CLINICAL STUDY PROTOCOL

An Exploratory Trial to Evaluate the Clinical Effectiveness of a Topical Application of BMX-010 in Subjects with Rosacea

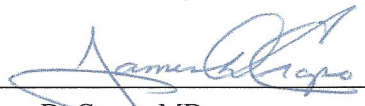
Sponsor:	BioMimetix JV, LLC 5340 South Quebec Street Suite 345N Greenwood Village, CO 80111
Funding Source:	BioMimetix JV, LLC
Protocol Number:	BMX-DERM-202
Version:	1.0
Investigational Product:	BMX-010
Indication:	Rosacea
Development Phase:	2
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Date:	October 5, 2018

1 APPROVALS

SPONSOR SIGNATURE PAGE

Protocol Number:	BMX-DERM-202
Version:	1.0
Protocol Title:	An Exploratory Trial to Evaluate the Clinical Effectiveness of a Topical Application of BMX-010 in Subjects with Rosacea
Version Date:	05 Oct 2018

Approved by:



James D. Crapo, MD
Manager, BioMimetix JV, LLC

11-October-2018
Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number:	BMX-DERM-202
Version:	1.0
Protocol Title:	An Exploratory Trial to Evaluate the Clinical Effectiveness of a Topical Application of BMX-010 in Subjects with Rosacea
Version Date:	05 Oct 2018

I acknowledge that I have read and understand the protocol named above and agree to carry out all of its terms in accordance with applicable regulations and laws.

I assure that the study drug supplied by the sponsor will be used only as described in the protocol named above.

Principal Investigator Name Signed _____ Date _____

Principal Investigator Name Printed _____

Clinical Center _____

Address _____

_____

_____

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3 LIST OF ABBREVIATIONS

AE	Adverse Event
BID	Twice Daily
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ET	Early Termination
FDA	Food and Drug Administration
HCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment Scale
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
Mn	Manganese
NOAEL	No Adverse Effect Level
PK	Pharmacokinetic
PRN	Pro re nata, When Necessary
PRO	Patient Recorded Outcome
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
UV	Ultraviolet
WIRB	Western Institutional Review Board

4 SYNOPSIS

<table>
<tr><td colspan="2">Protocol Title:
An Exploratory Trial to Evaluate the Clinical Effectiveness of a Topical Application of BMX-010 in Subjects with Rosacea</td></tr>
<tr><td>Protocol Number: BMX-DERM-202</td><td rowspan="2">Phase: 2</td></tr>
<tr><td>Protocol Version: 1.0</td></tr>
<tr><td>Test Drug: BMX-010</td><td>Indication: Rosacea</td></tr>
<tr><td colspan="2">Number and Country of Study Sites: Up to 20 study centers in the United States</td></tr>
<tr><td colspan="2">Objectives:
Part A
Primary Objectives
1. Determine whether the optimum frequency of topical application of BMX-010 0.03% is once per day or twice per day for a treatment interval of 7 to 28 days.
2. Determine whether the optimum frequency of topical application of BMX-010 0.1% is once per day or twice per day for a treatment interval of 7 to 28 days.
3. Determine if BMX-010 cream or gel provides better efficacy.
4. Evaluate the efficacy of BMX-010 0.03% in treatment of rosacea.
5. Evaluate the efficacy of BMX-010 0.1% in treatment of rosacea.
Secondary Objectives
1. Document, as possible, the clinical effects of BMX-010 in subjects with Rosacea through clinical photography.
2. Assess the mean percent reduction change in inflammatory papules/pustules counts from baseline to end of study.
Part B
Primary Objectives
1. Evaluate the efficacy of BMX-010 compared to placebo in a randomized, double-blind trial.
2. Determine the percent of subjects showing a 2 grade improvement in CEA score after treatment with BMX-010 compared to Placebo.
3. Determine the percent of subjects showing a 2 grade improvement in CEA score with full or partial clearing (final CEA score of 1 or 0) after treatment with BMX-010 compared to Placebo from baseline to end of study.
4. Determine the percent of subjects showing a 2 grade improvement in IGA score with full or partial clearing (final IGA score of 1 or 0) after treatment with BMX-010 compared to Placebo from baseline to end of study.
5. Determine the time to full clearing of rosacea after initiation of treatment with BMX-010.
Secondary Objectives:
1. Determine the percent of subjects showing a 1 grade improvement in the CEA score.
2. Determine the percent of subjects showing a 1 grade improvement in the IGA score.
3. Document, as possible, the clinical effects of BMX-010 in subjects with Rosacea through clinical photography.
4. Assess the mean percent reduction change in inflammatory papules/pustules counts from baseline to end of study.</td></tr>
</table>

Study Design:

This is a Phase 2 clinical trial of BMX-010 in adult men and women with rosacea which will be studied in two parts (Part A and Part B). Part A will involve up to 60 subjects treated with either BMX-010 0.03% or 0.1% given QD or BID for a minimum of 7 days and a maximum of 28 days. Information learned from Part A will be used to design Part B.

Part B is a randomized, double-blind, multi-center, placebo-controlled study of adult men and women with Rosacea. Subjects will be randomized and dosed with BMX-010 0.03% or 0.1% with the frequency of dosing (either QD or BID) for each dose of the study drug as determined optimal in Part A of this trial. Dosing will occur for a minimum of 7 days and a maximum of 28 days. An overview of the study design is presented in the schematics below, and details of study activities are provided in **Table 4a.**

In the Part A study, up to a total of up to 60 evaluable subjects with Rosacea will be dosed with BMX-010 (0.03% or 0.1%) topically applied either QD or BID. All subjects will dose for a minimum of 7 days and a maximum of 28 days. The dosing time frame will be at the discretion of the local clinician.

The sponsor may close enrollment once enough data has been obtained to determine the optimal dosing frequency and duration of dosing for each concentration (0.03% or 0.1%) of BMX-010 cream or gel to be studied in Part B.

In the Part B study, up to 150 evaluable subjects with Rosacea will be dosed with the concentration and formulation of BMX-010 determined optimal in Part A or Placebo given at the frequency determined optimal in Part A. The randomization scheme is 2:1, study drug : Placebo. All subjects will dose for a minimum of 7 days and a maximum of 28 days.

The sponsor may close enrollment once enough data has been obtained to assess the expected efficacy of 0.03% BMX-010 and 0.1% BMX-010. This data will be used to plan future studies.

The Clinical Erythema Assessment scale (CEA) will be utilized to assess erythema and will be limited to the face (described below).

Clinical Erythema Assessment Scale

Grade	**Description**
0 = Clear	Clear skin with no signs of erythema
1 = Almost clear	Almost clear; slight redness
2 = Mild	Mild erythema; definite redness
3 = Moderate	Moderate erythema; marked redness
4 = Severe	Severe erythema; fiery redness

Drug treatment and efficacy assessment by IGA will be limited to the face.

The Investigator Global Assessment (IGA) is a five scale (0 to 4) static evaluation of overall rosacea severity (as described below).

IGA

Grade	Description
0 = Clear	No papules and/or pustules; no erythema
1 = Minimal	Rare papules and/or pustules; faint, up to but not including mild erythema
2 = Mild	Few papules and/or pustules; mild erythema
3 = Moderate	Pronounced number of papules and/or pustules, but less than numerous papules and/or pustules; moderate erythema
4 = Severe	Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate to severe erythema

Subjects will also be asked a series of patient-reported outcome questions and will be asked to consent to optional photographs of the treated lesions.

Throughout both phases, subjects will be queried regarding adverse events (AEs), concurrent medical history and concomitant medication usage.

Subject Population:

Male or female at least 18 years of age with a clinical diagnosis of mild to severe facial rosacea.

