CLINICAL TRIAL PROTOCOL

SOLAR: A Phase 2, Randomized, Open-label, Parallel-group, Active Comparator, Multi-center Study to Investigate the Efficacy and Safety of Cobomarsen (MRG-106) in Subjects with Cutaneous T-Cell Lymphoma (CTCL), Mycosis Fungoides (MF) Subtype

Protocol Number: MRG106-11-201

EUDRACT NUMBER 2018-000727-13

Version 4.0

10 February 2020

miRagen Therapeutics, Inc.
6200 Lookout Road
Boulder, CO 80301, USA

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and clinical research guidelines established by the United States Code of Federal Regulations (21 CFR Parts 50, 56, and 312), the European Clinical Trials Directive 2001/20/EC and implementing national regulations, the European Clinical Trials Regulation No. 536/2014 (upon implementation), and the International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice.

PROTOCOL APPROVAL PAGE

By signing below, I affirm that this protocol and the attachments are approved by the clinical trial Sponsor, miRagen Therapeutics, Inc.

Protocol Approved by:

[redacted]

[redacted]

Date

miRagen Therapeutics, Inc.

[redacted]

[redacted]

Date

miRagen Therapeutics, Inc.

[redacted]

[redacted]

Date

miRagen Therapeutics, Inc.

INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor, and agree to the following:

- To conduct this trial in accordance with the design and provisions of this protocol
- To await IRB/IEC approval of the protocol and informed consent form before initiating enrollment into the study
- To ensure that the requirements for obtaining informed consent are met and to obtain informed consent from subjects before their enrollment into the study
- To provide sufficient and accurate financial disclosure and to update this information if any relevant changes occur during the investigation and for one year following the completion of the study
- To collect and record data as required by this protocol into the case report form
- To maintain the confidentiality of all information received or developed in connection with this protocol
- To conduct this trial in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements
- To permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents
- To prepare annual, final and adverse event reports as required by this protocol and by regulation under 21 CFR 312.64
- To maintain study documentation for the period of time required as stipulated in the protocol
- To report all adverse events to miRagen Therapeutics, Inc. or Authorized Representative within the timeframe specified
- To report all serious adverse events immediately and not later than 24 hours after becoming aware of the event as directed in the protocol
- To comply with the provisions of the Clinical Trial Agreement to which I will be a signatory, including but not limited to, the disclosure or publication of data collected during this trial, as stipulated in that agreement.

Signature of Investigator	Date
Investigator Name (print or type)	Site Number

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LIST OF ABBREVIATIONS

Abs	Absolute
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BIC	B-cell Integration Cluster
BSA	Body surface area
BUN	Blood urea nitrogen
°C	Degree(s) Celsius
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenzel
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRR	Complete response rate
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CYP	Cytochrome P450
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
GLDH	Glutamate dehydrogenase
°F	Degree(s) Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
Ha	Alternative hypothesis
HDAC	Histone deacetylase

HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
Ho	Null hypothesis
JAK	Janus kinase
IBM	Ideal body mass
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LNA	Locked nucleic acid
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
mSWAT	Modified Severity Weighted Assessment Tool
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer
ORR1	Objective response rate of at least 1 month duration
ORR4	Objective response rate of at least 4 months duration
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial response
PT	Prothrombin time
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula

RBC	Red blood cell(s)
RNA	Ribonucleic acid
ROA	Routes of administration
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SS	Sézary syndrome
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
Th	T helper
T_{max}	Time to maximum plasma concentration
Treg	Regulatory T-cells
TSEBT	Total skin electron beam therapy
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WBC	White blood cell(s)
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

PROTOCOL SYNOPSIS

Sponsor:	miRagen Therapeutics, Inc.
Protocol No.:	MRG106-11-201
Title:	SOLAR: A Phase 2, Randomized, Open-label, Parallel-group, Active Comparator, Multi-center Study to Investigate the Efficacy and Safety of Cobomarsen (MRG-106) in Subjects with Cutaneous T-Cell Lymphoma (CTCL), Mycosis Fungoides (MF) Subtype
Phase:	Phase 2
Investigational Product and Comparators:	Investigational Product: cobomarsen The Sponsor will provide cobomarsen (141 mg/mL) in single-dose stoppered glass vials as a liquid formulation in isosmotic phosphate buffer, pH 7.4 ± 0.5. Cobomarsen will be administered by 2-hour intravenous infusion at a dose of 282 mg. Active Comparator: vorinostat Vorinostat is available as 100 mg capsules. A 400 mg (four 100 mg capsules) dose of vorinostat will be administered orally, once daily with food, per approved label dosing instructions for MF. Subjects with abnormal ALT/AST (> ULN) or bilirubin (> 1.0 × ULN) at Screening will start vorinostat dosing at 300 mg (three 100-mg capsules) once daily with food, at approximately the same time each day, per dosing guidelines.
Population:	Males/females, ≥ 18 years of age, with a diagnosis of cutaneous T-cell lymphoma (CTCL), mycosis fungoides (MF) subtype
Number of Subjects Planned:	The planned total enrollment is approximately 126 subjects. Subjects will be randomized in a 1:1 ratio to receive cobomarsen or vorinostat.
Duration of Participation:	Estimated up to 365 days or longer, including: 28-day Screening, active treatment, and follow-up for progression.
Anticipated Study Duration:	Up to 36 months

Clinical Sites:	Approximately 25 centers globally

Objectives:

Primary:

The primary objective of the study is to evaluate the efficacy of cobomarsen in subjects with MF.

Secondary:

- Investigate the safety and tolerability of cobomarsen in subjects with MF.
- Characterize the population pharmacokinetics (PK) of cobomarsen in subjects with MF.
- During the crossover portion of the study:
    - Evaluate the efficacy, safety and tolerability of cobomarsen in subjects with MF who have shown disease progression following treatment with vorinostat.

Endpoints:

Primary:

Primary Efficacy Evaluation:

- Proportion of subjects achieving an objective skin response (complete response [CR] or partial response [PR]) of at least 4 months duration (ORR4) using the Modified Severity Weighted Assessment Tool (mSWAT) scoring.

Secondary:

Efficacy measures:

- Progression-free survival (PFS).
- Complete response rate (CRR).
- Time to progression (TTP).
- Time to maximal effect in skin (mSWAT).
- Proportion of subjects achieving ≥ 50% improvement in mSWAT of at least 28-days duration (ORR1).
- Proportion of subjects achieving ≥ 50% improvement in mSWAT from baseline at 28 days and at 4 months.
- Time to ≥ 50% improvement in mSWAT.
- Duration of response in skin (no progression after achieving ≥ 50% improvement in mSWAT).
- Change in pruritus medication utilization from baseline and incidence of pruritus medication utilization.

- During the crossover portion of the study:
  - Proportion of subjects achieving an objective skin response (complete response [CR] or partial response [PR]) of at least 4 months duration (ORR4) using the mSWAT scoring (see Appendix F).
  - Progression-free survival (PFS).
  - Complete response rate (CRR).
  - Time to progression (TTP).
  - Time to maximal effect in skin (mSWAT).
  - Proportion of subjects achieving ≥ 50% improvement in mSWAT of at least 28-days duration (ORR1).
  - Proportion of subjects achieving ≥ 50% improvement in mSWAT from baseline at 28 days and at 4 months.
  - Time to ≥ 50% improvement in mSWAT.
  - Duration of response in skin (no progression after achieving ≥ 50% improvement in mSWAT).
  - Change in pruritus medication utilization from baseline and incidence of pruritus medication utilization.

Safety and Tolerability Evaluations:

- Incidence and severity of clinically significant adverse events (AEs) (including grade 3 and 4 AEs, treatment-related AEs, serious adverse events [SAEs], and AEs requiring discontinuation), physical examination findings, changes in electrocardiograms (ECGs), changes in laboratory parameters and changes in vital signs.
- Characterization of anti-drug antibody generation.

Pharmacokinetic Evaluation:

- Population PK parameters.
- During the crossover portion of the study:
  - Pharmacokinetic C_{max} and trough concentration analysis

Study Design:

This is a Phase 2, randomized, open-label, parallel-group, active comparator, multi-center study to assess the efficacy and safety of cobomarsen compared to vorinostat in subjects with MF. The randomization will be stratified based on subjects with at least one skin tumor at Screening vs. no skin tumors at Screening. Subjects will also be stratified based on prognostic factors (age at diagnosis > 60 years and lactate dehydrogenase [LDH] level > the upper limit of normal [ULN] at diagnosis) (Scarisbrick et al., 2015). Subjects will be stratified based on having 0-1 vs 2 of these prognostic factors.

This study will have 2 periods, a randomized period and a crossover period. Subjects who are on the vorinostat arm in the randomized period and have confirmed skin disease progression may elect to participate in the crossover period of the study.

Randomized Period

Approximately 126 subjects are expected to be enrolled. An interim analysis will be conducted after approximately 40 subjects have been followed for a minimum of approximately 6 months; enrollment will be suspended after approximately 40 subjects have been enrolled until the completion of the interim analysis.

Methodology:

Subjects will be randomized in a 1:1 ratio to receive cobomarsen or vorinostat. Subjects will undergo Screening lasting up to 28 days from the time of informed consent, followed by active treatment, and then follow-up for response and disease progression.

Subjects will remain on their assigned study treatment until one of the following occurs:

1. Disease progression, defined as either:
    a. Confirmed progression in skin
    b. Clinical progression in other compartments, documented by assessments (flow cytometry and/or CT scan) completed per investigator discretion
    c. Partial or complete skin response followed by a confirmed loss of skin response as defined by an increase of mSWAT of greater than the sum of nadir plus 50% baseline score.

    Progressions based on mSWAT will be confirmed by repeated measurement 28 days (±3 days) after the first determination of progression.

    If confirmed, the date of progression will be based on the first determination of progression. Subjects will continue the study treatment until disease progression is confirmed.
2. Subject meets one of the other treatment discontinuation criteria described in the protocol.

Study Treatment and Assessments:

Subjects will be treated and monitored in the outpatient setting for the duration of the study. On Day 1, subjects will visit the clinic to undergo baseline assessments. Upon confirmation of eligibility and completion of all predose assessments, subjects will receive the first dose of study treatment (i.e., initiation of the randomized period) according to their randomized treatment assignment (cobomarsen or vorinostat). Subjects randomized to cobomarsen will remain in the clinic for PK sample collection and subjects in both groups will be monitored for safety for 4 hours postdose.

All subjects will return to the clinic on Day 2 for study assessments and on Days 3, 5, 8, 15, 22, and 29 for safety and study assessments. The cobomarsen group will continue to receive study treatment weekly and undergo study assessments. Infusions may be administered at satellite locations on dosing days without efficacy assessments.

After approximately 4 months of receiving the infusions and provided there are no safety concerns, subjects receiving cobomarsen may have the option of receiving their infusions at home using a research home health care service.

The vorinostat group will return to the clinic at Day 29, then weekly through Week 8 and every 4 weeks thereafter for study assessments.

The following study treatments will be administered according to randomized treatment assignment:

- Cobomarsen will be administered by intravenous 2-hour infusion at a dose of 282 mg on Days 1, 3, 5, 8, and weekly thereafter;
- A 400 mg (four 100 mg capsules) dose of vorinostat will be administered orally, once daily with food, at approximately the same time each day.
    - Subjects with abnormal ALT/AST (> ULN) or bilirubin (> 1.0 × ULN) at Screening will start vorinostat dosing at 300 mg (three 100-mg capsules) once daily with food, at approximately the same time each day, per dosing guidelines.

Safety assessments will include monitoring the incidence and severity of AEs and SAEs, physical examination findings, vital signs, ECG monitoring, and clinical laboratory assessments.

Samples will be collected for PK in the cobomarsen group on Days 1, 2, 3, 5, 8, 15, 29, and every 4 weeks from Weeks 9 through 81, every 8 weeks thereafter, and at follow-up/end of treatment visit.

mSWAT evaluations will be completed on Day 1 and Day 29, every 4 weeks through Week 81, then every 8 weeks thereafter, and at the End of Treatment and Follow-up Visits. Every effort will be made to perform a final disease assessment for subjects who withdraw from the study early.

Crossover Period

After completing the randomized period, subjects that have confirmed skin disease progression on the vorinostat arm can be assessed for eligibility for the crossover period. Eligible subjects may elect to enter this optional crossover period and must sign an informed consent form to proceed.

Potential subjects will need to complete the crossover screening activities and meet the entry criteria prior to enrollment into the crossover period of the study.

Subjects in the randomized period of the study who withdrew consent **without confirmation of skin disease progression** are **not eligible** to enroll in the crossover period. In addition, subjects who received any subsequent systemic therapy for MF following confirmed disease progression in the randomized period are not eligible for the crossover period.

Study procedures completed at the End of Treatment visit in the randomized period may be used for screening assessments in the crossover period, depending on the timing of the assessments. Subjects who initiate Screening in the crossover period > 28 days after completing the randomized period will need to complete all of the crossover Screening procedures.

Subjects will undergo Screening lasting up to 28 days from the time of the first screening procedure, followed by active treatment and follow-up for response and disease progression.

Subjects will remain on cobomarsen until one of the following occurs:

1. Disease progression, defined as either (see Appendix F):
    a. Confirmed progression in skin
    b. Clinical progression in other compartments, documented by assessments (flow cytometry and/or CT scan) completed per investigator discretion
    c. Partial or complete skin response followed by a confirmed loss of skin response as defined by an increase of mSWAT of greater than the sum of nadir plus 50% baseline score.

    Progressions based on mSWAT will be confirmed by repeated measurement 28 days (±3 days) after the first determination of progression.

    If confirmed, the date of progression will be based on the first determination of progression. Subjects will continue cobomarsen until disease progression is confirmed.
2. Subject meets one of the other treatment discontinuation criteria (see Section 5.4.1).

Cobomarsen will be administered by intravenous 2-hour infusion at a dose of 282 mg on Days 1, 3, 5, 8, and weekly thereafter.

Safety assessments will include monitoring the incidence and severity of AEs and SAEs, physical examination findings, vital signs, ECG monitoring, and clinical laboratory assessments.

Blood samples will be collected for PK on Days 1 and 29, every 4 weeks through Week 81, every 8 weeks thereafter, and at the End of Treatment and Follow-up visits.

mSWAT evaluations will be completed on Days 1 and 29, every 4 weeks through Week 81, every 8 weeks thereafter, and at the End of Treatment and Follow-up visits.

