Signature Date

Protocol Signature and Financial Disclosure Page

I have read and I understand all the provisions and requirements of this protocol, EpiCeram for skin protection in healthcare workers using personal protective equipment. Protocol # PPE-01.

I agree to perform the investigator's responsibilities exactly as set forth in the protocol according to the principles of Good Clinical Practice. I further understand that all information pertaining to this protocol is confidential and may not be disclosed in personal communications or professional presentations without the prior written consent of Primus, Inc.

_____ _____
Investigator signature/ Date

I certify that, other than the investigator stipend agreed upon in the contract and budget for this study, I have no other financial interest in Primus Pharmaceuticals, Inc. or any of its present or future products.

_____ _____
Investigator signature/ Date

ABBREVIATIONS

AE	Adverse Event
AMP	Antimicrobial Peptides
CRF	Case Report Form
COVID-19	Coronavirus Disease 2019
DDC	Direct Data Capture
EDC	Electronic Data Capture
FDA	U. S. Food and Drug Administration
FFA	Free Fatty Acids
HCW	Healthcare Workers
HIPAA	Health Insurance Portability and Accountability Act
ICD	Informed Consent Document
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
PPE	Personal Protective Equipment
qPCR	Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Events
SCH	Stratum Corneum Hydration
TEWL	Transepidermal Water Loss

EpiCeram for skin protection in healthcare workers using personal protective equipment.

Synopsis

Protocol #: PPE-01

Background

During the current COVID-19 pandemic, health care workers (HCW) report that the prolonged use of personal protective equipment (PPE), particularly gloves and face covering, results in irritant contact dermatitis manifested by symptoms of pain, itching, burning and non-specific discomfort of the hands and face and associated visible physical changes of erythema, dryness, roughening and cracking of the affected skin (Jiang, et al 2020). These changes are aggravated by frequent hand washing and antimicrobial alcohol use. These irritative changes are likely associated with defects in the normal barrier structure and function of the skin, including, but not limited to, lowering of surface pH, excessive water loss, alteration of skin microbiome, lowered resistance to penetration by allergens and pathogens and immunological dysfunction. It is unknown whether these changes could increase the likelihood of S. aureus skin contamination or, in people exposed to, but not systemically ill with, COVID-19 to act as "silent" carriers of coronavirus.

EpiCeram, a three, lipid emollient, has been shown to improve barrier structure and function, reduce skin pH, helps restore the microbiome toward normal, improve immunological function and reduce symptoms associated with disrupted skin surfaces (Elias 2014, Elias 2019 and Kircik 2014). In contrast, some readily available over the counter skin care products may actually increase barrier dysfunction and aggravate skin disease (Li 2017, Elias 2019).

Study Objectives

1. To evaluate the ability of EpiCeram to reduce signs and symptoms of skin irritation in HCW using PPE on the face and hands.
2. To evaluate the ability of EpiCeram to improve measurements of skin barrier function during continued use of PPE on the face and hands.
3. To evaluate the ability of EpiCeram to reduce skin surface S. aureus load.

Study design

This will be a one (1) month, open label study. Subjects must be HCW who have used face and hand PPE at least four (4) days a week for a minimum of one (1) month (or, depending on shift work, at least 24 hours/week) and who have new (after March 1, 2020) symptomatic skin irritation on the hands and/or face. No change to required hand washing protocols or other protective measures will be required.

At Visit 1 (Screening) the study will be explained, and an informed consent document (ICD) signed. Subjects will be entered into the electronic data capture (EDC) system using a direct data capture (DDC) tablet. Subjects will complete an overall skin irritation assessment on 0-10 scale where 0 = none and 10 = worst. If it is equal to or greater than 4, the subject may proceed to enrollment provided all other inclusion and exclusion are met.

If the subject has not used any lotions and emollients for the previous one (1) week on the face and hands, washout is not necessary, and Baseline visit activities may be performed at the Screening visit. Subjects requiring washout, will refrain from using any lotions and emollients for one (1) week between Visits 1 and 2 and then, for the duration of the study. Visit 2 (Baseline) will occur seven (7) days after Visit 1.

At Visit 2, subjects will complete an overall skin irritation assessment on a 0-10 scale where 0 = none and 10 = worst. Subjects will complete skin symptom scales of pain, redness, dryness, roughness, itching and cracking on a scale on a 0-10 scale where 0 = none and 10 = worst.
A manual describing detailed steps for collection of laboratory, photographic and skin surface measurements will be provided to the site by the sponsor. Vendors will supply training and references for the camera and EDC system.
Photographs: Digital 3D photographs will be taken of the face and back of the hand. The face photo will be a two (2) inch by three (3) inch area of the cheek without identifying features. The hand photo will be the worst area of involvement as selected by the subject.
Skin Function Testing: Measurements of transepidermal water loss (TEWL) with stratum corneum hydration (SCH) and surface skin pH will be taken on the web between the 3rd and 4th metacarpophalangeal (MCP) joints on the dorsum of the dominant hand used.
Laboratory Testing: Two types of specimens will be obtained; a swab and tape stripping. A single skin swab for bacterial qPCR will be obtained from the palm of the dominant hand. Non-invasive tape stripping of surface cells (3 strips/sample) will be performed at 2 sites; on the web between the 3rd and 4th metacarpophalangeal (MCP) joints on the dorsum of the dominant hand for antimicrobial peptides (AMP) and three (3) strips/sample from the web between the 2nd and 3rd MCP joints on the dominant hand for free fatty acids. See the manual for detailed instructions on specimen collection. The subject will then be directed to apply EpiCeram to the hands (wrist to fingertips, back and front) and face at least three (3) times daily (about every 8-10 hours), more often if the subject wishes.