Inclusion Criteria:

1. Male or female, at least 18 years of age;
2. A clinical diagnosis of mild to severe facial rosacea;
3. Screening and Baseline IGA score $\geq$ 2 (greater than or equal to 2);
4. A minimum Clinician Erythema Assessment (CEA) score of 2 at Screening and at Baseline Visits (prior to the investigational product application);
5. Willing to refrain from using any topical or systemic treatments for inflammatory skin disease, other than the investigational product;
6. Candidate for topical treatment of Rosacea;
7. If a cleanser, moisturizer or sunscreen is needed during the study, Subjects must be willing to use only allowed cleansers, moisturizers, sunscreens, or moisturizer/sunscreen combination products. If the subject wears makeup they must agree to use non-comedogenic makeup;
8. Females of child-bearing potential must have a negative urine pregnancy test within 48 hours prior to the first drug administration;
9. Females of child-bearing potential must be willing to use 2 methods of contraception deemed adequate by the investigator (for example, oral contraceptive pills plus a barrier method) through the trial and for 1 month thereafter to be eligible for, and continue participation in, the study;
10. Ability to complete the study in compliance with the protocol, including agreement in writing to apply study product only to the assigned areas; and
11. Ability to understand and provide written informed consent.

Exclusion Criteria:

1. Any dermatological conditions on the face that could interfere with clinical evaluations;
2. Any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive;
3. Presence of beard or excessive facial hair at Screening which would interfere with the study treatments or study assessments and refusal to remove for duration of study;
4. Subjects with any underlying disease that the Investigator deems uncontrolled, and poses a concern for the subject's safety while participating in the study;
5. Concomitant skin disease that could confound clinical evaluations or increase risk to the subject;
6. Use of medicated make-up (including anti-aging make-up) throughout the study;
7. Use during the study of 1) systemic steroids, 2) topical retinoids to the face, 3) antibiotics known to impact rosacea, 4) immunosuppressive agents, or immunomodulators;
8. Facial use of 1) topical steroids, 2) topical anti-inflammatory agents, 3) topical antimycotics, 4) any topical rosacea treatments or 4) topical antibiotics;
9. Use of medicated cleansers on the face (throughout the study);
10. Use of topical astringents or abrasives, medical topical preparations (prescription and OTC products) within 2 days prior to Baseline and throughout the study;
11. Systemic or skin infection requiring antimicrobial therapy;
12. Systemic chemotherapy or radiotherapy within 4 weeks of the Baseline Visit;
13. Immunocompromise of any cause, known human immunodeficiency virus infection, or acquired immunodeficiency syndrome;
14. Pregnancy, planned pregnancy, lactation, or inadequate contraception as judged by the investigator;
15. Active drug or alcohol dependence;
16. Significant acute or chronic medical, neurological, or psychiatric illness that, in the judgment of the investigator, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study;
17. Previous clinical trial participation for the indication being treated in this protocol.

Dose Regimen/Route- Duration of Treatment and Follow up:

Part A

Subjects will receive topical administration of either 0.03% BMX-010 or 0.1% BMX-010, to apply to rosacea on the face. Topical therapy with BMX-010 will be either QD or BID. The planned treatment duration is a minimum of 7 days and a maximum of 28 days. Completion of 28 days of treatment will be recommended to all subjects; however, subjects who have full clearing of the rosacea, as determined by the clinical center investigator, may stop study drug therapy and remain in the study with a final evaluation at Day 29 or Day 43 (at the discretion of the investigator).

Part B

Subjects will be randomized 2:1 to receive topical administration of BMX-010 or Placebo which will be dosed at the concentration and frequency as defined by Part A. Study product will be applied liberally to rosacea on the face. The planned treatment duration is a minimum of 7 days and a maximum of 28 days. Completion of 28 days of treatment will be recommended to all subjects; however, subjects who have full clearing of the rosacea, as determined by the clinical center investigator, may stop therapy and remain in the study with a final evaluation at Day 29 or Day 43 at the discretion of the investigator. There will be weekly visits with follow-up done at approximately Days 8, 15, 22, 29 and 43.

Dosage Form and Strength Formulation:

BMX-010

BMX-010 will be supplied at concentrations of 0.03% and 0.1%. BMX-010 will be manufactured by Albany Molecular Research, Inc. (AMRI), and formulation and packaging is done by Velesco Pharmaceutical Services, LLC. BMX-010 is yellow/brown in color and transient (up to 7 days) of yellow discoloration of skin can occur. BMX-010 is dispensed in approximately 10 mL tubes.

Placebo

The Placebo used will consist of a formulation containing the same excipients as the active drug product. The Placebo will be color-matched to the active study drug. Placebo will be supplied in 10 mL tubes. Formulation and packaging of the Placebo is done by Velesco Pharmaceutical Services, LLC.

Criteria for Evaluation:

Clinical Efficacy

Clinical effectiveness will be evaluated using the Five-scale IGA for Rosacea at baseline and end of study, the CEA at Baseline and end of study, Patient-reported outcomes, and counts of inflammatory lesions.

Safety Assessments

Safety will be assessed via AE monitoring, concomitant medication monitoring, physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count and chemistry), and pregnancy testing (if applicable).

Table 4.a Schedule of Observations and Procedures

Assessment	Screening[7]	Treatment Period[18]						Follow-up	
	Day -14 to Day -1	Baseline Day 1	Day 8 (+/- 2 days)	Day 15 (+/- 2 days)	Day 22 (+/- 2 days)	Day 28 [8]	Day 29 (+/- 2 days)	Day 43 (+/- 2 days)	Follow-Up [9]
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical history/demographics	X								
Concurrent medical conditions	X	X	X	X	X		X	X	
Medication history	X								
Concomitant medications	X	X	X	X	X		X	X	
Physical examination, including vital signs and weight[1]	X	X	X	X	X		X	X	
Height	X								
IGA	X	X	X	X	X		X	X	
CEA [2]	X	X	X	X	X		X	X	
Lesion Counts (Face)		X	X	X	X		X	X	
PRO questions [3]			X	X	X		X	X	
Clinical safety laboratory assessments[4]		X						X	
Urine pregnancy test[5]	X							X	
Randomization *Part B only		X							
Dosing[6]		X	X	X	X	X			
Discoloration Review			X	X	X		X	X	
Photographs (optional)		X	X	X	X		X	X	
Phone Follow up									X
Pre- and post-treatment AE monitoring	X	X	X	X	X		X	X	

1 Includes sitting blood pressure, pulse rate and temperature.
2 CEA is the Clinician's Erythema Assessment 5-scale score (0 to 4).
3 All subjects will be asked questions regarding the study drug, clearing and color, these are the Patient Reported Outcome (PRO) questions (see Appendix A).
4 Clinical safety laboratory assessments will include CBC with differential and CMP.
5 Females of child-bearing potential must have negative results within 48 hours prior to start of drug treatment for inclusion. The Day 43 test is performed for females of child-bearing potential who receive at least one application of study drug.
6 In Part A, subjects who meet the inclusion/exclusion criteria will be dispensed BMX-010 (concentration provided to be at the discretion of the local clinical investigator). In Part B, subjects will be randomized to BMX-010 (0.03% or 0.1%) or Placebo (2:1 active:placebo); In Part A, study drug will be applied topically QD or BID at the discretion of the local clinical investigator. In Part B, the dosing frequency will be set as defined from Part A. Dosing will be applied to all active lesions for a minimum of 7 days and up to Day 28.

[7] The screening and baseline visits may be combined.
[8] Day 28 is not a clinic day. The subject should stop dosing on Actual Day 28 of the study.
[9] After the Day 43 final clinic visit, the clinical center may call or mail the subject at approximately 1, 2, and/or 3 months later to ask the questions listed in Appendix B.

5 BACKGROUND

Rosacea is a chronic relapsing inflammatory skin disease which typically onsets between the ages of 30 and 50 [1]. It is characterized by marked involvement of the face with transient or persistent erythema, inflammatory papules or pustules, telangiectasia, or hyperplasia of the connective tissue [2].

Rosacea has a high prevalence among adults of Northern European heritage with fair skin. Symptoms of Rosacea can present in different combinations and severity, is often chronic and can fluctuate between periods of remission and exacerbation [3]. Rosacea affects about 10% of the population [4].

There is presently no cure for rosacea. There are topical, systemic treatment and laser treatments available which may suppress its signs and symptoms and give relief.