Entry Criteria:

Randomized Period

Main Criteria for Inclusion:

1. Must provide written informed consent (signed and dated) and any authorizations required by law and be able to comply with all study requirements.
2. Males or females, ≥ 18 years of age at the time of informed consent.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
4. Biopsy-proven CTCL, MF subtype.
5. Clinical stage IB, II or III, with staging based on Screening assessments and following staging parameters set in this protocol (see Appendix H).
6. Minimum mSWAT score of 10 at Screening (see Appendix F, Table F1).
7. Receipt of at least one prior therapy for CTCL (per National Comprehensive Cancer Network [NCCN] guidelines for generalized skin involvement; e.g., topical, phototherapy, total skin electron beam therapy [TSEBT], or systemic therapy [see Appendix G]).
8. Meets the following criteria per the central laboratory at Screening:
   a. Calculated creatinine clearance ≥ 40 mL/min using 24-hour creatinine clearance OR modified Cockcroft-Gault equation (using ideal body mass [IBM] instead of mass);
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN; bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who may have bilirubin ≤ 3.0 × ULN following discussion with the Sponsor).
9. Females who had a menstrual cycle within 2 years of Screening must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on their first dosing day.
10. Subjects of childbearing potential must agree to use highly effective methods of contraception as defined in the protocol.

Main Criteria for Exclusion:

1. Previous enrollment in a cobomarsen study.
2. Prior therapy with vorinostat or other HDAC inhibitors, or contraindication to an HDAC inhibitor.

3. Sézary syndrome or mycosis fungoides with B2 involvement, defined as a documented history of B2 and/or B2 staging at the Screening visit. B2 means T-cell clone in peripheral blood + one of the following at Screening:
   a. ≥ 1000 Sézary cells by direct examination OR
   b. ≥ 1000/μL CD4+ CD26- OR
   c. ≥ 1000/μL CD4+ CD7-
4. Current evidence of large cell transformation (LCT), defined as > 25% of the lymphocytes at least 4 × the size of normal lymphocytes. Current evidence refers to LCT diagnosis from biopsy performed within 4 months prior to randomization. Subjects with a history of LCT but with a negative current biopsy (within 4 months) are eligible, provided there is no clinical indication for chemotherapy.
5. Evidence of enlarged peripheral or central lymph node(s) > 1.5 cm in the long diameter or > 1.0 cm in the short diameter, by radiographical imaging at Screening. A subject with one or more enlarged lymph node(s) may be allowed, provided that a representative lymph node has been confirmed (via biopsy or positron emission tomography [PET] scan) to be N_0-N_2 or SUV ≤ 5 within the 3 months prior to Day 1, and there has not been an appearance of new abnormal lymph nodes since the biopsy or PET scan. Subjects with uncharacterized enlarged lymph nodes (i.e. not confirmed by biopsy or PET scan) will not be allowed.
6. Any palpable peripheral node, regardless of size, that on physical examination is firm, irregular, clustered, or fixed, unless histologically confirmed to be non-malignant.
7. Evidence of visceral involvement related to MF at Screening.
8. Recent history of alcoholism (within the past 1 year).
9. Known or suspected substance abuse within the past 1 year.
10. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), grade 0 or 1.
11. Receipt of any of the following treatments:
    - Macrolide or tetracycline antibiotics within 28 days prior to Screening;
    - More than 3 short courses (≤ 7 days) of prednisone equivalent > 10 mg per day within 8 weeks prior to Screening; however, a stable regimen of systemic prednisone equivalent to ≤ 10 mg per day (or steroid equivalent) is permitted;
    - Total skin electron beam therapy or radiotherapy within 4 weeks prior to Screening;
    - Investigational small molecule drug within 5 half-lives prior to Screening;
    - Investigational biologic drug within 5 half-lives prior to Screening;
    - Phototherapy within 4 weeks prior to Screening;

- Antibody-directed or immunoglobulin-based immune therapy or other monoclonal antibody therapies within 8 weeks prior to Screening;
- Previous chronic (more than 20 days total) high potency topical corticosteroid use within 4 weeks of Screening. Stable doses of low to medium potency topical corticosteroids are allowed;
- Previous chronic (more than 20 days total) use of topical MF treatments (not listed in the bullets above) within 4 weeks prior to Screening;
- Previous systemic MF treatments (not listed in the bullets above) within 4 weeks prior to Screening;
- Previous treatment with an oligonucleotide.
- Patients on chronic *prophylactic* (for prevention, more than 20 days per month) nonsteroidal antipruritic medications within 4 weeks of screening are excluded. Patients on *symptomatic* (for current symptoms) stable nonsteroidal antipruritic medications (dose and frequency remain the same for at least 1 month prior to screening) for symptomatic pruritus are allowed.

12. Positive test for blood (including trace) on urinalysis considered by the investigator to be consistent with undiagnosed clinically significant renal pathology requiring further investigation.
13. An active or uncontrolled infection defined as subjects who require systemic antibacterial, antiviral, or antifungal therapy within the last 7 days prior to Screening.
14. Clinically significant liver disease within 1 year prior to Screening.
15. Positivity for human immunodeficiency virus (HIV), Hepatitis B surface antigen, or Hepatitis C at the time of Screening, per central laboratory. Subjects who are positive for Hepatitis C but have HCV RNA below the limit of quantitation, may be enrolled.
16. Clinically significant anemia (hemoglobin < 8 g/dL), neutropenia (absolute neutrophil count [ANC] < 1000/mm^3) or thrombocytopenia (platelets < 50,000/mm^3) at Screening.
17. Bleeding diathesis or unstable coagulopathy within 2 years prior to Screening.
18. Previous or concurrent malignancy with the following exceptions:
    - Adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry),
    - In situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study,
    - Or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry.
19. Presence on ECG of QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 470 msec for females or > 480 msec for subjects

with bundle branch block, based on a mean of the triplicate ECG measurements collected at Screening.

20. History of long QT syndrome and/or a history of persistent hypokalemia.
21. History of deep vein thrombosis and/or pulmonary embolism within 8 weeks of Screening.
22. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or inability to communicate or cooperate fully with the Investigator.
23. Lactating or pregnant.
24. Major surgery within 4 weeks of first dose of study treatment.
25. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure, as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
26. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
27. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
28. Psychiatric illness, disability or social situation that would compromise the subject's safety or ability to provide consent, or limit compliance with study requirements.
29. Clinically significant abnormalities in medical history, physical examination, or laboratory values, which, in the opinion of the Investigator, would make the subject unsuitable for inclusion in the study.
30. History of intolerance, or adverse or allergic reactions to oligonucleotide products and/or phosphate buffer solutions.

Crossover Period

Main Criteria for Inclusion:

1. Must provide or has provided written informed consent for the crossover period (signed and dated), and any authorizations required by law and be able to comply with all study requirements.
2. Must have participated in the comparator arm of the randomized period and completed the randomized period (confirmed disease progression in skin). Subjects who discontinued from the randomized period of SOLAR for any reason other than confirmed skin disease progression on the comparator arm are not eligible.

3. Meets the following criteria per the central laboratory at Screening:
    a. Calculated creatinine clearance ≥ 40 mL/min using 24-hour creatinine clearance OR modified Cockcroft-Gault equation (using ideal body mass [IBM] instead of mass).
    b. AST and ALT ≤ 2.5 × the ULN; bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who may have bilirubin ≤ 3.0 × ULN following discussion with the Sponsor).
4. Females who had a menstrual cycle within 2 years of Screening must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on their first dosing day.
5. Subjects of childbearing potential must agree to use highly effective methods of contraception as defined in Section 5.3.1.

Main Criteria for Exclusion:

1. Sézary syndrome or mycosis fungoides with B2 involvement, defined as a documented history of B2 and/or B2 staging at the Screening visit. B2 means T-cell clone in peripheral blood + one of the following at Screening:
    a. ≥ 1000/µL Sézary cells by direct examination OR
    b. ≥ 1000/µL CD4+ CD26- OR
    c. ≥ 1000/µL CD4+ CD7-
2. Current evidence of large cell transformation (LCT), defined as >25% of the lymphocytes at least 4 x the size of normal lymphocytes. Current evidence refers to LCT diagnosis from biopsy performed within 4 months prior to dosing in the crossover period. Subjects with a history of LCT but with a negative current biopsy (within 4 months) are eligible, provided there is no clinical indication for chemotherapy.
3. History of visceral involvement related to MF at Screening.
4. Unresolved toxicities from prior vorinostat treatment, defined as having not resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), grade 0 or 1.
5. Receipt of any of the following treatments:
    - Macrolide or tetracycline antibiotics within 28 days prior to Screening;
    - More than 3 short courses (≤ 7 days) of prednisone equivalent > 10 mg per day within 8 weeks prior to Screening; however, a stable regimen of systemic prednisone equivalent to ≤ 10 mg per day (or steroid equivalent) is permitted;
    - Any CTCL systemic therapy after completion of the randomization period and prior to Day 1 for the crossover period.

6. Positive test for blood (including trace) on urinalysis considered by the investigator to be consistent with undiagnosed clinically significant renal pathology requiring further investigation.
7. An active or uncontrolled infection defined as subjects who require systemic antibacterial, antiviral, or antifungal therapy within the last 7 days prior to Screening.
8. Clinically significant anemia (hemoglobin < 8 g/dL), neutropenia (absolute neutrophil count [ANC] < 1000/mm^3) or thrombocytopenia (platelets < 50,000/mm^3) at Screening.
9. Presence on ECG of QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 470 msec for females or > 480 msec for subjects with bundle branch block, based on a mean of the triplicate ECG measurements collected at Screening.
10. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or inability to communicate or cooperate fully with the Investigator.
11. Lactating or pregnant.
12. Major surgery within 4 weeks of the first dose of study treatment.
13. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
14. Clinically significant abnormalities in medical history, physical examination, or laboratory values that, in the opinion of the Investigator, would make the subject unsuitable for inclusion in the crossover period.
15. History of intolerance, or adverse or allergic reactions to oligonucleotide products and/or phosphate buffer solutions.

Statistical Methods:	Details of statistical testing and data summaries will be described in the Statistical Analysis Plan, which will be finalized prior to database lock. The analysis of the primary efficacy endpoint is the proportion of subjects in the randomized period achieving an ORR4 in skin by mSWAT assessments. The statistical test for the primary efficacy endpoint will be one-sided and will be split between the interim and final analysis and conducted using a total 0.025 significance level. Additional details of the primary efficacy endpoint in addition to the secondary efficacy endpoints will be detailed in the statistical analysis plan.

	Safety analyses will include AEs, concomitant medications, laboratory data, physical examination, and ECG data. The following analysis populations will be defined: **Intent to Treat Analysis Set (ITT)** The ITT will include all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat) and had at least one post-baseline assessment. **Safety Set** The Safety set will include all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat). **Per Protocol Set (PPS)** The PPS will consist of all subjects randomized to the study, who received study treatment, and completed assessments necessary for the evaluation of the primary endpoint with no major protocol deviations that would affect endpoint analysis. **Pharmacokinetic Analysis Set (PKAS)** The PKAS will consist of subjects randomized to cobomarsen who received at least one dose of cobomarsen and had at least one post baseline PK sample taken and analyzed.
Sample Size Justification:	Total enrollment of approximately 126 subjects randomized 1:1 provides greater than 80% power to detect a 25% difference (35% vs 10%) in the primary outcome, ORR4, between the investigational product and active comparator groups.
Planned Interim Analysis:	An interim analysis will be performed after approximately 40 subjects are followed for a minimum of approximately 6 months.
Trial-specific Committees:	**Data Monitoring Committee** The Data Monitoring Committee (DMC) will be responsible for reviewing safety data at regular intervals as well as to perform the interim analysis for futility. A separate DMC Charter will be established that outlines DMC membership, precisely what data will be reviewed, along with the timing and frequency of the reviews. DMC recommendation will be provided to the Sponsor in compliance with the DMC Charter.

	Steering Committee The study Steering Committee (SC) will be appointed by the Sponsor prior to the initiation of the study. The SC will include principal investigators from the study and Sponsor representatives. The SC will be involved in the oversight of the study and will ensure transparent management of the study according to the protocol through recommending modifications as circumstances require. Details on the role of the SC and working procedures will be defined in the SC Charter.
Protocol Version and Date:	Version 4.0, 10 February 2020

1 KEY STUDY CONTACTS

A contact information list for the Sponsor, Medical Monitor, Contract Research Organization (CRO), and selected service providers will be provided to each site. General advice on protocol procedures should be obtained through the monitor assigned to each trial site. Information on service providers is given in the study reference manual provided to each site.

The following table lists contact information for investigator reports of serious adverse events (SAEs) and pregnancies occurring in study subjects.

Table 1: Key Study Contacts

Role	Name and Affiliation	Phone	Email/Fax
Serious Adverse Event and Pregnancy Reporting	[redacted]	[redacted]	[redacted]

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Cutaneous T-cell Lymphoma

Cutaneous lymphomas of T-cell or B-cell origin comprise approximately 3.9% of all non-Hodgkin's lymphomas. Of these, approximately 53% are of T-cell origin (cutaneous T-cell lymphoma or CTCL). The prevalence of the disease in the United States (US) is estimated at 30,000 cases (Cutaneous Lymphoma Foundation 2014), although this estimate is acknowledged to be low due to the difficulty of diagnosis in the early stages of the disease. The annual age-adjusted incidence of CTCL in the US is estimated at 6.4 to 9.6 cases per million people (Jawed et al. 2014a).

CTCL presents in the skin with no evidence of extracutaneous disease at the time of diagnosis. Mycosis fungoides (MF) is the most prevalent subtype of CTCL, accounting for 50-70% of all primary cutaneous T-cell lymphomas. The second most prevalent subtype is Sézary syndrome (SS), comprising 15% of CTCL cases. MF is characterized by proliferation of atypical small- to medium-sized T lymphocytes with cerebriform nuclei that form patches, plaques, or nodular tumors in the epidermis. MF typically affects older adults (median age of diagnosis: 55 to

60 years) and has an indolent clinical course where patches and plaques precede or are concurrent with the formation of tumors. In some late tumor-stage cases, lymph node and visceral organ involvement are observed. During tumor-stage MF, the dermal infiltrates become more diffuse and the epidermotropism of the atypical T-cells may be lost. In contrast, SS is a more aggressive, leukemic form of CTCL, characterized by widespread redness and scaling of the skin (erythroderma), enlarged lymph nodes, and malignant cells in the peripheral circulation (Jawed et al. 2014a; Yamashita et al. 2012).

The trigger for atypical T-cell epidermotropism is unclear. Infectious agents such as the human T-cell lymphotropic virus type 1, Epstein-Barr virus, cytomegalovirus, and *Staphylococcus aureus* have been hypothesized as possible triggers, but a definitive link with any of these agents has not been established. Chronic antigen stimulation, due to inflammation or trauma has also been hypothesized as a driver of CTCL pathogenesis (Burg et al. 2002; Tan et al. 1974), as have medications (Samimi et al. 2013). Molecular analyses of tumor stage MF have revealed significant changes in gene expression compared to normal skin, inflamed skin and normal T-cells (van Kester et al. 2012), although the genetic or epigenetic origin of these differences in gene expression are unknown. Advanced stage and erythrodermic MF patients can exhibit immunosuppression, as demonstrated histopathologically by loss of T-cell surface antigens in patients as the disease progresses (Jawed et al. 2014a; Jawed et al. 2014b). Significant differences in the gene expression profiles of MF and SS cells have also been observed, consistent with a distinct pathogenesis for these variants of CTCL (Campbell et al. 2010; van Doorn et al. 2009).