At Visit 3 (Final), 28 days later subjects will complete an overall skin irritation assessment on a 0-10 scale where 0 = none and 10 = worst. Subjects will complete skin symptom scales of pain, redness, dryness, roughness, itching and cracking on a scale on a 0-10 scale where 0 = none and 10 = worst. Photos, skin function, swab and tape stripping will be in the same location as Visit 2.
Photographs: Digital 3D photographs will be taken of the face and back of the hand. The face photo will be a two (2) inch by three (3) inch area of the cheek without identifying features. The hand photo will be the worst area of involvement as selected by the subject.

Skin Function Testing: Measurements of transepidermal water loss (TEWL) with stratum corneum hydration (SCH) and surface skin pH will be taken on the dominant hand on the dorsum of the 3rd and 4th metacarpal phalanges.
Laboratory Testing: Two types of specimens will be obtained; a swab and tape stripping. A single skin swab for bacterial qPCR will be obtained from the palm of the dominant hand. Non-invasive tape stripping of surface cells (3 strips/sample) will be performed at 2 sites; on the web between the 3rd and 4th metacarpophalangeal (MCP) joints on the dorsum of the dominant hand for antimicrobial peptides (AMP) and three (3) strips/sample from the web between the 2nd and 3rd MCP joints on the dominant hand for lipids. The subject will then be directed to apply EpiCeram to the hands and face at least three (3) times daily (about every 8-10 hours), more often if the subject wishes.

Primary Endpoint

1. Change in patient reported outcome of face and hand skin symptoms from baseline to Day 28, of at least 2 points on a 0-10 point scale where 0 = none and 10 = worst.
    a. pain
    b. redness
    c. dryness
    d. cracking
    e. roughness
    f. itching
    g. overall skin irritation

Secondary endpoints

1. Change from baseline to Day 28 in pH.
2. Change from baseline to Day 28 in TEWL.
3. Change in S. aureus colonization from baseline to Day 28.

Inclusion Criteria

1. HCW using PPE at least 6 hours/day, 4 days/week or, depending on shift work, 24 hours/week, for at least one (1) month,
2. Men or women, any age
3. Overall skin irritation score of at least 4 on 0-10 scale where 0 = none and 10 = worst
4. Must be willing to stop use of any other emollient and lotion for one (1) week between screening and baseline visit and for the duration of the study.
5. Participant is willing to stop use of, or not begin, use of any topical corticosteroids, emollients and lotions to the hands and face for the duration of the trial.

Exclusion Criteria

1. History of any skin disorder existing prior to March 1, 2020 characterized by chronic visible lesions or skin irritation symptoms including, but not limited to atopic dermatitis, eczema, moderate-severe acne, chronic dry skin and psoriasis.
2. Use of topical or systemic corticosteroids within one (1) month of baseline visit.
3. History of any significant medical condition that, in the opinion of the investigator, might put the subject at risk in this trial.
4. Participation in another clinical trial within 30 days or 5 half-lives of the study agent, whichever is longer.

Study test item
EpiCeram® 90 gram tubes

Number Subjects
Fifty (50) subjects will be evaluated in this study. Accordingly, 55 subjects will be enrolled to allow for a 10% drop out rate.

Efficacy Measurements

1. Symptom scales
    a. pain
    b. redness
    c. dryness
    d. cracking
    e. roughness
    f. itching
    g. overall skin irritation
2. Surface Skin pH
3. TEWL
4. SCH
5. Antimicrobial peptides (LL-37, HBD-2)
6. Free fatty acids
7. Bacterial qPCR
    a. S. aureus
    b. MRSA
    c. S. epidermidis

Safety Measurements
Adverse Events

Statistics
Descriptive statistics will be calculated for all demographic and clinical characteristics at baseline and study outcomes for each time period. Means and standard deviations will be presented for continuous variables (e.g., age) and proportions and frequencies for categorical

variables (e.g., sex). Paired t-tests will be used to assess unadjusted differences in primary outcomes of face and hand skin irritation symptoms (pain, redness, dryness, cracking, roughness, itching and overall skin irritation) and secondary outcomes of pH, TEWL, and S. aureus colonization level between the baseline visit and Day 28 follow-up visit. Analysis will be performed on the Intention-to-Treat (ITT) sample. Standard data quality checks will be performed. The sample size of $n = 50$ is sufficiently powered ($1 - \beta = 0.80$) to identify a medium effect size of $d = 0.4$ in a two-tailed test with α set at 0.05. Given the multiple primary endpoints, p-values will be reported with high precision (four percentage points) to allow for multiple comparisons adjustments as desired.

EpiCeram for skin protection in healthcare workers using personal protective equipment.

Protocol #: PPE-01

1. Introduction:

During the current COVID-19 pandemic, health care workers (HCW) report that the prolonged use of personal protective equipment (PPE), particularly gloves and face covering, results in irritant contact dermatitis manifested by symptoms of pain, itching, burning and non-specific discomfort of the hands and face and associated visible physical changes of erythema, dryness, roughening and cracking of the affected skin (Jiang, et al 2020). These changes are aggravated by frequent hand washing and antimicrobial alcohol use. These irritative changes are likely associated with defects in the normal barrier structure and function of the skin, including, but not limited to, lowering of pH, excessive water loss, alteration of skin microbiome, lowered resistance to allergens and pathogens and immunological dysfunction. It is unknown whether these changes could increase the likelihood of S. aureus skin contamination or, in people exposed to, but not systemically ill with, COVID-19 to act as "silent" carriers of coronavirus.