BioMimetix JV, LLC, has developed a topical gel and a topical cream formulation of BMX-010 for the treatment of inflammatory skin diseases, such as Rosacea. BMX-010 (MnTE-2-PyP) is a manganese (Mn) porphyrin drug; porphyrins are made up of 4 pyrrole rings connected by methine bridges. These molecules often form complexes with metals by incorporating them into the nucleus of the porphyrin structure, situated between the interiorly-located vertices of the pyrrole rings. Such Mn-porphyrin-based compounds are potent anti-inflammatory agents that can catalytically inactivate a range of reactive oxygen species, including peroxynitrite and superoxide anion [5,6].

BMX-010 (MnTE-2-PyP) exhibits extremely high enzymatic redox activity for a broad range of oxidant species including O2-, H2O2, and ONOO- (ROS). The drug has catalytic antioxidant activity capable of scavenging ROS as well as the mimicking of superoxide dismutase. Unlike other antioxidants, this class of agents is catalytic and can repetitively eliminate ROS. BMX-010 acts as a scavenger in the cell cytoplasm, as in the context of reduced TACE oxidation [7] and yet functions as an oxidizer in the nucleus, inhibiting the reduction of the p50 subunit of NF-κB and effectively blocking DNA binding [8]. As a result of the complex mechanism of action, BMX-010 and other metalloporphyrin compounds exhibit an unexpected potency in inflammatory injury models at doses 100 to 1000 times less than would be expected if they were acting primarily as stochiometric antioxidants [9,10]. BMX-010 and related compounds mechanism of action is reflected in diverse preclinical models.

T cells become hypo-responsive after BMX-010 treatment [7,11]. BMX-010 treatment promotes metabolic quiescence, impedes diabetogenic autoimmune responses by restricting the metabolic pathways for energy production and affects anabolic processes necessary for cell proliferation [12]. This metabolic reduction decreases T cell differentiation, returning T cells to stasis or quiescence, all while retaining viability [9,13,14]. A lowered aerobic glycolysis in T cells suggests the potential for treating chronic inflammatory dermatologic conditions, such as atopic dermatitis or psoriasis.

In pancreatic islet cells, oxidative stress develops during organ harvesting, during the isolation process, and during storage and transport. Isolation insults result in osmotic, mechanic ischemic, and oxidative stress for the islet cells. These events lead to increased production of pro-

inflammatory cytokines and free radicals by pancreatic acinar cells, passenger leukocytes, and islet cells themselves, leading ultimately to β cell dysfunction and death. Therefore, the ability to reduce these early nonspecific proinflammatory events (i.e., free radical generation and cytokine production) during islet cell isolation should afford increased β cell mass as well as improved and more stable metabolic function [15,16]. Experiments in such models show that BMX-010 modulates Th1 cells and effector cytokine production [7,10,11] and protects islets during isolation for transplantation [13,17].

In models of acute central nervous system injury and ischemic stroke, BMX-010 treatment reduces NF-κB activation [8] and CD8 T cell effector function [14] enhancing neurologic function [18,19]. In cancer models, BMX-010 blocks HIF-1 activation, decreases hypoxia, reduces tumor-protective cytokine release and ultimately suppresses tumor growth [20]. HIF-1 is critical for facilitating glycolysis in times of low oxygen, and tumor cells depend heavily on glycolysis to survive.

In order to evaluate toxicity of the MnTE-2-PyP drug substance, a full good laboratory practice nonclinical safety assessment was conducted. BMX-010 was evaluated in *in vitro* genotoxicity studies, local tissue tolerance evaluation, safety pharmacology core battery studies, and single- and repeat-dose intravenous (IV) toxicity studies in mice and monkeys [15]. BMX-010 was determined not to be genotoxic or hemolytic, did not demonstrate flocculation or elicit adverse pharmacologic effects on respiration and the central nervous system, and had limited transitory effects on the cardiovascular system only at levels well above the therapeutic target dose. The IV clinical solution did not cause venous irritation in rabbits. The no observed adverse effect level (NOAEL) in mice was determined to be 10 mg/kg/day after 18 consecutive days of bolus IV dosing once daily (QD) in the morning. The NOAEL in monkeys after 14 days of bolus IV dosing in the morning was determined to be 5 mg/kg/day. At doses relevant to clinical use in humans, neither study revealed any indication of any specific target organ toxicity, including the classic heme porphyrin kidney, liver, CNS, or cardiac toxicities, or manganese toxicity. Mortality seen shortly after dosing in individual animals at higher doses was not accompanied by any organ or clinical pathology indications, suggesting a functional pharmacological-mediated effect.

Based on the demonstrated activity of BMX-010 to reverse persistent dermal inflammation, we believe adding BMX-001 as a topical therapy for patients with Rosacea, may be a relevant contribution to this disease model either as monotherapy or as combination therapy.

Completed Phase 1 safety studies on BMX-010 have indicated no identifiable toxicities.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A

1. Determine whether the optimum frequency of topical application of BMX-010 0.03% is once per day or twice per day for a treatment interval of 7 to 28 days.
2. Determine whether the optimum frequency of topical application of BMX-010 0.1% is once per day or twice per day for a treatment interval of 7 to 28 days.
3. Determine if BMX-010 cream or gel provides better efficacy.
4. Evaluate the efficacy of BMX-010 0.03% in treatment of rosacea.
5. Evaluate the efficacy of BMX-010 0.1% in treatment of rosacea.

Part B

1. Evaluate the efficacy of BMX-010 compared to placebo in a randomized, double-blind trial.
2. Determine the percent of subjects showing a 2 grade improvement in CEA score after treatment with BMX-010 compared to Placebo.
3. Determine the percent of subjects showing a 2 grade improvement in CEA score with full or partial clearing (final CEA score of 1 or 0) after treatment with BMX-010 compared to Placebo from baseline to end of study.
4. Determine the percent of subjects showing a 2 grade improvement in IGA score with full or partial clearing (final IGA score of 1 or 0) after treatment with BMX-010 compared to Placebo from baseline to end of study.
5. Determine the time to full clearing of rosacea after initiation of treatment with BMX-010.

6.2 Secondary Objectives

Part A

1. Document, as possible, the clinical effects of BMX-010 in subjects with Rosacea through clinical photography.
2. Assess the mean percent reduction change in inflammatory papules/pustules from baseline to end of study.

Part B

1. Determine the percent of subjects showing a 1 grade improvement in the CEA score.
2. Determine the percent of subjects showing a 1 grade improvement in the IGA score.
3. Document, as possible, the clinical effects of BMX-010 in subjects with Rosacea through clinical photography.
4. Assess the mean percent reduction change in inflammatory papules/pustules counts from baseline to end of study.

7 STUDY DESIGN

The purpose of this study is to first explore the optimum formulation (gel vs. cream), concentration (0.03% vs. 0.1%), and dosing frequency (QD vs. BID) of BMX-010 in subjects with Rosacea in Part A. In Part B, the optimal formulation, concentration, and frequency will be used to study the efficacy of BMX-010, as determined by IGA and CEA scores and PROs.

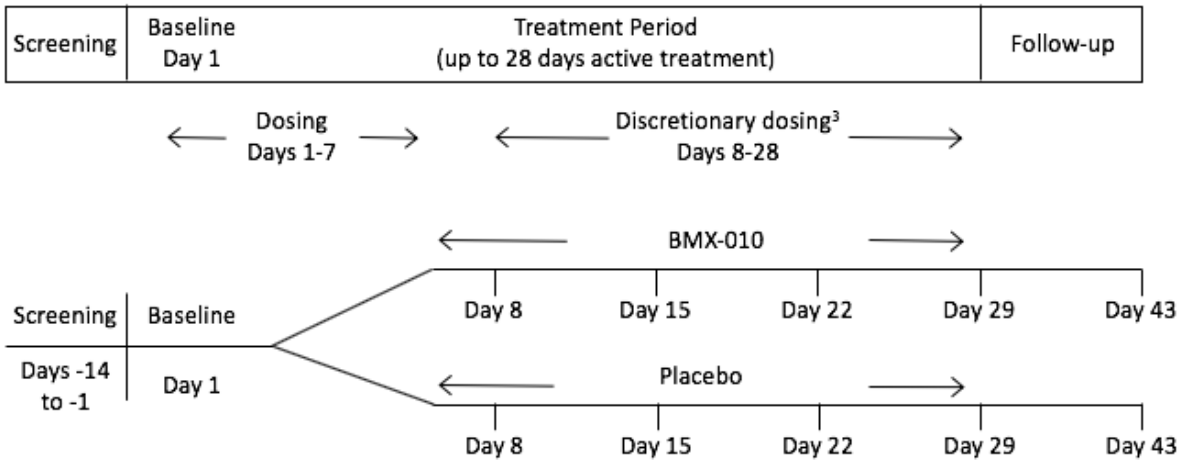
7.1 Part A Study Design

Subjects will be dispensed either 0.03% BMX-010 or 0.1% BMX-010 (gel or cream) at the discretion of the clinical center investigator, to apply to rosacea on the face. Topical therapy with BMX-010 will be either QD or BID, also at the discretion of the clinical center investigator. The planned treatment duration is a minimum of 7 days and a maximum of 28 days. Completion of 28 days of treatment will be recommended to all subjects; however, subjects who have full clearing of the rosacea, as determined by the clinical center investigator, may stop study drug therapy and remain in the study with a final evaluation at Day 29 or Day 43 (at the discretion of the investigator).