Currently there are no therapies that cure or prolong the survival of late-stage CTCL patients (Prince et al. 2009). Treatments for CTCL patients at an early-stage of disease are palliative and non-aggressive with careful physician monitoring. More advanced stage CTCL patients are typically treated with systemic drugs, such as retinoids (bexarotene) or histone deacetylase inhibitors (vorinostat or romidepsin), phototherapy or total skin electron beam irradiation. Patients with MF expressing the CD30 cell surface antigen may be eligible for treatment with brentuximab vedotin, an anti-CD30 monoclonal antibody-cytotoxic drug conjugate. Multiagent chemotherapy or radiotherapy is reserved for patients with advanced, refractory disease and can result in partial disease regression but not full eradication. Many treatments have serious side effects or lose efficacy over time. Thus, there remains an unmet medical need for new therapies to treat CTCL.

2.1.2 Human microRNA-155-5p

2.1.2.1 miR-155-5p in Normal Physiology and Immune Response

miR-155-5p is a microRNA (miRNA) that, in humans, is encoded by the MIR155 host gene, MIR155HG. This gene, also known as BIC (B-cell integration cluster) was originally identified as a common site for retroviral insertion in avian leukosis virus-induced lymphomas (Tam et al. 1997). The 23 nucleotide, single-stranded miR-155-5p is encoded in exon 3 of the parent gene. The sequence of miR-155-5p is highly conserved across species. In non-human primates, the sequence of the microRNA is identical to the human sequence, while in mice and rats, the C at position 12 in the human sequence is replaced with a U in the rodent miRNA (miRbase, http://www.mirbase.org/).

miR-155-5p is expressed in hematopoietic cells including B-cells, T-cells, monocytes and granulocytes (Landgraf et al. 2007). miR-155-5p is an essential molecule in the control of both myelopoiesis and erythropoiesis. This miRNA is highly expressed in hematopoietic stem-progenitor cells at an early stem-progenitor stage and blocks their differentiation into a more mature hematopoietic cell (e.g., lymphocyte, erythrocyte). miR-155-5p expression progressively decreases as cells mature along these lineages and is ~200-fold lower in mature hematopoietic cells (Masaki et al. 2007; Lu et al. 2014; Burocchi et al. 2015; Kroesen et al. 2015).

miR-155-5p plays an important role in mediating inflammatory and immune responses. Mice lacking miR-155-5p show a normal number and distribution of T- and B-lymphocyte subpopulations, but display a deficient immune response, specifically in regulating T helper cell differentiation and the germinal center reaction to produce an optimal T-cell dependent antibody response (Rodriguez et al. 2007; Thai et al. 2007). miR-155-5p controls differentiation of CD4+ T-cells into the T helper type 1 (Th1), Th2, and Th17 subsets of T helper cells, and affects the development of regulatory T-cells (Treg) (Baumjohann et al. 2013). miR-155-5p also regulates effector and memory CD8+ T-cell responses to viral infection (Dudda et al. 2013; Gracias et al. 2013), as well as normal B-cell differentiation and antibody production. In humans, miR-155-5p expression is low in nonlymphoid organs as well as in resting, naïve CD4+ T-cells. miR-155-5p expression is greatly enhanced by antigen receptor stimulation of B- and T-cells (Tam 2001; Haasch et al. 2002; van den Berg et al. 2003; Rodriguez et al. 2007; Thai et al. 2007; Vigorito et al. 2007; Banerjee et al. 2010), and by Toll-like receptor agonist stimulation of macrophages and dendritic cells (Taganov et al. 2006; O'Connell et al. 2007; Ceppi et al. 2009; Mao et al. 2011). MIR155HG activation involves both AP1- and NFκB-mediated mechanisms.

2.1.2.2 miR-155-5p in Cutaneous T-Cell Lymphoma, Mycosis Fungoides Subtype

miRNAs have been reported to be differentially expressed and potentially involved in the pathogenesis of CTCL. miR-155-5p is among the miRNAs most up-regulated in MF (Kopp et al. 2013a; Kopp et al. 2013b). Conversely, a distinct subset of dysregulated miRNAs is observed in SS, and miR155-5p is not up-regulated in this subtype of CTCL (Ballabio et al. 2010).

Increased miR-155-5p in MF patient skin biopsies compared to control skin biopsies has been reported by several groups (van Kester et al. 2011; Maj et al. 2012; Kopp et al. 2013b; Moyal et al. 2013). In one study, miR-155-5p levels were more than 4-fold higher in tumor-stage biopsies compared to early MF biopsies (Moyal et al. 2013), suggesting that miR-155-5p levels may be correlated with disease progression. In a second study to further define the specific cell types that express miR-155-5p, the miRNA was found by *in situ* hybridization to be expressed in both malignant and non-malignant T-cells in the CTCL lesions (Kopp et al. 2013b).

miR-155-5p dysregulation is linked to signaling pathways that have been implicated in CTCL pathogenesis. Specifically, malignant T-cells are reported to constitutively express the interleukin (IL)-2 receptor complex and the associated Janus kinases (JAK) that activate transcription via the STAT proteins. miR-155-5p expression has been linked to the STAT5 pathway in CTCL malignant T-cells in culture: chromatin immunoprecipitation experiments found STAT5 to be associated with the promoter of MIR155HG. Inhibition of the JAK/STAT pathway resulted in down regulation of miR-155-5p expression, and treatment of cells with cytokines activating STAT5 resulted in increased miR-155-5p levels (Kopp et al. 2013a). These results suggest that miR-155-5p may play a role in the pathogenesis of CTCL. In support of this hypothesis, the authors showed that CTCL cells grown in the presence of an inhibitor to miR-155-5p had a reduction in cellular proliferation (Kopp et al. 2013a). These data suggest that inhibition of miR-155-5p may have therapeutic effects by affecting the malignant T-cells of MF patients.

2.1.3 Investigational Product: Cobomarsen

miRagen has identified an antagonist of miR-155-5p, cobomarsen (also referred to by the company code, MRG-106), by screening a panel of synthetic oligonucleotides for inhibitory activity as measured by target gene de-repression in cultured cells. Cobomarsen is designed to interact with miR-155-5p through base-pairing complementarity to competitively inhibit the interaction of miR-155-5p with its mRNA targets.

In vitro pharmacology data demonstrate that exposure of cultured miR-155-5p-expressing MF cell lines to cobomarsen results in de-repression of miR-155-5p direct mRNA targets. Further, two of three MF cell lines that were exposed to cobomarsen in culture showed significantly reduced proliferation and increases in protein markers of apoptosis. An SS cell line that does not express high levels of miR-155-5p was not similarly responsive to the drug. These data support the further evaluation of cobomarsen for its safety, tolerability and potential to provide therapeutic benefit in patients with MF.

2.1.3.1 Nonclinical Background

miRagen has conducted *in vitro* and *in vivo* studies to investigate the pharmacology, pharmacokinetics (PK) and toxicology of cobomarsen. Details of nonclinical studies conducted to date are provided in the cobomarsen (MRG-106) Investigator's Brochure.

Cobomarsen regulates miR-155-5p seed-matched target mRNAs in human CTCL cell lines, in a miR-155-5p-dependent and sequence-dependent manner. Inhibition of miR-155-5p by cobomarsen reduces proliferation and cell survival, with induction of apoptosis, in human mycosis fungoides cell lines in a cobomarsen dose responsive manner. Genome-wide expression analysis demonstrates that cobomarsen regulates numerous genes implicated in cell cycle and apoptosis, consistent with the pharmacologic impact on cell survival. A subset of these genes has been identified as potentially translatable biomarkers to monitor cobomarsen activity in clinical samples.

Experience with phosphorothioate and locked nucleic acid (LNA)-modified oligonucleotide drugs has been well described in the literature and much is understood about the relationship between toxicities observed in non-clinical studies and their potential clinical manifestations. Some of the class-related effects of oligonucleotides are known to be species specific, while others are related to PK, including plasma clearance time, and tissue accumulation and clearance. As such, monkeys are considered the most predictive toxicology species for humans because of their phylogenetic similarity to man and the ability to extrapolate plasma concentrations and clearance rates between primates and man on the basis of mg/kg dosing (Geary et al. 2003; FDA 2005; Yu et al. 2007).

The toxicities observed in 28-day, repeat subcutaneous dose studies conducted in rats administered 10 cobomarsen doses of 3, 8 or 20 mg/kg and in monkeys administered 10 doses of 3, 10 or 30 mg/kg were primarily those expected of LNA-modified phosphorothioate oligonucleotides. The most notable adverse finding in rats was dose dependent (≥ 3 mg/kg) renal proximal tubule degeneration, characterized by vacuolation and fragmentation of the cytoplasm

of convoluted tubule epithelial cells, as well as changes in serum and urinary biochemical markers indicative of mild changes in renal function at doses ≥ 8 mg/kg. These effects were largely reversed by 8 weeks after the last dose. The rat is known to be more sensitive to renal toxicity from a variety of insults, including treatment with phosphorothioate oligonucleotides (Berman et al. 2014). This is confirmed for cobomarsen as no similar changes in renal morphology or parameters of kidney function were observed in monkeys at doses up to and including 30 mg/kg.

In monkeys, follicular atrophy in the thyroid gland with a concurrent decrease in thyroid organ weight was observed after subcutaneous administration of 30 mg/kg in males and ≥ 3 mg/kg in females. Examination of thyroid-stimulating hormone (TSH) plasma levels demonstrated that this finding did not result in a significant difference in individual monkey's TSH levels between predose Day 1 and Day 28. Furthermore, no clinical indications of gross metabolic imbalance were observed in the monkeys over the course of the study. Following the 28-day recovery period, there was evidence of partial recovery in both incidence and severity of the thyroid atrophy and organ weight. No similar changes in the thyroid were observed in the rat at doses up to 20 mg/kg.

In monkeys, a single 30 mg/kg dose administered as a subcutaneous injection or a 1-minute intravenous bolus injection was well tolerated, with no clinically significant effects on coagulation or complement activation. Transient increases in liver transaminases (< 5-fold in aspartate aminotransferase [AST] and < 3-fold in alanine aminotransferase [ALT]), fibrinogen (< 2-fold) and creatine kinase (CK; < 5-fold intravenous and < 34-fold for subcutaneous dosing) values were observed 24 hours postdose but returned to within the normal range by Day 7, the next time point evaluated. These clinical pathology findings were similar between intravenous bolus and subcutaneous dosing suggesting that the increased C_{max} following intravenous injection did not contribute to the transient effects.

Cobomarsen is considered to have a very low risk of genotoxicity based on literature reports and published regulatory opinion regarding the genotoxic potential of oligodeoxynucleotides (EMEA/CHMP/SWP/199726/2004) and LNA-containing oligonucleotides (Guérard et al. 2017).

Cobomarsen has recently been evaluated for potential genotoxicity using standard *in vitro* testing methods, including the bacterial reverse mutation (Ames) assay and the micronucleus assay in human peripheral blood lymphocytes. The negative results of these studies confirm that the genotoxicity risk of cobomarsen is very low.

2.1.3.2 Clinical Background

Cobomarsen is being evaluated in a Phase 1 clinical trial to investigate its safety, tolerability and PK, as well as exploratory measures of pharmacodynamics (PD) and efficacy in subjects with CTCL, mycosis fungoides subtype. The study has also enrolled a limited number of subjects with chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) and adult T-cell leukemia/lymphoma (ATLL). Details of the Phase 1 clinical trial results are provided in the cobomarsen (MRG-106) Investigator's Brochure.

Study MRG106-11-101 has completed enrollment of subjects who had prior treatment for CTCL, mycosis fungoides subtype, stages I, II or III. As of 23 July 2019, 6 subjects with CTCL have been treated in Part A with 75 mg cobomarsen by intratumoral injection, and 37 subjects with CTCL have been treated in Part B with 300, 600 or 900 mg cobomarsen by subcutaneous injection, or intravenous infusion or injection. Of note, 2 subjects that had completed Part A were re-enrolled in Part B (with new unique identification numbers) following an 8-week washout period, as permitted in the protocol. In addition, cobomarsen has been explored in other indications and at additional dose levels, as detailed in the Investigator's Brochure.

Overall, the study treatment has been well tolerated. The majority of AEs have been mild or moderate in severity (grade 1 or 2) and there have been no safety signals indicative of clinically significant adverse effects on renal, liver, coagulation, platelets or thyroid function at the dosing regimens evaluated to date. Two subjects experienced dose-limiting toxicities (pruritus and disease flare) resulting in study discontinuation, per protocol. Ninety-two percent (92%) of subjects treated with systemic administration showed improvement in skin disease as measured by the mSWAT score. Sixty-three percent (63%) of subjects treated with 300 mg IV infusion (5 of 8 subjects) achieved a partial response. Being well tolerated, this dose and mode of administration has been selected for the SOLAR trial. Full details on safety and efficacy of cobomarsen in CTCL are found in the Investigator's Brochure.

Pharmacodynamic effects of cobomarsen were assessed in lesion biopsies taken before and after treatment in both parts of the study. In Part A of the clinical trial, high levels of cobomarsen (48-204 µg per gram of tissue) were detected in injected tumors 24 hours after the last dose. Accumulation of cobomarsen was also observed in a lesion distant from the site of injection at low levels (4 µg per gram of tissue). Analysis of injected tumors also indicated an increased expression of several direct targets of miR-155, suggesting that the drug may be inhibiting its intended molecular target. A similar pattern of gene regulation was observed in a lesion not directly injected with drug that had 4 µg cobomarsen per gram of tissue, suggesting the minimum effective dose level in skin lesions may be near this level. After treatment, histology

revealed fewer cancerous cells or a reduction in cancer cell density or depth in most patients. Cobomarsen was also measured in skin biopsies collected from systemically-treated patients in Part B, at doses ranging from 300 to 900 mg. Levels measured showed a mean of 12 µg per gram of tissue, with no clear dose response relationship. Similar patterns of cobomarsen target-gene expression changes were observed in patient biopsies after systemic dosing as were seen in the Part A lesions.

In general, there has been no indication that cobomarsen is affecting the general leukocyte populations in patients that have been treated for up to 18 months except for an increase in natural killer (NK) cells in patients receiving 900 mg doses by multiple routes of administration. Analysis of the functional T-cell subsets have demonstrated that chronic dosing of cobomarsen does not affect the proportions of naïve, effector, and central or effector memory CD4+ and CD8+ T-cells, and the expected expansion and contraction of these effector cells occurs as would be expected during documented common respiratory or skin infections that occurred in several patients during the course of cobomarsen treatment. For full details on pharmacodynamic effects of cobomarsen, please refer to the Investigator's Brochure.