EpiCeram, a marketed product, is a three lipid emollient that has been shown to improve barrier structure and function, reduce skin pH, helps restore the microbiome components toward normal, improve immunological function and reduce symptoms associated with disrupted skin surfaces (Elias 2014, Elias 2019 and Kircik 2014). In contrast, some readily available over the counter skin care products may actually increase barrier dysfunction and aggravate skin disease (Li 2017, Elias 2019).

2. Hypotheses

a. The signs and symptoms of skin irritation secondary to extensive use of PPE will be accompanied by measurable defects in skin barrier structure and function.
b. EpiCeram will improve measurements of skin barrier integrity.
c. Signs and symptoms of skin irritation will improve after one month of EpiCeram use.
d. Improvement of skin barrier function will restore reduce skin colonization by pathogenic bacteria.

3. Study design

This will be a one (1) month, open label study. Subjects must be HCW who have used face and hand PPE at least four (4) days a week for a minimum of one (1) month (or, depending on shift work, at least 24 hours/week) and who have new (after March 1, 2020) symptomatic skin irritation on the hands and/or face. No change to required hand washing protocols or other protective measures will be required.

At Visit 1, Screening the study will be explained and an informed consent document (ICD) signed. Subjects will be entered into the electronic data capture (EDC) system using a direct data capture (DDC) tablet. Subjects will complete an overall skin irritation assessment on 0-10 scale where 0 = none and 10 = worst. If it is equal to or greater than 4, the subject may proceed to

enrollment provided all other inclusion and exclusion are met. If the subject has not used any lotions and emollients for the previous one (1) week on the face and hands, washout is not necessary, and Baseline visit activities may be performed at the Screening visit. Subjects requiring washout, will refrain from using any lotions and emollients for one (1) week between Visits 1 and 2 and then, for the duration of the study. Visit 2 (Baseline) will occur seven (7) days after Visit 1.

At Visit 2, subjects will complete an overall skin irritation assessment on a 0-10 scale where 0 = none and 10 = worst. Subjects will complete skin symptom scales of pain, redness, dryness, roughness, itching and cracking on a scale on a 0-10 scale where 0 = none and 10 = worst.
A manual describing detailed steps for collection of laboratory, photographic and skin surface measurements will be provided to the site by the sponsor. Vendors will supply training and references for the camera and EDC system.
Photographs: Digital 3D photographs will be taken of the face and back of the hand. The face photo will be a two (2) inch by three (3) inch area of the cheek without identifying features. The hand photo will be the worst area of involvement as selected by the subject.
Skin Function Testing: Measurements of transepidermal water loss (TEWL) with stratum corneum hydration (SCH) and surface skin pH will be taken on the web between the 3rd and 4th metacarpophalangeal (MCP) joints on the dorsum of the dominant hand used.
Laboratory Testing: Two types of specimens will be obtained; a swab and tape stripping. A single skin swab for bacterial qPCR will be obtained from the palm of the dominant hand. Non-invasive tape stripping of surface cells (3 strips/sample) will be performed at 2 sites; on the web between the 3rd and 4th metacarpophalangeal (MCP) joints on the dorsum of the dominant hand for antimicrobial peptides (AMP) and three (3) strips/sample from the web between the 2nd and 3rd MCP joints on the dominant hand for free fatty acids. See the manual for detailed instructions on specimen collection. The subject will then be directed to apply EpiCeram to the hands (wrist to fingertips, back and front) and face at least three (3) times daily (about every 8-10 hours), more often if the subject wishes.

At Visit 3 (Final), 28 days later subjects will complete an overall skin irritation assessment on a 0-10 scale where 0 = none and 10 = worst. Subjects will complete skin symptom scales of pain, redness, dryness, roughness, itching and cracking on a scale on a 0-10 scale where 0 = none and 10 = worst. Photos, skin function and laboratory testing will be in the same location as Visit 2.
Photographs: Digital 3D photographs will be taken of the face and back of the hand. The face photo will be a two (2) inch by three (3) inch area of the cheek without identifying features. The hand photo will be the worst area of involvement as selected by the subject.
Skin Function Testing: Measurements of transepidermal water loss (TEWL) with stratum corneum hydration (SCH) and surface skin pH will be taken on the dominant hand on the dorsum of the 3rd and 4th metacarpal phalanges.
Laboratory Testing: Two types of specimens will be obtained; a swab and tape stripping. A single skin swab for bacterial qPCR will be obtained from the palm of the dominant hand. Non-invasive tape stripping of surface cells (3 strips/sample) will be performed at 2 sites; on the web between the 3rd and 4th metacarpophalangeal (MCP) joints on the dorsum of the dominant hand

for antimicrobial peptides (AMP) and three (3) strips/sample from the web between the 2nd and 3rd MCP joints on the dominant hand for free fatty acids. See the manual for detailed instructions on specimen collection. The subject will then be directed to apply EpiCeram to the hands (wrist to fingertips, front and back) and face at least three (3) times daily (about every 8-10 hours), more often if the subject wishes. The investigator will assess the subject' Response to Therapy on a scale of 1-5 with 1 = no response and 5 = best response. Subjects may then be discharged from the study.