7.2 Part B Study Design

Subjects will be randomized 2:1 to receive topical administration of BMX-010 or Placebo which will be dosed at the concentration and frequency as defined by Part A. Study product will be applied liberally to rosacea on the face. The planned treatment duration is a minimum of 7 days and a maximum of 28 days. Completion of 28 days of treatment will be recommended to all subjects; however, subjects who have full clearing of the rosacea, as determined by the clinical center investigator, may stop therapy and remain in the study with a final evaluation at Day 29 or Day 43 at the discretion of the investigator. There will be weekly visits with follow-up done at approximately Days 8, 15, 22, 29 and 43.

Figure 7.a Study Design for both parts



Following written informed consent, subjects will undergo screening evaluations within 14 days prior to the first application of study drug. The screening evaluations will include complete medical history, complete physical examination (including vital signs, weight, and height), clinical laboratory evaluations, urine pregnancy test for females of child-bearing potential (a negative pregnancy test is required within 48 hours prior to the start of drug treatment), concurrent medical conditions, and concomitant medication assessments.

Subjects will be scored by the clinician for IGA and CEA. The clinician will also obtain counts of the inflammatory lesions on the face.

The subject will be asked a series of Patient Reported Outcomes (Appendix A).

In **Part A**, all eligible Subjects enrolled will receive the active study drug, BMX-010. Subjects will treat their rosacea on the face with the study product. This will be demonstrated at the Baseline visit. Subjects will be instructed by the clinical center staff and informed how often they should dose each day (QD or BID).

In **Part B**, all eligible Subjects enrolled will be randomized to the study drug (BMX-010) or Placebo. Subjects will treat their rosacea on the face with the study product. This will be demonstrated at the Baseline visit. Subjects will be instructed by the clinical center staff and informed how often they should dose each day, which will have been confirmed by Part A of the study.

Randomization will occur after completion of all screening assessments, once the subject is determined to be eligible. At Baseline, subjects will undergo confirmation study eligibility assessments as specified in Table 4.a. The first dose of study drug will be administered in the clinic under the supervision and direction of study staff and subjects will be trained on the amount of study product to use and where to apply it.

Subjects will be instructed to bring all study drug (including empty tubes) with them when they return to the clinic each week for assessment of study drug use by the clinical center.

Subjects will be asked a series of questions (Appendix A) during in-clinic study visit days.

Subjects will be able to consent to optional photographs the treated lesions. Since the Rosacea to be treated is on the face, the photos may include the face.

Throughout both phases, subjects will be queried regarding adverse events (AEs), concurrent medical history, and concomitant medication usage.

7.2.1 Stopping Rules

The following stopping criteria will be implemented:

1. Subject stopping criteria: If a subject experiences an AE that is deemed by the clinical center Principal Investigator to be at least “possibly” drug-related and is Grade ≥2 in severity (using the Common Terminology Criteria for Adverse Events (CTCAE v 5), that subject will be withdrawn from dosing, return for all scheduled evaluation visits, and be followed until the AE resolves or stabilizes.

2. Cohort stopping criteria: If 1 subject in a cohort experiences an AE that is deemed by the clinical center Principal Investigator to be probably or definitely drug-related and is Grade ≥3 in severity by CTCAE, or if 2 subjects in a cohort experience AEs that are deemed by the clinical center Principal Investigator(s) to be at least "possibly" drug-related and are Grade 3 in severity by CTCAE, dosing further subjects will be suspended until data is reviewed by the sponsor.
3. Dose stopping criteria: If the Rosacea is deemed as cleared by the study investigator (IGA=0), the subject will be instructed to stop dosing or continue based on the discretion of the clinical center investigator. Rosacea should be considered clear if it is not showing any inflammatory signs of disease. If it is decided by the local investigator to stop drug treatment, the clinical center investigator will determine which of the following scenarios will be implemented :
    - The subject should return to the clinical center weekly for further assessment.
    - The subject should return the following week to complete the end of study (Day 43) follow up visit.

    If the subject is still in the study, and the Rosacea returns, the subject should contact the clinical center and resume treatment (through Day 28) and weekly visits until the planned Day 43.

8 SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 Inclusion Criteria

1. Male or female, at least 18 years of age;
2. A clinical diagnosis of mild to severe facial rosacea;
3. Screening and Baseline IGA score $\geq$ 2 (greater than or equal to 2);
4. A minimum Clinician Erythema Assessment (CEA) score of 2 at Screening and at Baseline Visits (prior to the investigational product application);
5. Willing to refrain from using any topical or systemic treatments for inflammatory skin disease, other than the investigational product Candidate for topical treatment of Rosacea;
6. If a cleanser, moisturizer or sunscreen is needed during the study, Subjects must be willing to use only allowed cleansers, moisturizers, sunscreens, or moisturizer/sunscreen combination products. If the subject wears makeup they must agree to use non-comedogenic makeup;
7. Females of child-bearing potential must have a negative urine pregnancy test within 48 hours prior to the first drug administration;
8. Females of child-bearing potential must be willing to use 2 methods of contraception deemed adequate by the investigator (for example, oral contraceptive pills plus a barrier method) through the trial and for 1 month thereafter to be eligible for, and continue participation in, the study;
9. Ability to complete the study in compliance with the protocol, including agreement in writing to apply study product only to the assigned areas; and
10. Ability to understand and provide written informed consent.

8.2 Exclusion Criteria:

1. Any dermatological conditions on the face that could interfere with clinical evaluations;
2. Any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive;
3. Presence of beard or excessive facial hair at Screening which would interfere with the study treatments or study assessments and refusal to remove for duration of study;
4. Subjects with any underlying disease that the Investigator deems uncontrolled, and poses a concern for the subject's safety while participating in the study;
5. Concomitant skin disease that could confound clinical evaluations or increase risk to the subject;
6. Use of medicated make-up (including anti-aging make-up) throughout the study;
7. Use during the study of 1) systemic steroids, 2) topical retinoids to the face, 3) antibiotics known to impact rosacea, 4) immunosuppressive agents, or immunomodulators;
8. Facial use of 1) topical steroids, 2) topical anti-inflammatory agents, 3) topical antimycotics, 4) any topical rosacea treatments or 4) topical antibiotics;
9. Use of medicated cleansers on the face (throughout the study);
10. Use of topical astringents or abrasives, medical topical preparations (prescription and OTC products) within 2 days prior to Baseline and throughout the study;
11. Systemic or skin infection requiring antimicrobial therapy;
12. Systemic chemotherapy or radiotherapy within 4 weeks of the Baseline Visit;
13. Immunocompromise of any cause, known human immunodeficiency virus infection, or acquired immunodeficiency syndrome;

14. Pregnancy, planned pregnancy, lactation, or inadequate contraception as judged by the investigator;
15. Active drug or alcohol dependence;
16. Significant acute or chronic medical, neurological, or psychiatric illness that, in the judgment of the investigator, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study;
17. Previous clinical trial participation for the indication being treated in this protocol.