Analysis of cobomarsen clinical PK data reveal biphasic plasma concentration time curves, indicative of multi-compartmental pharmacokinetics. Apparent half-lives ($t_{1/2}$) measured over the first 24-hours were similar for all routes of administration (ROA), ranging from 5.0 to 8.2 hours. Trough plasma samples collected once a month during prolonged administration of cobomarsen generally increased from the first extension cycle sample collection over the next one to two cycles, where they achieved maximum concentrations and then plateaued or declined over subsequent cycles. This may indicate steady state concentrations being achieved after 3 or 4 cycles of dosing, or after approximately 12-16 weeks of regular cobomarsen administration, suggesting a terminal elimination half-life of approximately 2.5 to 3 weeks. Despite the observed differences in C_{max} and T_{max}, dose normalized systemic exposure (AUC_{0-24}/Dose) for all dose levels in the intratumoral, subcutaneous, and intravenous 2-hour infusion cohorts were similar, demonstrating good dose proportionality across those ROAs and dose concentrations. Accumulation ratios (multiple dose C_{max}/first dose C_{max} or multiple dose AUC_{0-24}/first dose AUC_{0-24}) indicated no significant accumulation at the 900 mg dose level for any route of administration. For full details on PK profile of cobomarsen in CTCL, please refer to the Investigator's Brochure.

2.1.4 Active Control: Vorinostat

Vorinostat is a histone deacetylase (HDAC) inhibitor approved in the US, Canada and Australia for the treatment of CTCL. This drug is not approved in Europe, and thus remains an investigational product for sites in that region. Complete information on vorinostat, including risks, precautions and adverse effect profile are included in the package insert.

2.2 Scientific Rationale and Dose Selection

Based on the nonclinical and clinical data collected to date, cobomarsen is hypothesized to offer clinical benefit to subjects with MF. The current protocol is a randomized, open-label, parallel-group, active comparator, multi-center, outpatient efficacy study designed to determine the efficacy, safety, and PK of cobomarsen compared with vorinostat in subjects with MF.

Due to a lack of in vivo preclinical models to help define the optimal dose and route for cobomarsen administration, skin lesion biopsies have been collected from a subset of Phase 1 human clinical trial participants dosed with cobomarsen by intralesional injection or systemically by the subcutaneous (SC) or intravenous (IV) routes at three dose levels. These samples are being analyzed for drug concentration and pharmacodynamic activity through molecular analysis of gene expression changes. The results obtained to date suggest that cobomarsen drug levels in individual lesions are highly variable from subject to subject, possibly due to differences in lesion morphology (patch, plaque, tumor) and the vascularity at each biopsy site. The cobomarsen concentration in lesion biopsies collected 24 hours after the last dose ranged from 48.6 to 206 µg/g after multiple 75 mg doses administered by direct intratumoral (IT) injection and from 3.10 to 53.2 µg/g after systemic administration of multiple doses by SC, IV infusion or IV bolus. Based on this small data set, there is not a strong correlation between dose or route of administration and skin biodistribution in systemically treated subjects. However, gene expression analysis demonstrates that concentrations as low as 3 µg/g tissue (0.6 µM) are sufficient to provide pharmacodynamically relevant exposure to the drug in the skin lesions of mycosis fungoides patients. The pharmacodynamic response to cobomarsen was evaluated by measuring the levels of approximately 600 mRNAs in skin lesion biopsies collected from study subjects before and after cobomarsen administration. This panel of mRNAs was identified in preclinical studies as potential direct or indirect targets of miR-155-5p based on their coordinated regulation in three MF cell lines following exposure to cobomarsen (refer to IB section 4.1.1.5). The data showed exposure-related changes in gene expression pathways expected to be modulated by inhibiting miR-155 and suggest that effective cobomarsen levels can be reached in MF lesions using either the subcutaneous or intravenous dosing routes and the 300 mg dose level

is sufficient to achieve the desired pharmacodynamic effects. For more details please see the Investigator's Brochure.

The dosing regimen of cobomarsen that will be administered in this study (282 mg active moiety, administered by intravenous infusion, equivalent to 300 mg of the sodium salt form) is based on above pharmacodynamic data, as well as safety and clinical efficacy data from Phase 1 study. This dose and mode of administration was well tolerated in the Phase 1 study in subjects with MF, who received systemic doses of up to 900 mg (sodium salt). The 300 mg 2-hour intravenous infusion dose regimen was selected based on the generally favorable safety and tolerability data from the ongoing Phase 1 trial. Additionally, compared to the 600 and 900 mg doses, the 300 mg dose appeared to have similar PD and clinical effects. For further efficacy data, please see Investigator's Brochure.

Vorinostat was selected as the active comparator. As this clinical trial will be conducted at multiple sites within the European Union, North America and Australia, it is necessary to select an active comparator that is acceptable for use in all regions, but that is not first line of treatment in any region, as this would exclude many patients from participating in the study. Vorinostat is more typically used as a second-line systemic treatment in the US, Canada and Australia and is not an approved therapy in the European Union. Hence, the majority of the indicated study population in all regions will not have had previous exposure to the drug.

Vorinostat is an HDAC inhibitor, a class of small molecules being evaluated in clinical trials for a number of different malignancies. Vorinostat was the first HDAC inhibitor approved by the US Food and Drug Administration (FDA) in 2006 for treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent or recurrent disease on or following two systemic therapies. In two Phase 2 trials, vorinostat was safe and effective at an oral dose of 400 mg/day with an overall response rate at one month of 31% in refractory advanced patients with CTCL, including large cell transformation and Sézary syndrome. Vorinostat also has a significant symptomatic effect on pruritus, a major symptom in this patient population that directly impacts quality of life (Zinzani et al. 2016). The most frequent side effects of vorinostat include gastrointestinal symptoms, fatigue and thrombocytopenia (Duvic and Ju, 2007). The safety profile of the drug is well known, with clear guidelines for dose reduction to decrease gastrointestinal side effects (see vorinostat package insert). Vorinostat is one of the drugs considered as standard of care in the US (Horwitz et al. 2018) and Australia for ≥ stage IB disease.

2.3 Potential Risks and Benefits

The potential risks and benefit of cobomarsen treatment are detailed in the Investigator's Brochure. The potential risks and benefit of vorinostat are in the package insert, which provides the full prescribing information for vorinostat in the US.

2.3.1 Known Potential Risks of Cobomarsen

In clinical studies of phosphorothioate oligonucleotides, most of the observed side effects are believed to be hybridization-independent and related to the physical and chemical characteristics of this class of agents. Certain adverse effects have been observed repeatedly during clinical investigations of systemically administered phosphorothioate oligonucleotide drugs, with the most commonly observed side effects including dermatological reactions at subcutaneous injection sites, constitutional symptoms such as fever, chills, and myalgia primarily associated with initial doses, and dose-dependent prolongation of activated partial thromboplastin time (aPTT) when the drugs are given intravenously, but not when administered subcutaneously. In general, these effects are mild and transient, and resolve spontaneously.

In the ongoing Phase 1 study of cobomarsen, there have been no safety signals indicative of clinically significant adverse effects on coagulation, platelets, or renal, liver, or thyroid function at the dosing regimens (300-900 mg) evaluated in CTCL patients. For full details of all cobomarsen Phase 1 safety data (across all indications) to date, refer to the current cobomarsen Investigator's Brochure and any new safety updates.

Potential risks of exaggerated pharmacology of miR-155 inhibition, specifically immunosuppression, have not been observed in the Phase 1 study in CTCL.

2.3.2 Known Potential Benefits of Cobomarsen

The ongoing Phase 1 study in CTCL was designed primarily to evaluate safety, with efficacy collected as a secondary endpoint. Preliminary evidence of antitumor activity has been observed and potentially outweighs the risks and warrants further investigation.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of cobomarsen in subjects with MF.

3.1.2 Secondary Objectives

Secondary study objectives are to:

- Investigate the safety and tolerability of cobomarsen in subjects with MF.
- Characterize the population PK of cobomarsen in subjects with MF.
- During the crossover portion of the study:
    - Evaluate the efficacy, safety and tolerability of cobomarsen in subjects with MF who have shown disease progression following treatment with vorinostat.

3.2 Endpoints

3.2.1 Primary Endpoint

Primary Efficacy Evaluation:

- Proportion of subjects achieving an objective skin response (complete response [CR] or partial response [PR]) of at least 4 months duration (ORR4) using the mSWAT scoring (see Section 12.4.3 and Appendix F).

3.2.2 Secondary Endpoints

Efficacy measures:

- Progression-free survival (PFS).
- Complete response rate (CRR).
- Time to progression (TTP).
- Time to maximal effect in skin (mSWAT).
- Proportion of subjects achieving ≥ 50% improvement in mSWAT of at least 28-days duration (ORR1).
- Proportion of subjects achieving ≥ 50% improvement in mSWAT from baseline at 28 days and at 4 months.
- Time to ≥ 50% improvement in mSWAT.
- Duration of response in skin (no progression after achieving ≥ 50% improvement in mSWAT).
- Change in pruritus medication utilization from baseline and incidence of pruritus medication utilization.

- During the crossover portion of the study:
    - Proportion of subjects achieving an objective skin response (complete response [CR] or partial response [PR]) of at least 4 months duration (ORR4) using the mSWAT scoring (see Appendix F).
    - Progression-free survival (PFS).
    - Complete response rate (CRR)
    - Time to progression (TTP).
    - Time to maximal effect in skin (mSWAT).
    - Proportion of subjects achieving ≥ 50% improvement in mSWAT of at least 28-days duration (ORR1).
    - Proportion of subjects achieving ≥ 50% improvement in mSWAT from baseline at 28 days and at 4 months.
    - Time to ≥ 50% improvement in mSWAT.
    - Duration of response in skin (no progression after achieving ≥ 50% improvement in mSWAT).
    - Change in pruritus medication utilization from baseline and incidence of pruritus medication utilization.

Safety and Tolerability Evaluations:

- Incidence and severity of clinically significant AEs (including grade 3 and 4 AEs, treatment-related AEs, SAEs, and AEs requiring discontinuation), physical examination findings, changes in electrocardiogram (ECGs), changes in laboratory parameters and changes in vital signs.
- Characterization of anti-drug antibody generation.

Pharmacokinetic Evaluation:

- Population PK parameters.
- During the crossover portion of the study
    - Pharmacokinetic C_{max} and trough concentration analysis

4 STUDY DESIGN

This is a Phase 2, randomized, open-label, parallel-group, active comparator, multi-center study to assess the efficacy and safety of cobomarsen compared to vorinostat in subjects with MF (Figure 1). The randomization will be stratified based on subjects with at least one skin tumor at Screening vs. no skin tumors at Screening. Subjects will also be stratified based on prognostic factors (age at diagnosis > 60 years and lactate dehydrogenase [LDH] level > the upper limit of normal [ULN] at diagnosis) (Scarisbrick et al., 2015). Subjects will be stratified based on having 0-1 vs 2 of these prognostic factors.

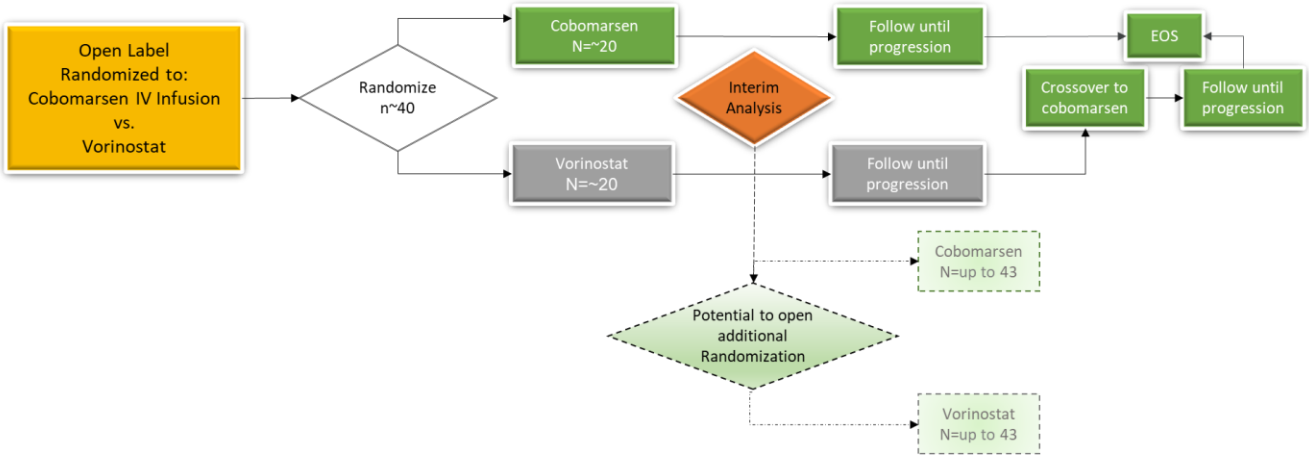
This study will have 2 periods, a randomized period and a crossover period. Subjects who are on the vorinostat arm in the randomized period and have confirmed skin disease progression may elect to participate in the crossover period of the study.

4.1 Randomized Period

Approximately 126 subjects are expected to be enrolled. An interim analysis will be conducted after approximately 40 subjects have been followed for a minimum of approximately 6 months; enrollment will be suspended after approximately 40 subjects have been enrolled until the completion of the interim analysis.

Subjects will be randomized in a 1:1 ratio to receive cobomarsen or vorinostat. Subjects will undergo Screening lasting up to 28 days from the time of informed consent, followed by active treatment, and then follow-up for response and disease progression.

Figure 1. SOLAR Study Design Schematic



Subjects will remain on their assigned study treatment until one of the following occurs:

1. Disease progression, defined as either (see Appendix F):
   a. Confirmed progression in skin
   b. Clinical progression in other compartments, documented by assessments (flow cytometry and/or CT scan) completed per investigator discretion
   c. Partial or complete skin response followed by a confirmed loss of skin response as defined by an increase of mSWAT of greater than the sum of nadir plus 50% baseline score.

   Progressions based on mSWAT will be confirmed by repeated measurement 28 days (±3 days) after the first determination of progression.

   If confirmed, the date of progression will be based on the first determination of progression. Subjects will continue the study treatment until disease progression is confirmed.
2. Subject meets one of the other treatment discontinuation criteria (see Section 5.4.1).

Safety assessments will include monitoring the incidence and severity of AEs and SAEs, physical examination findings, vital signs, ECG monitoring, and clinical laboratory assessments.

Samples will be collected for PK in the cobomarsen group on Days 1, 2, 3, 5, 8, 15, 29, and every 4 weeks from Weeks 9 through 81, every 8 weeks thereafter, and at the follow-up/end of treatment visit.

mSWAT evaluations will be completed on Days 1 and 29, every 4 weeks through Week 81, every 8 weeks thereafter, and at the End of Treatment and Follow-up visits. Every effort will be made to perform a final disease assessment for subjects who withdraw from the study early.

4.2 Crossover Period

After completing the randomized period, subjects that have confirmed skin disease progression on the vorinostat arm can be assessed for eligibility for the crossover period. Eligible subjects may elect to enter this optional crossover period and must sign an informed consent form to proceed.