4. **Primary endpoints**
   a. Change in patient reported outcome of overall face and hand skin irritation symptoms from baseline to Day 28, of at least 2 points on a 0-10 point scale where 0 = none and 10 = worst.
   b. Change in any two of the following specific skin irritation symptoms of at least 2 points on a 0-10 point scale where 0 = none and 10 = worst.
      1. pain
      2. redness
      3. dryness
      4. cracking
      5. roughness
      6. itchiness
      7. overall skin irritation

5. **Secondary endpoints**
   a. Reduction from baseline to Day 28 in pH
   b. Reduction from baseline to Day 28 in TEWL
   c. Reduction in S. aureus colonization from baseline to Day 28

6. **Subject Selection Criteria**

6.1 Inclusion Criteria

a. HCW using PPE at least 6 hours/day, 4 days/week or, depending on shift work, 24 hours/week, for at least one (1) month
b. Men or women, any age
c. Overall skin irritation score of at least 4 on 0-10 scale where 0 = none and 10 = worst
d. Willing to stop use of any other emollient and lotion for one (1) week between screening and baseline visit and for the duration of the study.
e. Participant is willing to stop use of or not begin use of any topical corticosteroids, emollients and lotions to the hands and face for the duration of the trial.

6.2 Exclusion Criteria

a. History of any skin disorder existing prior to March 1, 2020 characterized by chronic visible lesions or skin irritation symptoms including, but not limited to

atopic dermatitis, eczema, moderate-severe acne, chronic dry skin and psoriasis.

b. Use of topical corticosteroids within one (1) month of baseline visit.
c. History of any significant medical condition that, in the opinion of the investigator, might put the subject at risk in this trial.
d. Participation in another clinical trial within 30 days or 5 half-lives of the study agent, whichever is longer.

7. Test Item and Proscribed Treatments

This is an open label study. All subjects will receive EpiCeram, delivered in 90 gm tubes. The EpiCeram cream will be applied to face and hands at least three (3) times per day, about every 8 hours taking care to apply after bathing and before applying any makeup. Subjects are prohibited from using any other skin lotion by prescription or over the counter. Subjects are specifically prohibited from using any corticosteroid containing skin products.

8. Number of Subjects

Fifty (50) subjects will be evaluated in this study. To account for subjects who fail to complete the trial fifty-five (55) subject will be enrolled.

9. Safety measurements

Adverse events

10. Efficacy measurements

a. Symptom scales
b. TEWL
c. Hydration
d. Skin pH
e. Skin surface bacterial qPCR

11. Study Procedures

11.1 Screening visit

At least one (1) week prior to the baseline visit patients will be evaluated for inclusion in the study. Patients will have the study thoroughly explained to them and all their questions will be answered. Patients will sign the Informed Consent Document (ICD) before any study related procedures are performed. By definition, a patient becomes a study subject once he/she has signed the informed consent document. Every patient must have the opportunity to take home an unsigned copy of the ICD to discuss the study with family or friends and consider their decision whether to participate.

Screening and Baseline procedures may occur on the same day the study is first presented if the patient elects to proceed at that time and meets the inclusion and exclusion criteria including the washout requirement. A manual describing detailed steps for collection of laboratory, photographic and skin surface measurements will be provided to the site by the sponsor.

At the Screening visit, each subject will be entered into the EDC system using a DDC tablet which will issue a unique identifier.

Subjects who agree to participate will perform the following:

a. Review and sign the Informed Consent Document including consent for photos.
b. Assess for overall irritation score of $\geq$ 4 on the previously described scale of 0-10.
c. Assess for meeting all inclusion and exclusion criteria.
d. The subject will be instructed to stop using (washout) emollients and lotions currently in use on the hands and face for one (1) week and for the duration of the study.
e. The subject will be instructed to return in one (1) week for the Baseline visit. If washout requirement is met, Baseline visit activities may be performed at the Screening visit. Instruct subjects to refrain from washing hands and face for 2-hours prior to each visit.

11.2 Baseline Visit

Perform photos, skin function testing and laboratory testing in the order listed below.

a. Assess for overall irritation score of $\geq$ 4 on the previously described scale of 0-10.
b. Assess for adverse events and changes to skin routine.
c. Complete skin symptom rating scales.
d. Take digital photos of hand and face.
e. Measure skin surface TEWL and SCH.
f. Measure face and hand skin surface pH.
g. Swab the dominant hand for bacterial qPCR.
h. Perform tape stripping for free fatty acids and AMPs.
i. Dispense one unit of EpiCeram.
j. Subject will apply EpiCeram TID at home to clean face and hands (wrist to fingertips, back and front).

11.3 Final Visit (4 weeks)

Perform photos, skin function testing and laboratory testing in the order listed below.

a. Assess for overall irritation score of $\geq$ 4 on the previously described scale of 0-10.
b. Assess for adverse events and changes to skin routine.
c. Complete skin symptom rating scales.
d. Take digital photos of hand and face.
e. Measure skin surface TEWL and SCH.
f. Measure face and hand skin surface pH.
g. Swab the dominant hand for bacterial qPCR.
h. Perform tape stripping for free fatty acids and AMPs.
i. Investigator assessment of subject's Response to Therapy on a 1 – 5 scale, with 1 = no response and 5 = best response.
j. Resolve AEs.