8.3 Criteria for Discontinuation or Withdrawal of a Subject

All subjects are free to withdraw from study participation at any time, for any reason, and without prejudice to their further medical care. In addition, the investigator may terminate a subject from the study at any time. The primary reason for discontinuation should be recorded on the case report form (CRF) using one of the following categories:

1. Adverse event. The subject experiences an AE that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of an AE.
2. Lack of therapeutic effect. The investigator has determined that study drug administration is not benefitting the subject, and continued participation poses an unacceptable risk to the subject.
3. Inclusion/exclusion criteria violation. The investigator discovers that the subject did not meet all of the inclusion/exclusion criteria after study enrollment.
4. Protocol noncompliance. The subject has a significant protocol deviation, does not comply with study drug administration schedule, or fails to adhere to other study requirements as stated in the protocol.
5. Lost to follow-up. The subject does not return to the clinic for scheduled assessments, and does not respond to the site's attempts to contact the subject.
6. Voluntary withdrawal. The subject wishes to withdraw from the study. The clinical center should attempt to determine the underlying reason for the voluntary withdrawal and document it on the CRF; if the underlying reason is documented as an AE or lack of efficacy, the category of withdrawal should be marked in the corresponding category and not as voluntary withdrawal.
7. Study termination. The sponsor, Institutional Review Board (IRB), or regulatory agency terminates the study.
8. Pregnancy.
9. Other. Any reason that does not fall into 1 of the above categories. The specific reason should be recorded on the CRF.

Following early discontinuation (early termination or ET) from the study, the subject will be informed regarding the additional study evaluations that are necessary to monitor his/her safety. These subjects will be encouraged to participate in the procedures as indicated in the final follow up study visit.

In order to meet the number of specified evaluable subjects, a discontinued or withdrawn subject may be replaced and the newly enrolled subject will be assigned the identical treatment of the withdrawn subject.

9 TREATMENT OF SUBJECTS

9.1 Treatments Administered

9.1.1 Phase 1/Phase 2 Cohorts

Part A

BMX-010 0.03% or BMX-010 0.1% or Placebo QD
BMX-010 0.03% or BMX-010 0.1% or Placebo BID

Part B

BMX-010 Dose determined in Part A or Placebo, QD or BID as determined in Part A

In this study, up to 210 subjects will be enrolled.

In **Part A**, up to 60 subjects will be enrolled. Subjects will not be randomized and treatment concentration and dosing frequency will be at the discretion of the clinical center investigator. All subjects will receive study drug at either 0.03% or 0.1%. They will dose either QD or BID as indicated by the clinical center investigator during the baseline and other weekly visits throughout the study.

In **Part B**, up to 150 subjects will be enrolled. This will be a double-blind study, where the investigator and subject both will not know whether study drug or Placebo has been dispensed. Subjects will be randomized to BMX-010 or Placebo (2:1) in accordance with the randomization schedule. The Placebo cream is color-matched to the study drug, the Placebo gel is not. Up to 100 subjects will be randomized to BMX-010 and up to 50 subjects will be randomized to Placebo.

In both parts, the study product will only be applied to Rosacea of the face.

When subjects apply QD, it can be applied any time of the day. When it is applied BID it should generally be applied 12 hours apart.

9.1.2 Blinding in Part B

The sponsor has a standard operating procedure regarding randomization and blinding. The sponsor also will have a designated list of personnel who have un-blinded access. The sites will be provided with a key if un-blinding is required during the trial.

9.2 Identity of Investigational Products

9.2.1 BMX-010 Drug Substance

9.2.1.1 Structure

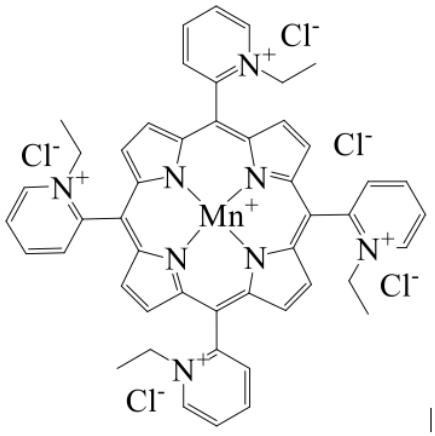


Figure 9.1: Structure of BMX-010

9.2.1.2 General Properties

Formula Weight: 965.12
Chemical Name: Mn(III) tetrakis(*N*-ethylpyridinium-2-yl)porphyrin pentachloride
Empirical Formula: $C_{48}H_{44}Cl_5MnN_8$
CAS RN: 219818-60-7
Appearance: Dark brown or purple solid

9.2.1.3 Manufacturer

Drug substance Lot #9739-C-R0-01-21-01, which will be used to manufacture the clinical trial material for the presently proposed trials, was manufactured, tested and released under cGMP by Albany Molecular Research, Inc., Albany, NY (AMRI). A 3-year stability study is being performed by AMRI according to ICH guidelines.

9.2.2 BMX-010 Gel Drug Product

9.2.2.1 Description and Composition

The gel drug product is a preserved aqueous gel comprising 0.03% or 0.1% BMX-010 and having the batch composition indicated in Table 9.a. The gel is filled at 10 g/tube into 0.5 ounce white LDPE squeeze tubes with screw caps. BMX-010 is yellow/brown in color and transient (up to 7 days) of yellow discoloration of skin is not considered to be an AE.

Table 9a: Batch Composition of BMX-010 Gel

	Quantity per batch, g *(wt%)*		
Component, Quality *(Function)*	**Placebo**	**0.03% BMX-010**	**0.1% BMX-010**
BMX-010, AMRI *(API)*	___	3 *(0.03%)*	10 *(0.10%)*
Natrosol™ 250 Hydroxyethylcellulose HX, Pharm, NF *(gelling agent)*	300 *(3.00%)*	300 *(3.00%)*	300 *(3.00%)*
Propylene Glycol, USP *(gelling agent)*	500 *(5.00%)*	500 *(5.00%)*	500 *(5.00%)*
Potassium Sorbate Powder, NF *(preservative)*	15 *(0.15%)*	15 *(0.15%)*	15 *(0.15%)*
Sodium Benzoate, NF *(preservative)*	30 *(0.30%)*	30 *(0.30%)*	30 *(0.30%)*
Titanium Dioxide, USP *(colorant)*	200 *(2.00%)*	200 *(2.00%)*	200 *(2.00%)*
Glacial Acetic Acid, USP *(buffer)*	15.2 *(0.15%)*	15.2 *(0.15%)*	15.2 *(0.15%)*
Sodium Hydroxide 1*N* solution, USP *(buffer)*	164.4 *(1.64%)*	164.4 *(1.64%)*	164.4 *(1.64%)*
Sterile Purified Water, USP *(solvent)*	8775.4 *(87.75%)*	8772.4 *(87.72%)*	8765.4 *(87.65%)*
Medical Air, USP *(blowing agent)*	0	0	0
Total batch weight	10000	10000	10000

9.2.3 BMX-010 Cream Drug Product

9.2.3.1 Description and Composition

The cream drug product is a preserved oil-in-water emulsion cream comprising 0.03% or 0.1% BMX-010 and having the batch composition indicated in Table 9.a. The cream is filled at 10 g/tube into 0.5 ounce white LDPE squeeze tubes with screw caps. BMX-010 is yellow/brown in color and transient (up to 7 days) of yellow discoloration of skin is not considered to be an AE.