Potential subjects will need to complete the crossover screening activities and meet the entry criteria prior to enrollment into the crossover period of the study.

Subjects in the randomized period of the study who withdrew consent **without confirmation of skin disease progression** are **not eligible** to enroll in this period. In addition, subjects who received any subsequent systemic therapy for MF following confirmed disease progression in the randomized period are not eligible for the crossover period.

Study procedures completed at the End of Treatment visit in the randomized period may be used for screening assessments in the crossover period, depending on the timing of the assessments. Subjects who initiate Screening in the crossover period > 28 days after completing the randomized period will need to complete all of the crossover Screening procedures.

Subjects will undergo Screening lasting up to 28 days from the time of the first screening procedure, followed by active treatment and follow-up for response and disease progression.

Subjects will remain on cobomarsen until one of the following occurs:

1. Disease progression, defined as either (see Appendix F):
    a. Confirmed progression in skin
    b. Clinical progression in other compartments, documented by assessments (flow cytometry and/or CT scan) completed per investigator discretion
    c. Partial or complete skin response followed by a confirmed loss of skin response as defined by an increase of mSWAT of greater than the sum of nadir plus 50% baseline score.

    Progressions based on mSWAT will be confirmed by repeated measurement 28 days (±3 days) after the first determination of progression. If confirmed, the date of progression will be based on the first determination of progression. Subjects will continue cobomarsen until disease progression is confirmed.
2. Subject meets one of the other treatment discontinuation criteria (see Section 5.4.1).

Safety assessments will include monitoring the incidence and severity of AEs and SAEs, physical examination findings, vital signs, ECG monitoring, and clinical laboratory assessments.

Blood samples will be collected for PK on Days 1 and 29, every 4 weeks through Week 81, every 8 weeks thereafter, and at the End of Treatment and Follow-up visits.

mSWAT evaluations will be completed on Days 1 and 29, every 4 weeks through Week 81, every 8 weeks thereafter, and at the End of Treatment and Follow-up visits.

4.3 Treatments Administered

Subjects will be treated and monitored in the outpatient setting for the duration of the study.

Randomized Period

On Day 1, subjects will visit the clinic to complete baseline assessments. Upon confirmation of eligibility and completion of all predose assessments subjects will receive the first dose of study treatment (i.e., initiation of the randomized period) according to their randomized treatment assignment (cobomarsen or vorinostat).

- Cobomarsen will be administered by intravenous 2-hour infusion at a dose of 282 mg on Days 1, 3, 5, 8, and weekly thereafter;
- Vorinostat will be administered orally at a dose of 400 mg (four 100-mg capsules) once daily with food, at approximately the same time each day.
    - Subjects assigned to vorinostat with abnormal ALT/AST (> ULN) or bilirubin (> 1.0 × ULN) at Screening will start vorinostat dosing at 300 mg (three 100-mg capsules) once daily with food, at approximately the same time each day, per dosing guidelines.

Subjects randomized to cobomarsen will remain in the clinic for PK sample collection and subjects in both groups will be monitored for safety 4 hours postdose.

All subjects will return to the clinic on Day 2 for study assessments and on Days 3, 5, 8, 15, 22, and 29 for safety and study assessments. The cobomarsen group will continue to receive study treatment weekly and undergo study assessments. Infusions may be administered at satellite locations on dosing days without efficacy assessments.

The vorinostat group will return to the clinic at Day 29, then weekly through Week 8 and every 4 weeks thereafter for study assessments.

Crossover Period

On Day 1, subjects will visit the clinic to undergo baseline assessments. Upon confirmation of eligibility and completion of all predose assessments, subjects will receive the first dose of cobomarsen (i.e., initiation of the crossover period) as a 2-hour intravenous infusion at a dose of 282 mg. Subjects will remain in the clinic and will be monitored for safety for a minimum of 4 hours postdose.

Subjects will return to the clinic on Day 2 for study assessments and on Days 3, 5, and 8 for cobomarsen infusions and safety and study assessments. Subjects will continue to receive

cobomarsen weekly and undergo study assessments. Infusions may be administered at satellite locations on dosing days without mSWAT assessments.

4.3.1 Research Home Infusions

Randomized and Crossover Periods

Subjects assigned cobomarsen in the randomized or crossover period of the study will have access to optional research home intravenous infusion services after 4 months of treatment with cobomarsen. In addition to completing at least 4 months of treatment at the study site, investigators must confirm the patient is suitable for home infusions based on the investigator's clinical judgement. If a patient/site is deemed eligible for home infusion services, additional training of study site staff and coordination with the research home infusion vendor nurse will be required.

Home infusions are optional to lighten the burden of the trial on eligible subjects. If site and/or IRB/IEC policies do not allow for the option of research home infusions, the option will not be presented to the subject.

miRagen has chosen a Research Home Infusion Vendor to provide home infusion services in the study. Trained research nurses from the vendor will work in conjunction with the clinical sites' staff to coordinate home infusion visits, facilitate the controlled management of investigational study drug, and transmit records from the home infusion visits to the clinical site staff. The research nurses will work collaboratively with the study site Principal Investigator and staff to identify, report, and manage adverse events documented during home visits. Detailed procedures for the research home infusion visits and the collection of study-related documentation during these visits are provided in the Off-Site Nursing Manual.

5 ENROLLMENT, DISCONTINUATION AND WITHDRAWAL OF STUDY SUBJECTS

5.1 Randomized Period Entry Criteria

5.1.1 Inclusion Criteria, Randomized Period

Individuals must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Must provide written informed consent (signed and dated), and any authorizations required by law and be able to comply with all study requirements.
2. Males or females, ≥ 18 years of age at the time of informed consent.

3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
4. Biopsy-proven CTCL, MF subtype.
5. Clinical stage IB, II, or III, with staging based on Screening assessments and following staging parameters set in this protocol (see Appendix H).
6. Minimum mSWAT score of 10 at Screening (see Appendix F, Table F1).
7. Receipt of at least one prior therapy for CTCL (per National Comprehensive Cancer Network [NCCN] guidelines for generalized skin involvement; e.g., topical, phototherapy, total skin electron beam therapy [TSEBT], or systemic therapy [see Appendix G]).
8. Meets the following criteria per the central laboratory at Screening:
    a. Calculated creatinine clearance ≥ 40 mL/min using 24-hour creatinine clearance OR modified Cockcroft-Gault equation (using ideal body mass [IBM] instead of mass).
    b. AST and ALT ≤ 2.5 × the ULN; bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who may have bilirubin ≤ 3.0 × ULN following discussion with the Sponsor).
9. Females who had a menstrual cycle within 2 years of Screening must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on their first dosing day.
10. Subjects of childbearing potential must agree to use highly effective methods of contraception as defined in Section 5.3.1.

5.1.2 Exclusion Criteria, Randomized Period

Individuals who meet any of the following exclusion criteria are not to be enrolled in this study.

1. Previous enrollment in a cobomarsen study.
2. Prior therapy with vorinostat or other HDAC inhibitors, or contraindication to an HDAC inhibitor.
3. Sézary syndrome or mycosis fungoides with B2 involvement, defined as a documented history of B2 and/or B2 staging at the Screening visit. B2 means T-cell clone in peripheral blood + one of the following at Screening:
    a. ≥ 1000 Sézary cells by direct examination OR

b. ≥ 1000/μL CD4+ CD26- OR

c. ≥ 1000/μL CD4+ CD7-

4. Current evidence of large cell transformation (LCT), defined as > 25% of the lymphocytes at least 4 × the size of normal lymphocytes. Current evidence refers to LCT diagnosis from biopsy performed within 4 months prior to randomization. Subjects with a history of LCT but with a negative current biopsy (within 4 months) are eligible, provided there is no clinical indication for chemotherapy.
5. Evidence of enlarged peripheral or central lymph node(s) > 1.5 cm in the long diameter or > 1.0 cm in the short diameter by radiographical imaging at Screening. A subject with one or more enlarged lymph node(s) may be allowed, provided that a representative lymph node has been confirmed (via biopsy or positron emission tomography [PET]) scan) to be N_0-N_2 or SUV ≤ 5 within the 3 months prior to Day 1, and there has not been an appearance of new abnormal lymph nodes since the biopsy or PET scan. Subjects with uncharacterized enlarged lymph nodes (i.e. not confirmed by biopsy or PET scan) will not be allowed.
6. Any palpable peripheral node, regardless of size, that on physical examination is firm, irregular, clustered, or fixed, unless histologically confirmed to be non-malignant.
7. Evidence of visceral involvement related to MF at Screening.
8. Recent history of alcoholism (within the past 1 year).
9. Known or suspected substance abuse within the past 1 year.
10. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), grade 0 or 1.
11. Receipt of any of the following treatments:
    - Macrolide or tetracycline antibiotics within 28 days prior to Screening;
    - More than 3 short courses (≤ 7 days) of prednisone equivalent > 10 mg per day within 8 weeks prior to Screening; however, a stable regimen of systemic prednisone equivalent to ≤ 10 mg per day (or steroid equivalent) is permitted;
    - Total skin electron beam therapy or radiotherapy within 4 weeks prior to Screening;
    - Investigational small molecule drug within 5 half-lives prior to Screening;

- Investigational biologic drug within 5 half-lives prior to Screening;
- Phototherapy within 4 weeks prior to Screening;
- Antibody-directed or immunoglobulin-based immune therapy or other monoclonal antibody therapies within 8 weeks prior to Screening;
- Previous chronic (more than 20 days total) high potency topical corticosteroid use within 4 weeks of Screening. Stable doses of low to medium potency topical corticosteroids are allowed;
- Previous chronic (more than 20 days total) use of topical MF treatments (not listed in the bullets above) within 4 weeks prior to Screening;
- Previous systemic MF treatments (not listed in the bullets above) within 4 weeks prior to Screening;
- Previous treatment with an oligonucleotide.
- Patients on chronic *prophylactic* (for prevention, more than 20 days per month) nonsteroidal antipruritic medications within 4 weeks of screening are excluded. Patients on *symptomatic* (for current symptoms) stable nonsteroidal antipruritic medications (dose and frequency remain the same for at least 1 month prior to screening) for symptomatic pruritus are allowed.

12. Positive test for blood (including trace) on urinalysis considered by the investigator to be consistent with undiagnosed clinically significant renal pathology requiring further investigation.
13. An active or uncontrolled infection defined as subjects who require systemic antibacterial, antiviral, or antifungal therapy within the last 7 days prior to Screening.
14. Clinically significant liver disease within 1 year prior to Screening.
15. Positivity for human immunodeficiency virus (HIV), Hepatitis B surface antigen, or Hepatitis C at the time of Screening, per central laboratory. Subjects who are positive for Hepatitis C but have HCV RNA below the limit of quantitation, may be enrolled.
16. Clinically significant anemia (hemoglobin < 8 g/dL), neutropenia (absolute neutrophil count [ANC] < 1000/mm^3) or thrombocytopenia (platelets < 50,000/mm^3) at Screening.
17. Bleeding diathesis or unstable coagulopathy within 2 years prior to Screening.

18. Previous or concurrent malignancy with the following exceptions:
    - Adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry),
    - In situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study,
    - Or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry.
19. Presence on ECG of QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 470 msec for females or > 480 msec for subjects with bundle branch block, based on a mean of the triplicate ECG measurements collected at Screening.
20. History of long QT syndrome and/or a history of persistent hypokalemia.
21. History of deep vein thrombosis and/or pulmonary embolism within 8 weeks of Screening.
22. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or inability to communicate or cooperate fully with the Investigator.
23. Lactating or pregnant.
24. Major surgery within 4 weeks of first dose of study treatment.
25. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure, as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
26. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
27. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
28. Psychiatric illness, disability or social situation that would compromise the subject's safety or ability to provide consent, or limit compliance with study requirements.

29. Clinically significant abnormalities in medical history, physical examination, or laboratory values, which, in the opinion of the Investigator, would make the subject unsuitable for inclusion in the study.
30. History of intolerance, or adverse or allergic reactions to oligonucleotide products and/or phosphate buffer solutions.

5.2 Crossover Period Entry Criteria

5.2.1 Inclusion Criteria, Crossover Period

Individuals must meet all of the following inclusion criteria to be eligible for participation in the crossover period.

1. Must provide or has provided written informed consent for the crossover period (signed and dated), and any authorizations required by law and be able to comply with all study requirements.
2. Must have participated in the comparator arm of the randomized period and completed the randomized period (confirmed disease progression in skin). Subjects who discontinued from the randomized period of SOLAR for any reason other than confirmed skin disease progression on the comparator arm are not eligible.
3. Meets the following criteria per the central laboratory at Screening:
    a. Calculated creatinine clearance ≥ 40 mL/min using 24-hour creatinine clearance OR modified Cockcroft-Gault equation (using ideal body mass [IBM] instead of mass).
    b. AST and ALT ≤ 2.5 × the ULN; bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who may have bilirubin ≤ 3.0 × ULN following discussion with the Sponsor).
4. Females who had a menstrual cycle within 2 years of Screening must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on their first dosing day.
5. Subjects of childbearing potential must agree to use highly effective methods of contraception as defined in Section 5.3.1.

5.2.2 Exclusion Criteria, Crossover Period

Individuals who meet any of the following exclusion criteria are not to be enrolled in the crossover period.

1. Sézary syndrome or mycosis fungoides with B2 involvement, defined as a documented history of B2 and/or B2 staging at the Screening visit. B2 means T-cell clone in peripheral blood + one of the following at Screening:
    a. ≥ 1000/μL Sézary cells by direct examination OR
    b. ≥ 1000/μL CD4+ CD26- OR
    c. ≥ 1000/μL CD4+ CD7-
2. Current evidence of large cell transformation (LCT), defined as >25% of the lymphocytes at least 4 x the size of normal lymphocytes. Current evidence refers to LCT diagnosis from biopsy performed within 4 months prior to dosing in the crossover period. Subjects with a history of LCT but with a negative current biopsy (within 4 months) are eligible, provided there is no clinical indication for chemotherapy.
3. History of visceral involvement related to MF at Screening.
4. Unresolved toxicities from prior vorinostat treatment, defined as having not resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), grade 0 or 1.
5. Receipt of any of the following treatments:
    - Macrolide or tetracycline antibiotics within 28 days prior to Screening;
    - More than 3 short courses (≤ 7 days) of prednisone equivalent > 10 mg per day within 8 weeks prior to Screening; however, a stable regimen of systemic prednisone equivalent to ≤ 10 mg per day (or steroid equivalent) is permitted;
    - Any CTCL systemic therapy after completion of the randomization period and prior to Day 1 for the crossover period.
6. Positive test for blood (including trace) on urinalysis considered by the investigator to be consistent with undiagnosed clinically significant renal pathology requiring further investigation.
7. An active or uncontrolled infection defined as subjects who require systemic antibacterial, antiviral, or antifungal therapy within the last 7 days prior to Screening.