12.0 Study Withdrawal

Subjects may be withdrawn from the study for one or more of the following reasons.

a. Request for withdrawal by the subject for any reason whether or not related to an AE.
b. Lost to follow-up.
c. Noncompliance with the protocol.
d. Unacceptable adverse event. In this case the decision to remove the subject from the study may be made by the subject, the investigator or Primus.
e. Determination by the investigator or Primus, that, withdrawing from the study is in the best medical interest of the subject.
f. Administrative reasons such as early termination of the study.
g. Treatment failure requiring an increase or addition of concomitant medication (s) or the use of any excluded medication.
h. If the subject is discontinued prior to receiving the first dose of study product AEs and SAEs will be collected until the termination visit. If the subject has received study medication AEs and SAEs will be collected until the termination visit or until 30 days after the last dose of study product, whichever is later All AEs and SAEs must be followed until resolution or stability.

According to FDA and the Declaration of Helsinki a subject in a clinical trial has the right to withdraw at any time and for any reason without prejudicing his/her future medical care at the investigative site. In the case of early withdrawal of a subject, the investigator should make all reasonable efforts to have the subject attend a termination visit and document all details of the early termination on the appropriate data collection tool/CRF.

13.0 Early Termination Visit Procedures

If a subject wishes to end his/her participation in the study prematurely, whether because of an AE or any other reason, he/she should be asked to complete a termination visit at the next scheduled appointment or within 14 days, whichever is more convenient. The investigator should make every reasonable attempt to perform the final assessment. Whenever possible, all final visit procedures should be performed at the time of an early termination visit. All outstanding AEs should be followed to resolution or stability. The reason for early termination should be clearly stated in the source and data collection tool.

All adverse events that result in a subject's withdrawal from the study must be reported to the Project Manager of Clinical Investigation, Mary Sanstead, BSN (480-250-6689 cell), within 24 hours.

14.0 Safety

14.1 Definition of Adverse Event

An AE is any untoward or unexpected medical occurrence in a subject participating in a clinical study whether or not there is a possible relationship between the investigative agent and the event and regardless of whether or not the subject has received any study product. Once a patient signs an informed consent document, he/she becomes a study subject and AE data will

be collected from that point until the end of the study or 30 days after the last dose of study product, whichever is longer. An AE may be an untoward, unintended or unexpected sign, symptom, disease or worsening of disease, an abnormal laboratory finding considered by the investigator to be clinically significant. Laboratory tests that deviate significantly from the normal range should be repeated with prior permission of the sponsor. If the abnormality persists and the investigator considers this a clinically significant abnormality, then efforts should be made to ascertain the etiology. If the abnormality is increasing, particularly if it was not there at baseline, the Director of Clinical Investigation should be notified.

14.2 Serious Adverse Events

SAEs require special attention, management and documentation. All SAEs must be reported to Primus within 24 hours **whether or not** they are considered by the investigator to be related to the study agent (s). Although cancer is no longer considered an SAE by the USFDA, Primus requires notification of such diagnoses within 48 hours of the time the investigator first learns of the event. An SAE is any medical event that:

a. results in death
b. is life threatening—the investigator believes the subject's life is in immediate danger. This does not include events that, had they been more severe, might have been life threatening.
c. requires in-patient hospitalization or prolongation of an existing hospitalization.
d. results in permanent disability.
e. is a congenital anomaly or birth defect.
f. requires medical or surgical intervention to prevent one of the outcomes above.

14.3 Severity of Adverse Events

The investigator must rate every AE for severity according to the following guidelines:

- mild — does not interfere with daily activities.
- moderate — discomfort and/or dysfunction enough to interfere with, but not prevent, daily activities
- severe — significant impairment of ability to perform daily activities.

14.4 Assessment of Causality

Investigators will be responsible for determining the relationship of the study product(s) to the AE and will record their conclusions on the data collection tool, adverse event page. It is recognized that causality often cannot be established with certainty. Investigators must use their best clinical judgment keeping in mind the following questions:

a. Was study product administered?
b. What was the temporal relationship between the administration of study product and the AE? Was this consistent with the nature of the AE?
c. Was there another obvious or possible cause for the AE?
d. Was the AE consistent with the known effects of the study product?
e. Were there any features of the subject's clinical state, concomitant medications or diseases or environmental factors that could have caused or modified the AE?

f. Did the AE resolve, improve, remain stable or worsen after the study product was stopped or the dose reduced?
g. If the subject was re-exposed to the study product (re-challenge), did the AE recur, worsen or remain unchanged? Re-challenge should be attempted only after careful consideration and only after discussion with Primus.

Investigators should use their best clinical judgment and the guidelines above to assign all AEs and SAEs to one of the following four categories:

Not Related	Those AEs for which other etiologies can clearly and conclusively be defined.
Possibly Related	Those events for which other etiologies cannot be clearly demonstrated, and for which a relationship to the study agent cannot be positively excluded.
Probably Related	After careful scrutiny of the available medical facts, there is a reasonable, but inconclusive, certainty that the event is related to the study product.
Definitely Related	After careful medical evaluation there is little or no doubt that the study product is the direct etiologic cause of the AE. This situation is most commonly seen when an AE recurs after re-challenge with study product.