Table 9a: Batch Composition of BMX-010 Cream

	Quantity per batch, g *(wt%)*		
Component, Quality *(Function)*	**Placebo**	**0.03% BMX-010**	**0.1% BMX-010**
BMX-010, AMRI *(API)*	___	1.8 *(0.03%)*	6 *(0.10%)*
Mineral Oil, NF *(emollient)*	720 *(12.00%)*	720 *(12.00%)*	720 *(12.00%)*
Petrolatum, *USP (emollient)*	540 *(9.00%)*	540 *(9.00%)*	540 *(9.00%)*
Cetostearyl alcohol, NF *(emollient, viscosity increasing agent)*	720 *(12.00%)*	720 *(12.00%)*	720 *(12.00%)*
Propylene glycol, USP *(humectant)*	480 *(8.00%)*	480 *(8.00%)*	480 *(8.00%)*
Glacial Acetic Acid, USP *(buffer)*	9 *(0.15%)*	9 *(0.15%)*	9 *(0.15%)*
Sodium Hydroxide 1*N* solution, NF *(buffer)*	102.6 *(1.71%)*	102.6 *(1.71%)*	102.6 *(1.71%)*
Sterile Purified Water, USP *(solvent)*	3,236.4 *(53.94%)*	3276.6 *(54.61%)*	3272.4 *(54.54%)*
Tween 20-LQ-(AP) *(emulsifier)*	60 *(1.00%)*	60 *(1.00%)*	60 *(1.00%)*
Isopropyl palmitate, NF *(emollient, viscosity increasing agent)*	60 *(1.00%)*	60 *(1.00%)*	60 *(1.00%)*
Imidazolidinyl urea, NF *(preservative)*	12 *(0.20%)*	12 *(0.20%)*	12 *(0.20%)*
Methylparaben, NF *(preservative)*	12 *(0.20%)*	12 *(0.20%)*	12 *(0.20%)*
Propylparaben, NF *(preservative)*	6 *(0.10%)*	6 *(0.10%)*	6 *(0.10%)*
Iron Oxides, NF *(colorant)*	42 *(0.7%)*	___	___
Medical Air, USP *(blowing agent)*	0	0	0
Total batch weight	6000	6000	6000

9.2.4 Manufacturer

The drug product will be manufactured, tested and released under cGMP by Velesco Pharmaceutical Services, LLC, Kalamazoo, MI (Velesco). Stability adequate to support the proposed clinical study of the BMX-010 gel and cream will be demonstrated by Velesco. Stability studies will be conducted in accordance with ICH Q1A (R2) using a cGMP qualified stability indicating analytical method.

9.2.5 Labeling

The drug product labels will include a brief description of the drug product, the sponsor, lot number, storage information, emergency contact, and the statement, “Caution: New Drug – Limited by Federal Law to Investigational Use.” Lot numbers are not listed in the protocol as Phase 2 studies using the cream will be double-blinded.

BMX-010 Gel or Cream –Lot X
BioMimetix JV, LLC
Caution: New Drug – Limited by Federal Law to Investigational Use
Emergency contact: Dr. Elizabeth Regan, cell 303-921-1880 Store at RT or Refrigeration

Exemplary Label BMX-010 – Depending if the study product is a cream or gel, this will dictate the storage instructions. The gel is stored at room temperature and the cream is stored under refrigerated conditions.

9.2.6 Placebo

Placebo (vehicle) will consist of the same excipients as the active drug product, but without the API. The placebo gel is white in color and does not match the color of the active drug. Placebo will be supplied in 10 mL tubes. The placebo cream is color-matched to facilitate blinding.

9.3 Handling of Drug and Placebo at Clinical Centers

Both BMX-010 and Placebo will be delivered to the clinical centers in bags containing 20 or 10 tubes. Each bag will contain tubes of only one concentration of drug or the placebo. Both the bags and the tubes will be labeled as to the lot number but not the strength.

9.3.1 Supply, Receipt and Storage

The drug supplies described in Section 9.3 will be shipped to each clinical center. The drugs will be refrigerated, in a locked, physically secure environment according to the clinical center or sponsor standard procedures for storage of investigational drug products. Drug accountability records will be maintained by each clinical center for all clinical trial products.

9.3.2 Compliance and Accountability

Drug accountability records will be maintained for all clinical trial products.

9.3.3 Final Accountability of Clinical Center Drug Supply

Subjects will be instructed to bring all study drug tubes (even if empty) back to the clinical centers during their weekly visit for review. Empty tubes will be collected from the subject and disposed once final drug accountability is performed by BioMimetix. They will be destroyed according to the clinical center or sponsor policy after final accountability by BioMimetix has been performed. At the end of the study all remaining un-used investigative product and placebo will be returned to the sponsor, BioMimetix JV, LLC, after drug accountability is performed, according to instructions which will be provided by sponsor. The clinical center will maintain documentation of the number and identification of BMX-010 and Placebo tubes that are returned to the sponsor and which are destroyed by the clinical center. Copies of these documents will be provided to BioMimetix JV, LLC.

9.4 Randomization Schedule

The sponsor or designee will generate the randomization schedules. Randomization will occur once final eligibility is confirmed after completion of the screening procedures.

Part A of the study is not blinded. All subjects will receive BMX-010

Part B of the study is double-blind, where both the subject and the clinical center staff will be blinded to the treatment assigned. BMX-010 and Placebo will be dispensed 2:1 (study drug: placebo).

9.5 Treatment Compliance

During the weekly visit during the treatment period a question will be asked of the subject to monitor treatment compliance (see Appendix B).

At the baseline visit, the clinical staff will instruct the subjects to apply the study drug to the face and this will be demonstrated the first time it is applied. Appropriate application should be discussed with the subject at each weekly visit. Assessment of drug use will take place at each weekly visit by clinical center staff.

9.6 Excluded Medications and Treatments

Period of Exclusion	Excluded Medication/Treatment
≤ 4 weeks prior to Baseline Visit	Systemic chemotherapy or radiotherapy
≤ 4 weeks prior to Baseline and throughout study	Systemic retinoids, corticosteroids, or immunosuppressive agents (e.g., methotrexate, cyclosporine)
	UV or Dead Sea therapy
≤ 30 days prior to Screening Visit and throughout study	Investigational drug or vaccine trial
≤ 2 weeks prior to Baseline and throughout study	High potency topical corticosteroids (Class I-III), Vitamin D analogs, keratolytics, coal tar (other than on the scalp, palms, groin, and/or soles), phototherapy, calcineurin inhibitors, antihistamines or any other therapeutic agents besides bland emollients
5 times its circulating half-life, or 30 days, whichever is longer, prior to the Baseline Visit or throughout study	Biological agent (such as a monoclonal antibody)

9.7 Diet

Subjects will be asked to fast overnight (8 hour fast prior to the blood draw) prior to collection of blood samples for clinical laboratory safety testing; otherwise, there are no dietary restrictions for this study.

10 RISK/BENEFIT ASSESSMENT

10.1 Potential Benefits of BMX-010

The potential benefits may include protection against skin inflammation such as that experienced in Rosacea. The benefits may be long lasting. Because this clinical protocol is experimental, it cannot be guaranteed that subjects will receive any benefit as a result of participating in this research study.

10.2 Risks of BMX-010

This study is designed to determine the effectiveness of this agent when administered topically to subjects having inflammatory skin conditions.

Phase 1 studies in BMX-010 have completed and no toxicities have been identified. We have studied pharmacokinetics already on BMX-010 in 14 subjects. The data is summarized below.

Phase 1 of BMX-DERM-01 on patients with diagnosed Atopic Dermatitis and Plaque Psoriasis: Eight subjects have been studied: 2 dosed with 0.01% BMX-010, 3 dosed with 0.03% BMX-010, and 3 dosed with 0.1% BMX-010 given once per day to one lesion, and testing has determined that there is no quantifiable systemic absorption for the Part 1a treatment protocol. There have been no toxicities identified in the 33 subjects enrolled at the time of writing this protocol amendment. In Part 1b, 3 subjects have been studied, dosed with 0.1% gel up to 4 times a day to all lesions on the body. The lesions occupied 2% BSA in two subjects and 10% BSA in one subject. Two of the three subjects had no quantifiable systemic absorption, one was found to have a plasma level of 1.95 ng/ml at 24 hours following topical administration. This patient had AD involving 10 percent BSA and administered 0.1% gel 2 times per day.

Phase 2 of BMX-DERM-01 on patients with diagnosed Atopic Dermatitis: PK was done on 3 subjects after application of BMX-010 cream twice per day for 8 days. There was no quantifiable plasma level of the drug in any of the three subjects on day 8 at pre-dose, 1, 2, 4 and 24 hours after applying BMX-010 0.03% cream topically. In one subject a detectable level of BMX-010 of 0.04 ng/mL in plasma was found 1 hour after topical administration and in one of the 3 subjects a level of 0.12 ng/mL was detected in the plasma at 24 hours (This patient had applied the drug topically at 12 hours on day 8 as part of bid dosing). The limit of detection (BLOD) for BMX-010 was 0.04 ng/mL and the limit of quantitation (BLOQ) for BMX-010 was 0.121 ng/mL.