8. Clinically significant anemia (hemoglobin < 8 g/dL), neutropenia (absolute neutrophil count [ANC] < 1000/mm^3) or thrombocytopenia (platelets < 50,000/mm^3) at Screening.
9. Presence on ECG of QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 470 msec for females or > 480 msec for subjects with bundle branch block, based on a mean of the triplicate ECG measurements collected at Screening.
10. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or inability to communicate or cooperate fully with the Investigator.
11. Lactating or pregnant.
12. Major surgery within 4 weeks of the first dose of study treatment.
13. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
14. Clinically significant abnormalities in medical history, physical examination, or laboratory values that, in the opinion of the Investigator, would make the subject unsuitable for inclusion in the crossover period.
15. History of intolerance, or adverse or allergic reactions to oligonucleotide products and/or phosphate buffer solutions.

5.3 Lifestyle Guidelines

5.3.1 Contraception Guidelines

Female subjects must be either postmenopausal (absence of menses) for at least 1 year and have menopause confirmed by follicle-stimulating hormone (FSH) levels, or must be postmenopausal for at least 2 years (over 50 years old and absence of menses for 2 years, no confirmation by FSH required), or must be surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy from Screening up to and including 105 days after the last dose of cobomarsen or 180 days after the last dose of vorinostat, if of childbearing potential.

Males must agree to take appropriate precautions to avoid fathering a child from Screening up to and including 105 days after the last dose of study treatment and must consent to using an acceptable method of contraception such as a condom and a highly effective second method

(examples provided below), surgical sterilization (by one of the partners), postmenopausal partner (meeting the definition above), or abstinence.

The following methods have been determined to be highly effective (< 1% failure rate per year when used consistently and correctly) (Trussell 2004; Clinical Trial Facilitation Group 2014) and are permitted under this protocol for use by the subject and his/her partner:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments, when this is in line with the preferred and usual lifestyle of the subject;
- Oral, intravaginal, or transdermal combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation;
- Oral, injectable, or implanted progestogen-only hormonal contraception associated with inhibition of ovulation;
    - Note: Progestogen-only "mini-pills" are not considered highly effective methods of contraception for this protocol because inhibition of ovulation is not their primary mechanism of action.
- Intrauterine device (IUD);
- Intrauterine hormone-releasing system (IUS)
- Vasectomy or vasectomized partner, provided that the partner is the sole sexual partner of the female trial participant and that the vasectomized partner has received medical assessment of the surgical success;
- Bilateral oophorectomy with or without hysterectomy or tubal ligation at least 6 weeks prior to taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up levels of luteinizing hormone, FSH, and/or estradiol.
    - Female subjects who have undergone surgical sterilization by oophorectomy alone will have FSH levels assessed at Screening.

5.3.2 Exercise Guidelines

Subjects should not embark on a new strenuous exercise regimen during Screening and while on study treatment. Specifically, physical activities, such as strenuous, unusual or new type of

exercise, that can result in significant increases in plasma CK levels, should be avoided 48 hours prior to laboratory assessments, including Screening assessments.

5.4 Subject Discontinuation or Withdrawal from Study

5.4.1 Reasons for Subject Discontinuation or Withdrawal of Consent

Subjects may withdraw their consent to participate in the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a subject withdraws consent, the date and reason for consent withdrawal should be documented. The clinical site staff will also need to document from what portion of the study the subject is withdrawing consent:

1. Withdrawing from treatment, but will continue to be followed for safety and progression;
2. Withdrawing from treatment and all study procedures, but agrees to complete End of Treatment and 28 day post treatment follow-up visit;
3. Complete study withdrawal with no additional follow-up.

Subjects meeting any of the following criteria should discontinue study treatment:

- Unacceptable AE(s) or failure to tolerate study treatment (see Section 10.2);
- Prolonged dose delay (i.e., more than 4 missed consecutive doses of cobomarsen, or a dose interruption of > 14 consecutive days of vorinostat), due to an AE or clinically significant laboratory abnormality, or significant noncompliance with study treatment administration, unless judged by the Investigator and Sponsor Medical Monitor or designee to be in the best interest of the subject to continue treatment;
- Changes in the subject's condition or development of an intercurrent illness that renders the subject unsuitable for further study treatment in the judgment of the Investigator;
- Disease progression (see Section 4);
- Initiation of non-protocol CTCL treatment;
- Withdrawal of consent;
- Pregnancy;
- Subject is lost to follow-up;
- Discretion of the Investigator;

- Termination of the study by the Sponsor.

Subjects meeting any of the following criteria should discontinue follow-up for disease progression:

- Confirmed disease progression (see Section 4);
- Withdrawal of consent;
- Initiation of a subsequent CTCL treatment;
- Subject is lost to follow-up;
- Death.

5.4.2 Procedures for Subject Discontinuation or Withdrawal

Wherever possible, the tests and evaluations listed for the post-treatment evaluation should be carried out and an effort should be made to continue follow-up. The Sponsor should be notified of all study withdrawals through the designated electronic case report forms (eCRFs) in a timely manner.

Subjects who discontinue prematurely will not be replaced.

6 STUDY PRODUCTS

Throughout this protocol, "study treatment" refers to either cobomarsen or vorinostat.

6.1 Study Product(s) Management

6.1.1 Acquisition

Cobomarsen and vorinostat will be supplied by the Sponsor and provided to clinical study sites.

6.1.2 Formulation, Appearance, Packaging, and Labeling

The cobomarsen Drug Product is manufactured according to current Good Manufacturing Practice (cGMP) regulations for use in clinical trials. The cobomarsen Drug Product is supplied as a sterile concentrate for solution for infusion. The Drug Product is formulated in an isosmotic phosphate buffer, pH 7.4 ± 0.5, containing 141 mg/mL of the active moiety (equivalent to 150 mg/mL of the active pharmaceutical ingredient or sodium salt form). The Drug Product is packaged in sterile, single-dose, Type 1 glass vials with rubber stoppers and an aluminum flip-off overseal, each containing 1.2 mL of a clear to slightly yellow liquid formulation.

Vorinostat is available as 100 mg white, opaque, hard gelatin capsules for oral administration. The capsules have "568" over "100 mg" printed within a radial bar in black ink on the capsule body. Capsules are packaged in plastic bottles, each containing 120 capsules.

Study treatment will be labelled to comply with local labelling regulations.

6.1.3 Storage and Stability

The cobomarsen Drug Product should be stored at 2 to 8°C (36 to 46°F), protected from light.

Vorinostat capsules should be stored at 20 to 25°C (68 to 77°F) with excursions permitted between 15 to 30°C (59 to 86°F).

6.1.4 Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study treatment. All study treatment supplies and associated documentation will be reviewed and verified by the Clinical Research Associate (CRA). Unused material cannot be disposed of until approval is obtained from the CRA. The study site is responsible for the disposal and/or destruction of all unused study treatment supplies, according to the site's standard operating procedures. If the site cannot dispose of these materials, arrangements should be made between the site and Sponsor's representative for destruction or return of the unused study treatment supplies.

6.2 Dosage, Preparation and Administration of Study Products

6.2.1 Dose and Regimen, Randomized Period

As outlined in Section 4.3, the following study treatments will be administered according to randomized treatment assignment (cobomarsen or vorinostat):

- Cobomarsen will be administered by 2-hour intravenous infusion at a dose of 282 mg on Days 1, 3, 5, 8, and weekly thereafter;
- Vorinostat will be administered orally at a dose of 400 mg (four 100 mg capsules) once daily with food, at approximately the same time each day.
    - Subjects assigned to vorinostat with abnormal ALT/AST (> ULN) or bilirubin (> 1.0 × ULN) at Screening will start vorinostat dosing at 300 mg (three 100 mg capsules) once daily with food, at approximately the same time each day, per dosing guidelines.

6.2.2 Dose and Regimen, Crossover Period

- Cobomarsen will be administered by 2-hour intravenous infusion at a dose of 282 mg on Days 1, 3, 5, 8, and weekly thereafter

6.2.3 Method of Assignment to Treatment

During the randomized period, subjects will be randomized in the Interactive Web Response System (IWRS), in a 1:1 ratio, to receive either cobomarsen or vorinostat. In the crossover period, eligible subjects will be assigned open label cobomarsen through the IWRS.

6.2.4 Dose Preparation and Administration

Cobomarsen must be prepared in accordance with local pharmacy practices using aseptic technique. Complete details on the preparation and administration of study treatment are provided in a separate Pharmacy Manual.

Subjects receiving intravenous doses of cobomarsen will have the total dose of study treatment administered via an intravenous infusion of approximately 2 hours (± 15 minutes). The start time and end time of the infusion must be recorded.

The subject should be observed for 4 hours following the Day 1 cobomarsen administrations. During this observation, an intravenous line could remain to allow administration of intravenous drugs, if necessary. All supportive measures consistent with optimal subject care will be given throughout the study according to institution standards.

Subjects assigned to vorinostat will receive an adequate supply of study treatment to last until the next scheduled study visit.

6.2.5 Assessment of Treatment Adherence

All cobomarsen study treatments will be administered by qualified study personnel.

Oral doses of vorinostat will be self-administered and subjects will record dosing information in paper subject diaries.

7 STUDY PROCEDURES

The procedures and assessments that are outlined in this section will be performed at the time points specified by study visit in Section 8 (Randomized Period) and Section 9 (Crossover Period), and summarized in Appendix A (Schedule of Events (Screening, Randomized Period)),

Appendix B (On Treatment and Post-Treatment Follow-up – Cobomarsen Group), Appendix C (On Treatment and Post-Treatment Follow-up – Vorinostat Group), Appendix D (Screening, Crossover Period) and Appendix E (Crossover On Treatment and Post-Treatment Follow-up).

Written informed consent must be provided by each subject prior to the initiation of any study procedure or assessment that is not part of standard of care.

As part of the informed consent process, the investigational site personnel will review the study design with the subject and confirm the subject's willingness and ability to participate in the clinical study if they are randomized to receive either cobomarsen or vorinostat, or if they elect to screen for the crossover period.

7.1 Clinical Assessments

7.1.1 Medical History

Medical history will be recorded at Screening. Any ongoing conditions and signs and symptoms observed prior to informed consent should be recorded as medical history with the relevant NCI CTCAE grade. Any conditions and signs and symptoms occurring after the time of informed consent should be reported as AEs.

Documentation of historical MF diagnosis by biopsy will be collected. In addition, historical CD30 status will also be captured, if available.

7.1.2 CTCL Staging

At Screening, CTCL staging will be assessed and recorded.

In the randomized period, staging will be based on current screening assessments (mSWAT, CT scan and flow cytometry); historical compartment staging must not be used.

In the crossover period, staging will be based on mSWAT and flow cytometry performed during the crossover screening period and the most recent CT scan performed during the study.

7.1.3 Prior MF Treatments

Any prior therapy (topical, systemic, phototherapy or other) for the treatment of CTCL will be recorded at Screening, including dates of therapy and reason for discontinuation.

7.1.4 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be measured at Screening and at the time points indicated in Appendix B, Appendix C and Appendix E.

All vital sign measurements must be performed prior to every cobomarsen administration.

7.1.5 Physical Examination

A complete physical examination will be performed by an investigator or sub-investigator at Screening and on Day 1. At a minimum, the following body systems will be assessed: General Appearance, Dermatological, HEENT (head, eyes, ears, nose, and throat), Pulmonary, Cardiovascular, Gastrointestinal, Genito-Urinary, Musculoskeletal, Neurological and Lymphatic.

Brief symptom-directed physical examinations should be performed at the subsequent time points specified in Appendix B, Appendix C and Appendix E.

Body weight will be measured as part of the physical examination when indicated. Height will be measured only at Screening. Any treatment-emergent abnormal findings or worsening of a preexisting condition will be recorded as AEs.

Subjects randomized to cobomarsen should have all physical examinations, occurring on dosing days, performed prior to receiving study treatment.

7.1.6 ECOG Performance Status

Assessment of ECOG Performance Status (Table 2) will be performed at Screening.

ECOG Performance Status should be obtained on the scheduled visit day, even if study treatment is being held.

Table 2: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

7.1.7 Prior and Concomitant Medications

All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered within 30 days before the first administration of study treatment (Day 1) through the End of Treatment Visit will be recorded on the eCRF, using generic names when possible. Additionally, any concomitant medications taken for MF will be recorded throughout the study until confirmation of disease progression. All medications taken for pruritus indication will be captured on a separate eCRF page.

7.1.7.1 Drug-Drug Interaction, Contraindications and Precautions

Cobomarsen:

Cobomarsen was neither an inhibitor nor an inducer of cytochrome P450 enzymes in cultured human hepatocytes treated with the drug.

Cobomarsen is highly protein bound. The interaction with other drugs with high protein affinity is not known. Subjects receiving concomitant medications known to be highly protein bound should be carefully clinically monitored while being treated with cobomarsen, since free drug levels could increase. When applicable, concomitant drug levels should be monitored. A non-exhaustive list of some commonly used drugs known to be highly protein-bound in blood is provided in Table 3.

Table 3: Medications Known to be Highly Protein-Bound in Blood

Drug Class	Drug Name
Oral anticoagulants	• Warfarin
Oral antidiabetics	• glimepiride, glipizide, glyburide
Lipid lowering drugs	• gemfibrozil, statins
NSAIDs	• indomethacine, phenylbutazone, ibuprofen, naproxen, diflunisal, diclophenac
Loop diuretics	• furosemide
Antihypertensives	• diazoxide, losartan
Cardiovascular drugs	• amiodarone, prazosin, felodipine, nicardipine, digitoxin, ticlopidine
Antiinfectives	• ceftriaxone, nalidixic acid, ketoconazole, itraconazole, suramin, nelfinavir
Benzodiazepines	• diazepam, midazolam
Others	• montelukast, zafirlukast, entacapone, leflunomide

Source: aok.pte.hu/en/download/index/2736. Accessed 11 January 2019.

Similar to other oligonucleotide-based compounds, cobomarsen is metabolized by endo- and exonucleases in plasma and tissues and does not induce or inhibit cytochrome P450 (CYP) enzymes. Therefore, it is not expected that cobomarsen will have clinical interactions with co-medications cleared primarily by CYP-dependent metabolism.

Vorinostat:

Prescribing information, including risks of concomitant medications, can be found in the vorinostat package insert.

Vorinostat is predominantly metabolized by the liver; therefore, use vorinostat with caution in subjects with hepatic disease or impairment. Thrombocytopenia and anemia have been reported with vorinostat therapy. Monitor complete blood counts closely throughout the study.

Use vorinostat with caution in subjects with renal impairment.

Dosage reduction or therapy discontinuation may be necessary in subjects who develop hematologic toxicity. Severe thrombocytopenia has been reported with concomitant use of vorinostat and other HDAC inhibitors. Concomitant use of vorinostat with other HDAC inhibitors is prohibited per protocol (see Section 7.1.7.2). However, subjects with prior history of thromboembolic disease, including pulmonary embolism and deep vein thrombosis, should be monitored closely during vorinostat therapy.

Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) have been observed in patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants. Investigators should monitor PT and INR more frequently in subjects concurrently administered vorinostat and coumarin derivatives.

Pre-existing nausea and vomiting should be controlled prior to initiating vorinostat therapy. Gastrointestinal adverse effects including nausea, vomiting, and diarrhea have been reported during vorinostat therapy and may require antiemetic and antidiarrheal medication. Fluids and electrolytes should be replaced to prevent dehydration. Instruct subjects to drink at least 2 L/day of fluids for adequate hydration during vorinostat therapy. Severe gastrointestinal bleeding has been reported with concomitant use of vorinostat and other histone deacetylases inhibitors, such as valproic acid. Subjects with diabetes mellitus or glucose intolerance should be monitored closely during vorinostat therapy due to reports of hyperglycemia during treatment. Adjustment of diet and/or therapy for glucose control may be necessary.

Use vorinostat with caution in subjects with cardiac disease or other conditions that may increase the risk of QT prolongation including cardiac arrhythmias, heart failure, bradycardia, myocardial

infarction, hypertension, coronary artery disease, hypomagnesemia, hypokalemia, hypocalcemia, or in subjects receiving medications known to cause electrolyte imbalances. Subjects with a history of long QT syndrome and/or persistent hypokalemia should not be enrolled. Vorinostat should be used with caution with drugs known to induce QT interval prolongation. See Table 4 for a list of commonly used drugs known to induce QT interval prolongation. For complete and up to date information please visit the following website: https://crediblemeds.org/.

Table 4: Medications Known to Prolong QT Interval and/or Cause Torsades de Pointes

- Aclarubicin
- Amiodarone
- Anagrelide
- Arsenic trioxide
- Astemizole
- Azithromycin
- Bepridil
- Chloroquine
- Chlorpromazine
- Cilostazol
- Ciprofloxacin
- Cisapride
- Citalopram
- Clarithromycin
- Cocaine
- Disopyramide
- Dofetilide
- Domperidone
- Donepezil
- Dronedarone
- Droperidol
- Erythromycin
- Escitalopram
- Flecainide
- Fluconazole
- Gatifloxacin
- Grepafloxacin
- Halofantrine
- Haloperidol
- Ibogaine
- Ibutilide
- Levofloxacin
- Levomepromazine (methotrimeprazine)
- Levomethadyl acetate
- Levosulpiride
- Mesoridazine
- Methadone
- Moxifloxacin
- Ondansetron
- Oxaliplatin
- Papaverine HCl (Intracoronary)
- Pentamidine
- Pimozide
- Probucol
- Procainamide
- Propofol
- Quinidine
- Roxithromycin
- Sevoflurane
- Sotalol
- Sparfloxacin
- Sulpiride
- Sultopride
- Terfenadine
- Terlipressin
- Terodiline
- Thioridazine
- Vandetanib

Source: https://crediblemeds.org/ Accessed 12 November 2018.

7.1.7.2 Prohibited and Limited Use of Concomitant Medications

Topical and systemic treatment for CTCL will be prohibited during the study, except in exceptional circumstances as noted below.

Systemic Corticosteroids

In principle, initiation of systemic corticosteroid treatment or increase in corticosteroid dose for CTCL-related symptoms is prohibited during the study. Subjects receiving a stable dose of oral prednisone of ≤ 10 mg daily (or steroid equivalent) at Screening are permitted to continue any such regimen, although the investigator should attempt to taper off or to decrease the dose to the

lowest dosage tolerable while on study. In specific cases, and only after Medical Monitor approval, a transient systemic corticosteroid therapy course for symptoms related or unrelated to CTCL, limited to 7 days per course, and no more than one course per 60 days is allowed.

Topical Corticosteroids and other Oral/Topical Medications

Subjects that enter the study on a stable dose of medium or low potency topical corticosteroids for the treatment of pruritus may continue use at the same dose, although the investigator should attempt to taper off or decrease the use to the lowest dosage tolerable while on study.

Initiation of new and transient topical high potency steroid therapy should be avoided unless needed to treat an acute non-CTCL condition. In this case, and only with Medical Monitor approval, a short course (≤ 7 days) of high potency topical corticosteroid is allowed, and not more than one short course per 60 days will be allowed.

Initiation of new and transient topical, low or medium potency steroid therapy and/or oral antihistamines for pruritus is permitted, but should be limited to 7 days per course, and no more than one course per 30 days.

Any new and transient use of topical corticosteroids should be recorded as a new medication in the concomitant medication or pruritus medication eCRF (depending on the indication), including the specific corticosteroid name, potency, formulation (ointment, cream, gel or lotion), indication and start and stop date.

miRagen has evaluated topical corticosteroids potency used in all countries where SOLAR is being conducted. A comprehensive, but not exhaustive list of low, medium and high potency topical corticosteroid lotions, ointments, gels, solutions, foams and creams, as per miRagen's determination, is provided in Appendix I. Though the determination of potency in few cases might slightly diverge from its clinical use in some countries, this list should be used to guide inclusion and exclusion criteria, prohibited medications, as well as exceptional new and transient use of topical corticosteroids during a subject's participation in this trial.

Use of topical emollients, moisturizers, camphor/menthol or pramoxine formulations (or other equivalent institutional standard of care therapies) should be limited where possible, but if used, should be recorded in the concomitant medication eCRF. Any use of other methods (herbal supplements, ice baths, etc.) to treat pruritus should be avoided, but if used, should likewise be recorded in the concomitant medication eCRF.

Nonsteroidal Anti-pruritic Medications

The use of new prophylactic systemic anti-pruritic agents is prohibited.

The use of new daily symptomatic systemic anti-pruritic agents is discouraged. **Under exceptional circumstances, and only after Medical Monitor approval**, these medications could be allowed. These medications include, but are not limited to doxepin, gabapentin, aprepitrant, mirtazapine, selective serotonin reuptake inhibitors, or naltrexone.

Short and intermittent courses of symptomatic systemic anti-pruritic agents should be avoided (with the exception of antihistamines, as noted above) including but not limited to doxepin, gabapentin, aprepitrant, mirtazapine, selective serotonin reuptake inhibitors, or naltrexone. However, in exceptional circumstances and with prior Medical Monitor approval, a short course (e.g. ≤ 7 days) of a new systemic anti-pruritic agent may be allowed. Any medications used to treat symptomatic pruritus should be recorded on the pruritus concomitant medication eCRF.

7.2 Safety Assessments

7.2.1 Adverse Events

AEs will be assessed at each study visit (in person or by telephone for telephone visits) by direct observation and subject interviews. The severity of AEs will be evaluated using the NCI CTCAE version 5.0. All AEs that occur from the time of informed consent up to and including 60 days after the last dose of study treatment, regardless of causality to study treatment, must be reported. Any treatment related AE reported by a subject during the clinical study, even if it occurs later than 60 days after the last dose of study treatment, should be reported in the eCRF.

7.2.2 Clinical Laboratory Assessments

Blood and urine samples will be collected for the tests listed in Table 5 at Screening and at the time points specified in Appendix B, Appendix C and Appendix E. Clinical laboratory assessments do not need to be performed on Day 1 if Screening laboratory assessments were performed within 3 days prior to Day 1 and subjects met inclusion/exclusion criteria based on Screening results.

Screening for HIV, hepatitis B, and hepatitis C, will be performed at Screening in the randomized period.

Female subjects who are not surgically sterile, must either have absence of menses for 1 year and have menopause confirmed by FSH levels at Screening, or must be postmenopausal for at least 2 years (over 50 years old and absence of menses for 2 years; no confirmation by FSH required).

Complement (C5a, Bb) testing will be performed on Day 1 and Day 2 only.

A central laboratory will be used for analysis of all blood and urine specimens collected, except for flow cytometry and a concomitant CBC used for calculation of absolute lymphocyte count, which will be performed by the site's local laboratory. At Screening, the central laboratory results will be used by the Investigator to determine the subject's eligibility for the study. Local laboratory results will not be used for eligibility determination, except for flow cytometry and the concomitant CBC used for calculation of absolute lymphocyte count. However, after Screening, results from the site's local laboratory may be utilized if needed for timely review by the Investigator (if central laboratory results are not available). Local site laboratory results obtained during the study will not be captured in the eCRF unless the Investigator determines they are needed to clarify why a treatment decision was made or if an AE was recorded based on the local results.

Additional clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion.

Site-specific handling instructions on the collection of blood and urine samples and their shipment to the central laboratory will be provided in the Laboratory Manual.

Table 5: Summary of Clinical Laboratory Tests

Hematology [a]	Chemistry	Urinalysis	Coagulation	Others
Abs Basophils	Albumin	Bilirubin	aPTT	TSH
Abs Eosinophils	Alkaline phosphatase	Blood	INR	
Abs Granulocytes	ALT	Color	PT	Complement (C5a, Bb)
Abs Lymphocytes	AST	Glucose, Urine		
Abs Monocytes	Bicarbonate	Ketones		For WOCBP:
Abs Neutrophils	Calcium	Leukocytes		Serum/urine pregnancy test
ANC	Chloride	Nitrite		
Basophils	Cholesterol	pH		At Screening in the Randomized Period only:
Eosinophils	CK[b]	Protein, Urine		
Hematocrit	C-Reactive Protein	Specific gravity		HIV
Hemoglobin	Creatinine			Hepatitis B
Lymphocytes	Creatinine clearance (calculated)	Urine Chemistry		Hepatitis C
Mean Corpuscular Hemoglobin	Bilirubin (total and direct)	Myoglobin, Urine		For confirmation of menopause only:
Mean Corpuscular Hemoglobin Concentration	Glomerular Filtration Rate	Protein, Urine		FSH
Mean Corpuscular Volume	GGT	Microalbuminuria		
Mean Platelet Volume	GLDH[c]	Creatinine, Urine (Enzymatic)		
Monocytes	Glucose	Protein/ Creatinine Ratio, Urine		
Neutrophils	LDH			
Platelets	Magnesium			
RBCs	Phosphorus			
WBCs	Potassium			
	Sodium			
	Total protein			
	Triglyceride			
	Urea (BUN)			
	Uric acid			

Abbreviations: Abs = Absolute; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; GGT = gamma-glutamyl transferase; GLDH = glutamate dehydrogenase; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; TSH = thyroids-stimulating hormone; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Hematology will include CBCs performed at the central lab and locally when performed concurrently with the flow cytometry

[b] For grade 2 or 3 total CK: measure CK, CK isoenzymes weekly for 3 weeks and if total CK remains ≤ the grade which triggered increased monitoring, continue to assess CK, CK isoenzymes along with regularly scheduled clinical chemistry assessments.

[c] GLDH will be done as a reflex test if a grade 3 or 4 ALT or AST is observed.

7.2.2.1 Pregnancy Test

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and negative urine pregnancy tests on Day 1 and at the subsequent time points specified in Appendix B, Appendix C and Appendix E.

Female subjects of nonchildbearing potential (see definitions in Section 5.3) do not require pregnancy tests.

Female subjects who have undergone surgical sterilization by oophorectomy alone will have FSH levels assessed at Screening.

All urine collections for pregnancy tests occurring on dosing days must be performed and assessed prior to study treatment administration. A positive pregnancy test will result in immediate discontinuation of study treatment. All pregnancies in study subjects or in female partners of male study subjects will be followed through to outcome and will be reported on the appropriate eCRFs.

7.2.3 Electrocardiograms

A triplicate 12-lead ECG with lead II rhythm strip (3 serial ECGs conducted within approximately 5-10 minutes total time) will be performed at Screening. The mean of the triplicate ECG measurement performed at Screening will be used to determine eligibility. Single 12-lead ECGs with lead II rhythm strip will be performed predose on Day 1 and during the active treatment and follow-up at the time points specified in Appendix B, Appendix C and Appendix E. Prior to performing the 12-lead ECG, subjects should rest in the supine position for at least 5 minutes.

Electrocardiogram parameters to be evaluated include the RR, QT, QRS, and PR intervals. In addition, Fridericia's formula should be used to calculate the QT interval corrected for heart rate (QTcF). Abnormal ECG measurements will be recorded as AEs only if they are considered to be clinically significant by the Investigator.

Post randomization 12-lead ECGs with non-clinically significant QTcF prolongation should be repeated in triplicate at the next dose visit with a lead II rhythm strip. Non-clinically significant QTcF prolongation is defined as a QTcF > 450 msec for males or > 470 msec for females or > 480 msec for subjects with bundle branch block but considered by the investigator to be non-clinically significant.

For subjects on cobomarsen, the repeat triplicate 12-lead ECG with a lead II rhythm strip should be performed after the end of the infusion (as soon as possible and ideally within

the 30 minutes following the infusion). Subjects should also have a PK sample obtained 5 minutes (± 5 minutes) before the end of infusion.

For subjects on vorinostat, the repeat triplicate 12-lead ECG with a lead II rhythm strip should be performed at the next scheduled visit.

If the QTc prolongation is considered clinically significant by the investigator, the subject should have a repeat triplicate 12-lead ECG immediately for confirmation, and if confirmed, the event should be entered as an AE. Please refer to Section 10.2.1 (Cobomarsen Interruptions or Permanent Discontinuation - Other Grade 3 and 4 Adverse Events) and Section 10.2.2 (Vorinostat Dose Modifications, Interruptions or Permanent Discontinuations) for additional instructions on dose delays or stopping rules due to clinically significant adverse events. If further dosing with study treatment is deemed appropriate, triplicate 12-lead ECGs with a lead II rhythm strip should be repeated as described above for non-clinically significant QTcF prolongation.

The sponsor may collect ECGs for central review during the course of the study.

7.3 Pharmacokinetic Sampling

Plasma PK samples will be collected at the pre- and postdose time points specified in Appendix B and Appendix E to measure cobomarsen concentrations and metabolites.

Pharmacokinetic samples will only be collected from subjects receiving cobomarsen in the randomized and crossover periods.

7.4 Pharmacodynamic and Anti-Drug Antibody Sampling

7.4.1 Blood Sample Collection

Serum samples for PD biomarkers will be collected predose on Day 1 and on study days specified in Appendix B and Appendix E to investigate the effects of cobomarsen on miRNAs, miR-155-5p target mRNA and/or protein levels and/or downstream indirect targets. Serum will also be collected to assess if anti-drug antibodies (ADA) are being generated over the course of cobomarsen treatment. Pharmacodynamic samples will only be collected from subjects receiving cobomarsen in the randomized and crossover periods.

7.5 Efficacy Assessments

7.5.1 Response and Disease Progression Evaluations and mSWAT

Response to study treatment and disease progression will be evaluated using skin response criteria for MF (Olsen et al. 2011; see Appendix F).

mSWAT evaluations should be performed per the visit schedule (see Appendix B, Appendix C, Appendix D and Appendix E) whether the subject is receiving study treatment or has discontinued treatment, until one of the following (whichever occurs first): disease progression in skin (confirmed by repeat measurement 28 days [± 3 days] after the first determination of progression), lymph nodes, blood or viscera, withdrawal of consent, initiation of subsequent MF treatment, lost to follow-up, or death.

mSWAT evaluations may also be performed at any time the Investigator suspects there is clinical evidence of disease progression.