14.5 Reporting Serious Adverse Events

SAEs must be reported to Primus by telephone or, if from a non-U.S. site, by e-mail within 24 hours from the time the investigator first learns of them. This should be followed by a faxed report outlining the details of the event and the investigator's assessment of the severity and relationship of the event to the study agent. All SAEs will be reported on both the AE and SAE pages of the data collection tool/case report forms. In addition:

a. A new SAE form must be completed and faxed to Primus within 24 hours.
b. Follow-up SAE forms must be completed and faxed to Primus whenever new information becomes available about the event.
c. A final SAE report must be completed and faxed to Primus when the event has resolved or its consequences have stabilized and all relevant information (including hospital records, laboratory and pathology reports, autopsy reports, etc.) have been received. It is the responsibility of the investigator to obtain copies of all relevant information in a timely manner.
d. It is the responsibility of the investigator to determine the severity and causality of the SAE.
e. The initial SAE report and all subsequent reports must be retained in the subject's study file together with a telephone log of all contacts with Primus and the subject. These should be recorded at the time of the conversation, dated and signed

by the investigator or his/her representative and should include the name of the person with whom the conversation was held.

Telephone contact should be made with Robert Levy, MD, Director Clinical Development
480-483-1410 (office)
480-415-6779 (mobile)
Fax 480-483-2604

If Dr. Levy is unavailable contact:
Mary Sanstead, BSN, Project Manager
480-483-1410
480-250-6689 (cell)
Fax 480-483-2604

Primus will review all SAEs with the investigator and a decision will be made regarding the need for further action. Primus' primary concern will be subject safety, both for the subject having the event as well as for the other subjects in the study. If, after detailed review, it is determined that a subject safety issue exists, Primus will notify all investigators participating in any trial with the same study product and the IRB(s) overseeing those trials, and may require one or more of the following:

a. Discontinuation or suspension of the study
b. Modification of the protocol
c. Modification of the informed consent document to reflect additional risk(s) to be signed by current and future subjects.
d. Addition of newly discovered adverse events to the investigator's brochure

14.6 Follow-Up of Adverse Events

All adverse events, whether serious or non-serious, must be followed until resolution or stability. This follow-up may extend beyond the end of the study. Primus considers AE follow-up to be part of a study. Therefore, a study cannot be closed at an investigative site if an AE is outstanding. Any serious AE occurring after the conclusion of a study must be reported to Primus if the investigator thinks the event ***may*** be causally related to the study agent.

14.8 Deaths

All deaths, regardless of cause, that, occur between the time a subject signs an informed consent document and the final study visit or 30 days after the last dose of study product, whichever is longer, must be reported to Primus by telephone with a follow-up fax within 24 hours of the investigator becoming aware of the death. This applies whether or not the

subject has received study product and whether or not the study product is thought to be causally related to the death. It is the investigator's responsibility to obtain all relevant medical records and autopsy reports and forward them to Primus as soon as possible.

14.9 Reporting Safety Information to IRB

It is the responsibility of the investigator to notify his/her IRB of any unexpected or unknown risk to study subjects. This includes death from any cause and all SAEs. The investigator should make this report within 14 days of the onset of the SAE. The report should include any action taken after discussion of the SAE with Primus.

14.10 Managing Adverse Events

All AEs and SAEs should be medically managed according to the best medical standards available in the investigator's community. Except in the case of emergent treatment and routine care, the management of the event should be discussed with Primus. Decisions regarding re-challenge with study drug **must** be made in consultation with Primus.

14.11 Pregnancy

EpiCeram is device whose ingredients include at least 2 occlusive products (petrolatum, dimethicone) that prevent systemic uptake and therefore the device has no impact on the reproductive system of the user. Pregnancy data will not be collected during this study.

DEFINITION OF DEVICE PER FDA: Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

…3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

15.0 Ethical Considerations

This study will be conducted in accordance with the principles of the Declaration of Helsinki, ICH guidelines and Good Clinical Practices (GCPs) and US FDA regulations.

15.1 Informed Consent

All patients must read and sign the institutional review board (IRB) approved Research Subject Information and Consent Form before they can be subjects in this research study. It is the investigator's responsibility to fully inform the patient about the procedures, risks

and benefits of the study and to answer, in a manner clearly understandable to the patient. The consent must be obtained and documented according to the instructions of the IRB. A copy of the signed and dated document must be given to the subject. The IRB approved document must not be modified in any way from its original form. The original copy must be retained with the subject's study file and is subject to inspection by representatives of Primus and regulatory agencies.

All written material read by or distributed to a subject during the study must be written in a language the subject can read and understand and approved by the IRB.

15.2 Institutional Review Board (IRB)

For all studies performed in the United States, Primus will assume responsibility for submitting the required documents to a central IRB. Before this can be done each investigator must submit the following to Primus:

a. Signed and dated protocol signature page.
b. Completed, signed and dated FDA Form 1572, when required.
c. Completed, signed and dated W-9 form.
d. Current curriculum vitae for investigator and all sub-investigators, signed and dated.
e. Investigator conflict of interest form.

If an investigator wishes to use an IRB other than that selected by Primus, he/she may do so after obtaining approval from Primus. In this case, the investigator will be responsible for all required submissions. Non-U.S.A. investigative sites will have IRB approval arranged by the contract research organization (CRO) engaged by Primus for the execution of the study. Any changes to the model consent must be first approved by Primus, in writing. The investigator must agree to all protocol amendments and, if necessary, make appropriate changes in the consent. The IRB should be notified of any such changes and IRB approval must be sought for any changes involving subject safety.

Serious or unexpected adverse events must be reported to the IRB according to their instructions.

All investigators will be responsible for completing reports as required by the IRB. One copy of those reports should be kept in the study regulatory file and another submitted to Primus.