Animal safety/toxicology studies have not demonstrated any significant adverse events for topical therapy other than skin discoloration and discoloration of materials coming into contact with the drug.

Studies have been performed using intravenous infusions of BMX-010 in multiple models including rats, mice, dogs, guinea pigs, and baboons with the finding of dose-related hypotension [15,22]. Redox-active metalloporphyrin compounds (such as BMX-010) are potent, catalytic antioxidants and have the potential to scavenge superoxide within the vascular system and thereby change the balance of superoxide and nitric oxide in the microvasculature. This would augment the vasodilating activity of nitric oxide and lead to hypotension [15,22]. This has been

found in animal models, but only as a transient side effect related to intravenous administration of the drug in doses orders of magnitude higher than that being considered for topical administration. Hypotension has not been identified in any animal model treated with BMX-010 by topical therapy or by subcutaneous injection.

Mild photosensitization is a possible side effect of BMX-010. While native porphyrins have been shown to be photosensitizers, the redox-active metalloporphyrins are not expected to show significant photosensitization. When native porphyrins are exposed to white light, the molecule can enter an excited state and on return to ground state emit fluorescent light, which is the cause for photosensitization. Redox-active metalloporphyrins such as BMX-010 contain a metal atom chelated into the middle of the porphyrin ring. The presence of this metal atom allows the molecule to give and take electrons and thus do redox chemistry. In the presence of white light, these redox-active metalloporphyrins would not be expected to enter an excitation state and would not be expected to emit fluorescence. A phototoxicity test in rabbits with BMX-010 demonstrated only weak phototoxicity with no test animals showing edema at any time point and 1 out of 5 animals exhibiting erythema at 24 hours and only very slight erythema at 72 hours. A summary of the possible adverse side effects that could be associated with BMX-010 administration is below. These possible side effects are dose-dependent, and the relatively low doses of this drug planned in this study have not been associated with side effects in animals other than those related to the color of the topically applied drug.

The most common side effects (expected to occur in more than 30% of subjects) are:

- Yellow to brown discoloration of the skin at the administration site which may take several days to resolve
- Discoloration of clothing or materials coming into contact with the treated skin

Less common side effects (expected to occur in less than 10% of subjects) are:

- Skin irritation at the administration site

Additional possible side effects are:

- Light-activated skin rash in response to sun exposure (this has not been reported by any patients enrolled in the study at the time of writing this protocol).
- It is also possible that previously unobserved and unexpected side effects could occur.

10.3 Risks of Phlebotomy

Drawing blood may result in bruising or swelling in the area of the needle insertion, bleeding at the site of the needle puncture, light headedness, fainting and very rarely, local infection. These risks are reduced by the fact that the blood will be drawn by a qualified physician, nurse or phlebotomist.

10.4 Unknown Risks

There may be risks which are unknown.

11 ASSESSMENT OF EFFICACY

The schedules of observations and procedures are provided in **Table 4.a.** Descriptions for the efficacy assessments are provided in this section.

11.1 IGA

The Investigator Global Assessment (IGA) is a five scale (0 to 4) static evaluation of overall rosacea severity (as described below). The change in IGA scores from Baseline through the final follow up visit will be assessed as endpoints in the study.

Drug treatment and efficacy assessment by IGA will be limited to the face.

Grade	Description
0 = Clear	No papules and/or pustules; no erythema
1 = Minimal	Rare papules and/or pustules; faint, up to but not including mild erythema
2 = Mild	Few papules and/or pustules; mild erythema
3 = Moderate	Pronounced number of papules and/or pustules, but less than numerous papules and/or pustules; moderate erythema
4 = Severe	Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate to severe erythema

11.2 Clinical Erythema Assessment (CEA)

The Clinical Erythema Assessment scale (CEA) will be utilized to assess erythema and will be limited to the face (described below). Tan et al. showed that when the CEA is used by trained raters, it is a reliable method for measuring the erythema of rosacea on the face [22]. The change in CEA scores from Baseline through the final follow up visit will be assessed as endpoints in the study.

Grade	Description
0 = Clear	Clear skin with no signs of erythema
1 = Almost clear	Almost clear; slight redness
2 = Mild	Mild erythema; definite redness
3 = Moderate	Moderate erythema; marked redness
4 = Severe	Severe erythema; fiery redness

11.3 Patient Reported Outcomes (PRO)

Questions (see Appendix A: Patient Reported Outcome (PRO) Questions) to assess patient assessment of disease and clearing will be asked to the subjects at each clinic visit. We will also ask a treatment compliance question.

11.4 Follow- Up Phone questions

After the Day 43 final clinic visit, the clinical center may call or mail the subject at approximately 1, 2, and/or 3 months later to ask the questions listed in Appendix B.

12 ASSESSMENTS FOR ALL SUBJECTS

The schedules of observations and procedures are provided in **Table 4.a.** Descriptions for the study assessments are provided in this section.

12.1 Physical Examination, Vital Signs, Weight, and Height

A general physical examination of major body systems will be performed on the visits as shown in Table 4.a. The delegated investigator will need to indicate for each system if abnormal or normal and whether if abnormal is clinically significant or not.

Height will be measured and documented at Screening only. Weight will be measured during the physical examinations.

Vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be measured during the physical examinations. Blood pressure and heart rate measurements will be taken while subjects are in a seated position after resting for 5 minutes.

12.2 Medical History

Standard medical history assessments will be conducted at Screening. Clinical centers should make every effort possible to obtain medical records to document the diagnosis of the applicable indication. At the screening visit, we will also ask about participation in previous investigational trials for the indication being treated in the study and the number of previous trials participated.

12.3 Medication History/Demographics and Concomitant Medications

At the screening visit subjects will be queried regarding concomitant medication use and medication history. Restricted medications were previously described in Section 9.6. Demographic information will consist of items such as age, race, gender, education, employment, smoking status.

12.4 Lesion Counts

All inflammatory lesions will be counted by the clinical center investigator at each weekly visit.

12.5 Discoloration Review

Discoloration is an assessment of skin color change related to the study product color remaining on the skin. It will be reviewed by delegated clinical center staff at the weekly visits as reflected in Table 4.a and one of the options below will be selected.

Discoloration	None	Minimal	Moderate	Marked

12.6 Photographs

Photographs of the rosacea optional based on subject consent and selection of specific clinical center participation by the sponsor. Photographs will be offered at each clinic visit.

12.7 Clinical Safety Laboratory Variables

12.7.1 Blood Tests

Fasting blood samples (following an at least 8-hour fast) will be collected during as shown in the table in Section 4.a. Clinical safety laboratory tests will include complete blood count with differential and comprehensive metabolic panel.

12.7.2 Urine Tests

Urine pregnancy tests (beta-human chorionic gonadotropin [HCG]) will be performed for women of childbearing potential within 48 hours prior to the start of drug treatment and repeated on the last visit.

13 SAFETY

13.1 Adverse Events

An AE is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of BMX-010, whether or not related to use of the BMX-010. Abnormal laboratory findings without clinical significance (based on the Principal Investigator's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered AEs.

From the time the subject signs the informed consent form through the Follow-Up Visit all AEs must be recorded in the subject medical record and CRF.

AEs will be assessed according to the CTCAE version 5, which has been harmonized to MedDRA (Medical Dictionary for Regulatory Activities) coding. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the BMX-010
- Probably: The AE is likely related to the BMX-010
- Possible: The AE may be related to the BMX-010
- Unlikely: The AE is doubtfully related to the BMX-010
- Unrelated: The AE is clearly NOT related to the BMX-010

13.1.1 Reporting of AEs

BioMimetix JV, LLC, should be notified of all treatment-related AEs on a regular basis (to be agreed upon by the study team and BioMimetix JV, LLC). Reports of these should be made to Elizabeth Regan, MD, PhD, at 303-921-1880 (cell).

13.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

13.2.1 Reporting of SAEs

Only AEs that the sponsor and/or Principal Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e., more likely than not) related to the research must be reported to the IRB. Those AEs will be submitted, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related AE;
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the research than unrelated.