15.3 Subject Confidentiality

Subject identities should always be protected. This is the legal responsibility of the investigator. Subjects should be identified in study documents only by initials and study number on any document sent to Primus or a regulatory agency. Documents that are only for office use must be kept in strict confidence. It is strongly recommended that the investigative site have its own HIPAA document in place and that patients read, sign and date this at the same time they sign the consent.

Investigators must allow representatives of Primus or government regulatory agencies to inspect study records with subject de-identification in place.

16.0 Administrative and legal obligations

16.1 Pre-study Documentation

Before an investigator can begin screening subjects and before shipment of study product can commence the investigator must complete and return the following to Primus:

a. Signed and dated protocol signature page
b. Completed, signed and dated FDA Form 1572, when required
c. Copy of IRB approved consent
d. Copy of IRB approval letter
e. Current CVs of the investigator and all sub-investigators, signed and dated
f. Name, address and telephone number of any local laboratories to be used in the study
g. Normal values for local laboratory
h. Agreement to dispose of unused drug supplies per their community requirements
i. Signed and dated contract to conduct the study under the conditions and financial arrangements specified
j. Financial disclosure form
k. Name and contact information of person(s) responsible for the day to day management of the study

16.3 Protocol Amendments

Protocol amendments may be made only by Primus. The investigator's IRB must be informed of any amendments that may affect subject safety or the conduct of the study. The IRB must issue a letter of approval of such amendments. The investigator must keep the original letter in the study's regulatory binder and forward a copy of the letter to Primus.

16.4 Study Termination

Both the investigator and Primus have the right to terminate their participation in the study. If this is done by the investigator, he/she must provide a detailed explanation of the action to Primus and the IRB and a copy of this account must be retained with the regulatory file.

Upon completion of the study the investigator is required to send a summary of his/her experience to Primus and to the IRB. This should include an impression of clinical response and an accounting of any AEs or SAEs thought to be possibly associated with the study product.

16.5 Source Documents

FDA regulations (21 CFR 312.62b) require an investigator "to prepare and maintain adequate and accurate case histories that record all the data and other observations pertinent to the investigation on each individual" participating in a clinical investigation whether or not they were administered the investigational product. "Case histories include the case report forms and supporting data including, for example, progress note of the physician, the individual's

hospital charts, and nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study." Source documents may be reviewed and compared with data collection tool/CRFs at all monitoring visits. All source documents and data collection tool/CRFs should be complete and up to date and filed in chronological order in the subject's study file.
The investigative site must maintain logs for the following:

a. Screening visits
b. Randomization
c. Study product dispensed and returned
d. Monitor visits
e. Study personnel
f. Telephone contact

16.6 Data Collection Tools/Case Report Forms

Primus will provide investigators with data collection tool (hard copy or electronic) bearing information identifying the study site and the principal investigator. All data obtained during the study will be recorded on the data collection tool. This data will be reviewed on site or electronically by a Primus clinical monitor (or an agent of Primus such as a contract research organization) who will forward one copy to Primus (if hard copy), the original to remain with the subject's study data file.

The data collection tool contains the critical study data and are the basis from which results are tabulated, analyses performed, and final reports made. Therefore, it is essential that data recorded be legible, complete and accurate. Forms should be typed or completed in black ball point ink (if hard copy). Corrections should be made by placing a single line through the error, adding the correct data then signing and dating the correction. Under no circumstances should the original entry be erased, overwritten, or obscured by white-out or some other method. The data collection tool should contain only de-identified information. All data points must be answered. If the information is unknown or unavailable the terms "NA" (not available), "ND" (not done), "SU" (subject unable) or "DP" (data pending) may be used.

The investigator must maintain all records in a complete and current state. All source documents and supporting materials must be available for inspection by Primus personnel or representatives of government agencies.

16.7 Final Study Documentation and Storage

Investigators must retain all study records in a secure location, safe from environmental damage, for the maximum time required by the FDA, Primus or his/her institution, whichever is longest. These records should include, but are not limited to, the following:

- Source documentation
- Data collection tool/CRFs

- Original reports of tests results
- Protocols with amendments
- Original signed and dated ICF(s)
- Product accountability and dispensing logs
- Correspondence with Primus, IRB and governmental agencies

The investigator must complete a summary report (form provided) and submit it to Primus upon completion of the study. All data and other information may be submitted to the governmental regulatory agencies as required by the regulations. No study document may be destroyed without the written permission of Primus. Any change in storage location or assignation of the records to another party must first be approved, in writing, by Primus. If, for any reason, the investigator becomes unable to store study documents Primus must be notified. Study documents should never be destroyed without the written consent of Primus.

17.0 Summary of Investigator responsibilities

Investigator responsibilities include, but are not limited to:

a. Will conduct the study according to the protocol and will make no changes without the consent of the sponsor. This requirement is not intended to limit the investigator's ability to deviate from the protocol to protect the health and welfare of a subject.
b. Will comply with all applicable regulatory requirements.
c. Will personally supervise the conduct of the study.
d. Will report any adverse events that occur during the study.
e. Will promptly treat or arrange for treatment of any AE or SAE.
f. Has read and understands the information contained in the investigator's Brochure or product information document.
g. Will attend any investigator meetings conducted by Primus.

17.1 Data Collection and Study Monitoring

This study will be monitored, in person or electronically, by Primus personnel or by clinical research associates (CRAs) employed by Primus for this project. Site visits, if necessary, will be scheduled at pre-established intervals and will be scheduled in advance. All site visits will be conducted according to Primus' standard operating procedures (SOPs). The monitor must be allowed free access to all study records and supporting in order to verify the accuracy, consistency and completeness to ensure the study is being conducted in accordance guidelines of good clinical practice. Some site visits may be conducted remotely using an internet, based system with which the monitor and coordinator can view and speak to each other and work simultaneously on documents in real time. Study coordinators must be available and be able to devote the required time to the site visit. The primary investigator or sub-investigator should also be available to offer comments and resolve any issues that may arise.

18.0 Audits

The investigative site may be subject to audit by Primus or by regulatory agencies. All areas of the site will be examined including, but not limited to, subject treatment rooms, laboratory, product storage and preparation areas, and document storage. To prepare for any audit all data and documentation must be complete and organized chronologically by document type. If a site is notified of impending regulatory agency audit the primary investigator should promptly inform Primus to arrange for audit preparation assistance.

19.0 Primus contacts

Questions related to study conduct, supplies or administrative matters should be directed to:
Ms. Mary Sanstead, BSN
Project Manager
480-483-1410 (Primus office) or
480-250-6689 (mobile)

Questions related to SAE's, medical observations or interventions should be directed to:
Robert Levy, MD
Director of Clinical Development
480-483-1410 (Primus office) or
480-415-6779 (mobile)

Primus Pharmaceuticals, Inc.
7373 N. Scottsdale Rd.
Ste. B-200
Scottsdale, AZ 85253
Tel: 480-483-1410
Fax: 480-483-2604

20.0 Publication/presentation of data

Primus regards all information obtained from the conduct of this study as confidential. If an investigator wishes to publish or present in oral or written form all or part of the data obtained during the study he/she must first submit a complete copy of such presentation to the director of Clinical Investigation for review and approval. This submission must occur no later than sixty (60) days before the anticipated date of presentation. The investigator will be required to incorporate any suggestions made by Primus consistent with its right to protect the confidentiality of the information.

21.0 Statistical considerations

Descriptive statistics will be calculated for all demographic and clinical characteristics at baseline and study outcomes for each time period. Means and standard deviations will be

presented for continuous variables (e.g. age) or proportions and frequencies for categorical variables (e.g., sex) to describe the sample.

Paired t-tests will be used to assess differences in the primary outcomes of face and hand skin irritation symptoms (pain, redness, dryness, cracking, roughness, itching and overall skin irritation) between the baseline visit and Day 28 follow-up visit. The same analysis will be conducted for the secondary outcomes of pH, TEWL, and S. aureus colonization level. All statistical tests for the primary outcomes will be conducted will be two-tailed with α set at 0.05. All *p*-values will be reported with high precision (to the 4^{th} decimal place) so that multiple comparisons adjustments may be applied, as desired. Table 1 below shows how the results will be presented.

The analysis will be performed on the Intention-to-Treat sample. If there is attrition over the course of the study, attritors will be compared to completers in terms of measures taken at baseline. Any significant differences will be reported.

All variables will be checked for outliers and skewness by visually examining boxplots. Further evaluation of any outliers identified through visual checks will be conducted to assess if any participants should be excluded from the analysis. The assumptions for each inferential statistical test will be evaluated. In the event assumptions are not met, results from a Wilcoxon signed rank test will also be reported.

22.0 References

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Appendix I

The World Medical Association
Declaration of Helsinki

World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix II

Schedule of Events

VISIT	V1	V2	V3
WEEK	Screen	Baseline**	DAY 28**
Window	-7 d	+/- 2d	+/- 2d
Informed Consent/Photo Consent	X		
Inclusion/Exclusion	X		
Demographics	X		
Current Face & Hand Treatment	X		
Medical History of Skin Disease	X		
Overall symptom rating	X	X	X
Skin symptoms rating		X	X
Photos of face and hand*		X	X
TEWL and SCH face and hand*		X	X
Skin pH face and hand*		X	X
Swab of dominant hand*		X	X
Tape Strip dominant hand*		X	X
Subject Response per PI			X
Dispense Product		X	
Collect Product			X
Adverse Events		X	X
Changes to skin care		X	X

* Perform in the order listed. ** Instruct subject to stop washing hands and face for 2-hours prior to visit.

Appendix III

Subject Questionnaire

PPE Use

1. Does your employer provide PPE?
2. Are you able to choose the type of mask?
3. What is the average number hours PPE used per week?
4. Do you work directly with COVID-19 patients?
5. What is the average number of hours you work, per week, in contact with COVID-19 patients?
6. Do you re-use PPE intended for single use?
7. Does your employer provide hygiene guidelines?
8. Do the enhanced hygiene measures plus PPE, affect your ability to perform your work?
9. Which mask do you use at work, mainly?
    a. N 95
    b. Cotton
    c. Paper
    d. Polyester containing
    e. none
    f. Other: _____
10. Which mask do you use at home, mainly?
    a. N 95
    b. Cotton
    c. Paper
    d. Polyester containing
    e. none
    f. Other: _____

Quality of Life

11. On average how many days in a row do you work?
12. How much does skin irritation interfere with your daily life?
13. Do skin symptoms interfere with your sleep?

Care

14. What is the average number of times per day you wash your hands?
15. What is the average number of times per day you use a sanitizer?
16. Does your employer provide skin care products for work hours?
17. Do you use vitamin supplements intended for skin health?
18. Do you take a multiple vitamin?
19. What is the average number of glasses of water you drink per day?