The Principal Investigator is responsible for compliance with all applicable regulations pertaining to the reporting of AEs to the IRB. To ensure patient safety, each study treatment-related serious adverse event (SAE) will also be reported to the sponsor, BioMimetix JV, LLC, within 24 hours by the Principal Investigator. Follow-up information on these events shall also be reported to BioMimetix JV, LLC, within 24 hours of receipt. Follow-up information may include hospital admission records, discharge summaries and autopsy reports, where applicable. The sponsor must report to the Food and Drug Administration (FDA), in an Investigational New Drug (IND) safety report, any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction (i.e., there is a reasonable possibility that the drug caused the AE)
- Serious
- Unexpected

If the AE does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The sponsor is required to report to the FDA all IND Safety reports in writing within 15 days (7 days for unexpected fatal or life-threatening suspected adverse reaction). The FDA Form 3500A can be found on the FDA website, www.fda.gov. All other AEs will be reported to the FDA in the IND Annual Report.

In addition to the above mentioned reporting responsibilities, after discontinuation of the study, all SAEs considered to be drug related will be reported to BioMimetix JV, LLC, by the Principal Investigator.

14 STATISTICS

A statistical analysis plan (SAP) will be prepared and finalized prior to data analysis. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

14.1 Analysis Sets

All subjects who have received at least one dose of study medication will be included in the Safety Population. All analyses of safety will be performed for the Safety Population.
The Intent-To-Treat (ITT) evaluable population will consist of all subjects in the Safety Population with CEA and IGA (when available) component scores recorded at screening and/or baseline and at least 1 post-baseline visit. The ITT population will be used to assess clinical activity data.

14.2 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose using descriptive statistics (e.g., means/standard deviations, percentiles, frequencies).

14.3 Treatments

The number of subjects treated at each dose level will be summarized using descriptive statistics.

14.4 Safety Analysis

All treatment-emergent AEs will be summarized by dose group and indication (AD or PS). Counts and percents will be presented by treatment group for each observed system organ class (SOC) and preferred medical diagnosis.
The preferred terms and SOCs will be summarized in the following set of tables:

- All AEs;
- All AEs by maximum level of intensity;
- All AEs by closest relationship to the study medication.

Laboratory test variables will be summarized by dose group and study visit using descriptive statistics. Laboratory data collected from baseline and up to 7 days after a subject's last dose of study drug (or the date of the final follow up visit) will be included in the analysis.
Descriptive statistics will be used to summarize vital signs by dose group and study visit. Vital sign data collected from baseline and up to 7 days after a subject's last dose of study drug (or the date of the final follow up visit) will be included in the analysis.

14.5 Interim Analysis

No interim analysis is planned.

14.6 Determination of Sample Size

The sample sizes will provide sufficient data for clinical interpretation of safety and efficacy assessments. Sample sizes are not based on statistical considerations. The proposed enrollment

counts will provide validation of the safety objectives and a basis to estimate potential efficacy for future studies.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Monitoring

BioMimetix JV, LLC, will monitor this study. The Principal Investigator at each clinical center should be available to the clinical trial monitor during monitoring visits and ensure that access to all documents and records is provided. The Principal Investigator agrees to cooperate with the clinical trial monitor to ensure that any problems detected in the course of these monitoring visits are resolved. All study documents must be made available upon request to the clinical trial monitor and other authorized regulatory authorities, including but not limited to the National Institute of Health and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

15.2 Audits

The study may be audited by an audit team originating from the sponsor or its designee, or outside regulatory agencies. The investigator agrees to cooperate with the auditor to ensure than any problems detected in the course of the audit visits are resolved.

15.3 Data Management and Processing

15.3.1 Study Documentation

BioMimetix JV, LLC, will have access to the electronic database, with edit rights, for this clinical trial and will provide monitoring to confirm the accuracy of data entered into this database.

15.3.2 Case Report Forms

Data generated per protocol will be provided in paper or entered into an eCRF database provided by BioMimetix JV, LLC. When the CRFs have been completed, the clinical trial monitor will work with the study site coordinator or data management team to verify all source documentations and review data. Copies of the photographs will be filed as source documents and provided to the sponsor.

16 DATA MANAGEMENT PROCEDURES AND DATA VERIFICATION

The Principal Investigator at each clinical center is responsible for maintaining adequate records to enable the conduct of the study to be fully documented. Subsequent electronic review of the data may result in queries being generated that will be forwarded simultaneously to the investigator or designee for resolution. All data modifications resulting from review or querying of the data will be electronically tracked.

Any errors detected by either the monitor or the investigator should be communicated to the sponsor.

Copies of all regulatory documents such as the protocol, study approval letters, all CRFs, drug dispensing and accountability logs, all original patient consent forms, and all correspondence pertaining to the conduct of the study should be kept by the investigator for the maximum period of time permitted by local regulations.

16.1 Study Closure

Following completion of the study, the Principal Investigator at each clinical center will be responsible for ensuring the following activities for all subjects enrolled from his/her clinical center:

1. Data clarification and/or resolution of queries
2. Accounting, reconciliation, and destruction/return of used and unused study drugs
3. Review of site study records for completeness
4. Shipment of all remaining laboratory samples to the designated laboratories
5. Final report to the IRB

17 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

17.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

17.2 Institutional Review Board

The primary IRB for this study will be Western Institutional Review Board (WIRB). The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the IRB for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the IRB.
All subsequent protocol amendments and changes to the informed consent form will be required to be approved by WIRB.

17.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually or audibly impaired. Potential subjects will have the opportunity to contact the Principal Investigator or authorized key personnel with questions and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored in a study-specific informed consent binder, and a copy of the informed consent form will be provided to the subject. The Principal Investigator and the study team are responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

17.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions

with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated compliant database, which is housed in an encrypted and password-protected file on a secure network drive. Access to electronic databases (without edit rights) will be limited to the Principal Investigator, the study coordinator, and the statistical team. The only personnel with both access and edit rights to the electronic databases are the data management team, including the clinical trials manager. Upon completion of the study, research records will be archived. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

17.5 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

1. at least 2 years after the date on which a New Drug Application is approved by the FDA, if an IND is involved
2. at least 2 years after formal withdrawal of the IND associated with this protocol, if an IND is involved

17.6 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

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19 Appendix A: Patient Reported Outcome (PRO) Questions

Weekly Visit

1. How often are you applying the study drug?
   - Once a Day
   - Twice A Day

2. Did you apply the study product as instructed?
   - Yes
   - No
     - If no: clarify with comments

3. Would you like to apply the study drug more often?
   - Yes
   - No

4. Do you feel that your quality of life has improved from using the study drug?
   - Yes
   - No

5. How would you assess the change in your rash since your previous visit?
   - Worse
   - No change
   - A little better
   - Definitely better
   - Drastically better
   - Clear

Clearing Questions- only to be asked if the rosacea has cleared or partially cleared. Indicate [ ] N/A if no clearing has occurred

1. On approximately what date did the rosacea clear?

2. Have any of your previously cleared lesion(s) come back? Yes/No
   a. If Yes, on what date did it come back?
   b. If Yes, where did it come back?
      i. Same area as before
      ii. New area, specify:

The following questions are for the last visit only

1. Do you feel that your quality of life has improved from using the study drug?
    - Yes
    - No

2. How would you assess the change in your rash since your previous visit?
    - Worse
    - No change
    - A little better
    - Definitely better
    - Drastically better
    - Clear

Clearing Questions- only to be asked if the rosacea has cleared or partially cleared.
Indicate [ ] N/A if no clearing has occurred

1. On approximately what date did the rosacea clear? _____

2. Have any of your previously cleared lesion(s) come back?
    - Yes
    - No

    If Yes, on what date did it come back?

    If Yes, where did it come back?

    - Same area as before
    - New area, specify:

      _____

      _____

Color Questions

1. Do you have any concerns about the color of the study product?
    - No concerns
    - Mild concerns
    - Major concerns

2. Did the study product stain (meaning the color stayed on after washing) your clothing/bedsheets, etc? Yes/No

20 Appendix B: Phone Follow-up Questions

1. What is the current status of your rosacea?

2. Are you currently on any medications or treatments for controlling your rosacea? If yes, obtain list.

3. Would you like to continue to use the study drug? Yes/No, Comments.