In the event the investigator declares disease progression in other compartments, based on assessments (flow cytometry or CT scan) performed at his/her own discretion, documentation of progression by standard Olsen criteria (Appendix F) should be provided.

7.5.1.1 mSWAT Evaluations (Skin Component)

mSWAT (see Appendix F) scoring will performed at Screening and before dosing at the time points outlined in Appendix B, Appendix C and Appendix E.

Every effort should be made to have the same mSWAT evaluator conduct all assessments of mSWAT for a subject at Screening and throughout the study to ensure consistency.

If the primary evaluator is not available during the visit window, the following should occur, in order of preference:

1. **The visit could be postponed or performed earlier by the primary evaluator.**
2. **The visit could be performed by another locally trained evaluator. If a different evaluator conducts an mSWAT a review of the previous mSWAT should occur prior to the evaluation of the current mSWAT. If the new assessment impacts a response or progression there should be clear documentation (e.g. photography) to support the results.**

7.5.1.2 Process to Determine Skin Response and Confirmation

Once the Investigator believes that the mSWAT evaluation has shown an objective response for 4 consecutive months (i.e., a PR or CR as assessed per mSWAT criteria, without loss of response, for 4 consecutive months; see Table F2 in Appendix F), the Investigator must schedule the subject for a visit within 28 days (± 3 days) to perform a confirmatory mSWAT.

Subjects who have a PR or CR cannot be downgraded to stable disease. Subjects who have a PR or CR can only have their response downgraded if they meet the criteria of loss of response (progression) see Table F2 in Appendix F.

Of note: An unconfirmed progression at any time during the study will not preclude the Investigator from assessing a future response (CR or PR).

7.5.1.3 Process to Determine Disease Progression

As stated in Section 4, disease progression is defined as either:

a. Confirmed progression in skin

b. Clinical progression in in other compartments, documented by assessments (flow cytometry and/or CT scan) completed per investigator discretion

c. Partial or complete skin response followed by a confirmed loss of skin response as defined by an increase of mSWAT of greater than the sum of nadir plus 50% baseline score.

Progressions based on mSWAT will be confirmed by repeat measurement 28 days (± 3 days) after the first determination of progression. If the subject is currently on study treatment, the study treatment should not be discontinued until confirmation of disease progression.

An unconfirmed progression would not preclude future responses (CR or PR).

Upon reassessment, if the original findings have not changed, and there is no alternate clinical explanation or etiology for the suspected progression, then disease progression should be considered confirmed and the date of disease progression should be reported as the date that it was first suspected.

Subjects who meet disease progression criteria in skin, or other compartment assessed per investigator discretion, should be discontinued from study treatment due to disease progression.

7.6 Screening Staging Assessments

7.6.1 mSWAT Assessments

See Section 7.5.1.1.

7.6.2 Radiological Imaging (Lymph Nodes and Viscera Components)

Radiological imaging will be performed at Screening in the randomized period.

While CT scans are the preferred method for radiological imaging, other modalities (e.g., MRI) can be used if needed. PET scan should only be used to confirm an abnormal lymph node found by other modalities, if a nodal biopsy is not possible. Nodal biopsy is the preferred method for disease staging assessment, if possible.

Radiological imaging will be performed locally (see Appendix A and Appendix D. At Screening, a CT/MRI scan of the neck, chest, abdomen and pelvis (at minimum) must be performed. The preferred radiologic technique is CT with intravenous contrast. If a subject is known to have a contraindication to CT contrast media or develops a contraindication during the clinical study, a non-contrast CT should be performed. Scans will be reviewed by both the local site staff and by the blinded central imaging laboratory during screening in the randomized period. A separate Imaging Manual will detail the collection, transfer and processing of the images to the central imaging laboratory. The blinded independent review of scans for screening in the randomized period will be performed per the Imaging Charter.

7.6.3 Flow Cytometry (Blood Component)

Whole blood will be collected and analyzed by flow cytometry (including a concomitant CBC used for calculation of absolute lymphocyte count) assessments performed by the site's local laboratory at Screening as specified in Appendix A and Appendix D to evaluate the T-cell subpopulations to determine the extent of tumor cell blood involvement for eligibility assessment for the randomized and crossover periods of the study.

The following flow cytometry markers will be used by the site's local laboratory to determine eligibility and for CTCL staging at Screening:

Antibodies to CD3, CD4, CD8, CD26, CD45 and CD7

8 STUDY SCHEDULE (RANDOMIZED PERIOD)

Before recruitment of subjects into the study, written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent and any additional subject information must be obtained.

The required visits for the clinical study are listed below. The investigator can bring the subject into the clinic for an unscheduled visit, at any time.

8.1 Screening for the Randomized Period (Day -28 to Day -1)

All Screening procedures to determine eligibility must be performed within the specific time windows. Eligibility is determined by results of the Screening assessments performed prior to randomization. Disease staging and eligibility will be confirmed by the Medical Monitor prior to randomization (24-48 hours should be allowed for Medical Monitor review).

Subjects may be rescreened once at the discretion of the Investigator (i.e., if a subject does not meet the Inclusion/Exclusion criteria during the first Screening assessments). Individual Screening assessments may be repeated, if the subject is still within the 28-day Screening window. If a subject is outside of the 28-day Screening window, then the subject must be reconsented and all Screening procedures should be repeated. If an assessment is repeated, the result obtained closest to randomization should be used for eligibility.

Screening may last up to 28 days from the time the first study screening procedure is completed.

During Screening, the IWRS will assign a unique subject identification number to each subject who signs informed consent for the study. Once a subject is in Screening or is randomized into the study, s/he will only be identified by the assigned identification number throughout the study. Subjects who reconsent and rescreen per the procedure described above will receive a new subject identification number.

The Investigator or designee is responsible for verifying that a subject is eligible before initiating the randomization. Eligibility must also be confirmed by the Medical Monitor, prior to randomization. Subjects must be treated within 3 working days of the date of randomization.

Prior to performing study related procedures:

Obtain informed consent of potential subject verified by written signature on an ICF.

From Days -28 to -3, the following evaluations will occur:

- Register the subject in the IWRS.

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform MF disease evaluation using the mSWAT (see Appendix F).
- Record medical history.
- Record prior and concomitant medications administered from 30 days prior to the first dose of study treatment.
- Record all prior MF treatments.
- Record ECOG performance status.
- Perform a complete physical examination (including documentation of height and weight).
- Perform a triplicate 12-lead ECG (3 serial ECGs conducted within approximately 5-10 minutes total time).
- Perform CT/MRI scan of neck, chest, abdomen and pelvis (at minimum). Must be performed within 28 days ± 7 days prior to randomization.
- Collect blood for the following central laboratory analysis:
  - Screening for HIV, Hepatitis B, and Hepatitis C;
  - Confirmation of menopause by FSH (when required, see Section 5.3);
  - Serum pregnancy test (for females of childbearing potential);
  - Hematology;
  - Clinical chemistry;
  - TSH;
  - Coagulation.
- Collect blood for flow cytometry and a concomitant CBC (performed locally; panels must include antibodies to CD3, CD4, CD8, CD26, CD45 and CD7).
- Collect urine for central laboratory analysis of urinalysis (with microscopy).
- Review eligibility of medical history and laboratory measurements according to inclusion/exclusion criteria.
- Review and record AEs.

From Days -3 to -1, the following evaluations will occur:

- Confirm eligibility of medical history and laboratory measurements according to inclusion/exclusion criteria.
- Confirm CTCL staging based on Screening assessments (see Appendix H).
- Re-review and record AEs.
- Enter all Screening data in the eCRF and initiate Medical Monitor review in the IWRS (Allow 24-48 for Medical Monitor review).
- After Medical Monitor approval, determine randomized treatment assignment using the IWRS.

Note: Subjects must receive the first dose of study medication within 3 working days of randomization.

8.2 Randomized Period

Subjects will be monitored and treated in the outpatient setting. After all dosing and study procedures are completed at each study visit, subjects will return home until the next visit.

8.2.1 Day 1 (First Day of Study Treatment)

- Perform CTCL disease evaluation using the mSWAT (predose) (see Appendix F).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a complete physical examination (including documentation of weight). May be performed within 2 days prior to the Day 1 visit.
- Collect blood for the following:
    - Complement C5a, Bb testing (cobomarsen predose and within the 10 minutes before the end of the infusion) (vorinostat predose and 2 hours post dose);
    - Hematology (predose);
    - Clinical chemistry (predose);
    - TSH (predose);
    - Coagulation (predose and at 3 hours [± 10 minutes] postdose);
    - Cobomarsen group only: PD and ADA (predose);

- Cobomarsen group only: PK (pre-dose, 60 ± 5 minutes after the start of the infusion, 5 ± 5 minutes before the end of the infusion, and 4 hours [± 10 minutes] after the end of the infusion).

- Collect urine for the following:
  - Urinalysis (predose; only if Screening measurement was performed > 3 days before Day 1);
  - Pregnancy test (predose, for females of childbearing potential).
- Perform a single 12-lead ECG
  - Cobomarsen group only: Predose and as soon as possible postdose, ideally within 30 minutes of the end of infusion.
- Vorinostat group only: Predose and 1 ± 0.5 hours postdose.
- IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion and keep the subject in the clinic for 4 hours for observation.
- Vorinostat group only: Administer first dose in the clinic with food following collection of laboratory samples and keep the subject in the clinic for 4 hours for observation.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only).
- Review and record AEs and concomitant medications.

8.2.2 Day 2

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Collect blood for the following:
  - Complement C5a, Bb testing (24 ± 4 hours) (predose for vorinostat);
  - Coagulation (predose for vorinostat);
  - Cobomarsen group only: PK (24 ± 4 hours after Day 1 dosing).
- Vorinostat group only: Administer the dose in the clinic with food following collection of laboratory samples.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only),

- Review and record AEs and concomitant medications.

8.2.3 Day 3 (+ 1 Day)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Cobomarsen group only: PK (single predose sample).
- Collect urine for urinalysis (predose).
- Cobomarsen group only: IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Administer the dose in the clinic with food following collection of laboratory samples.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only)
- Review and record AEs and concomitant medications.

8.2.4 Day 5 (± 1 Day)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Cobomarsen group only: PK (single predose sample).
- Cobomarsen group only: IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Confirm that subject has taken daily dose in the morning with food and recorded it in their diary
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only)
- Review and record AEs and concomitant medications.

8.2.5 Day 8 (± 1 Day)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Coagulation (predose);
  - Cobomarsen group only: PK (predose, and 5 ± 5 minutes before the end of the infusion).
- Collect urine for urinalysis (predose).
- Cobomarsen group only: IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Administer the dose in the clinic with food following collection of laboratory samples.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only)
- Review and record AEs and concomitant medications.

8.2.6 Day 15 (± 1 Day)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Cobomarsen group only: PK (predose);
  - Cobomarsen group only: PD and ADA (predose).

- Collect urine for urinalysis (predose).
- Cobomarsen group only: IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Administer the dose in the clinic with food following collection of laboratory samples.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only)
- Review and record AEs and concomitant medications.

8.2.7 Day 22 (± 2 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Cobomarsen group only: IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Confirm that subject has taken daily dose in the morning with food and recorded it in their diary
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only)
- Review and record AEs and concomitant medications.

8.2.8 Day 29 (± 3 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform CTCL disease evaluation using the mSWAT (predose) (see Appendix F).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Coagulation (predose);

  - Cobomarsen group only: PD and ADA (predose);
  - Cobomarsen group only: PK (pre-dose, 60 ± 5 minutes after the start of the infusion, 5 ± 5 minutes before the end of the infusion, and 4 hours [± 10 minutes] after the end of the infusion).
- Collect urine for the following:
  - Urinalysis (predose);
  - Pregnancy test (for females of childbearing potential).
- Perform a single 12-lead ECG
  - Cobomarsen group only: Predose and as soon as possible postdose, ideally within 30 minutes of the end of infusion.
  - Vorinostat group only: Predose and 1 ± 0.5 hours postdose
- IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Administer the dose in the clinic with food following collection of laboratory samples.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only).
- Review and record AEs and concomitant medications.

8.2.9 Weekly Assessments Starting at Week 6 (± 3 Days)

Starting at Week 6, the following assessments are required to be done weekly for subjects in both treatment groups. The weekly study visits for the vorinostat group can be conducted via telephone (except for Week 7, see Section 8.2.10 below), unless the investigator feels it is in the best interest of the subject to visit the clinic.

- Cobomarsen group only: Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Cobomarsen group only: IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.

- Vorinostat group only: Confirm that subject has taken daily dose in the morning with food and recorded it in their diary.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only).
- Review and record AEs and concomitant medications.

8.2.10 Week 7 Visit (± 3 Days) (for Vorinostat Subjects only)

- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - Coagulation (predose);
- Administer the dose in the clinic with food following collection of laboratory samples.

8.2.11 Every-4-Week Assessments from Weeks 9 through 81, then Every-8-Week Assessments Thereafter (± 3 Days)

NOTE: In addition to the weekly assessments listed above, the following additional assessments are required to be done every 4 weeks from Week 9 through Week 81 and then every 8 weeks thereafter, for subjects in both treatment groups:

- Perform CTCL disease evaluation using the mSWAT (predose) (see Appendix F).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Cobomarsen group only: PD and ADA;
  - Cobomarsen group only: PK (predose, and 5 ± 5 minutes before the end of the infusion through Week 25. Predose only from Weeks 29 through 81 and every 8 weeks thereafter, and at the end of treatment visit).

- Collect urine for the following:
  - Urinalysis (predose);
  - Pregnancy test (performed every 4 weeks while on study treatment), for females of childbearing potential).
- Perform a single 12-lead ECG (predose).
- IWRS Transaction (Study Treatment Dispensation).
- Cobomarsen group only: Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Vorinostat group only: Administer the dose in the clinic with food following collection of laboratory samples.
- Instruct subjects to record daily dosing in the provided diary (vorinostat group only).
- Review and record AEs and concomitant medications.

8.3 Post-treatment

The following are the definitions for post-treatment visits in this study:

- **End of Treatment:** Time at which the subject is permanently discontinued from study treatment for any reason.
  - The End of Treatment Visit should be performed as soon as possible but ≤ 14 days after the last dose of study treatment. See Section 8.4 for End of Treatment visit requirements.
- **Follow-up:** The subject has completed study treatment but remains on study and is being followed for response and/or progression.
  - Subjects who had an ongoing response or stable disease at the time that they discontinued study treatment must continue to be followed for response and/or disease progression in the Follow-up Period. See Section 8.5 and 8.6 for the follow-up visit frequency and requirements.
- **End of the Study**: The subject has completed all required follow-up on study and is no longer being followed for response or disease progression, in the study period.
  - If a subject withdraws consent for further follow-up at any time on study, the End of Study date is the date that consent is withdrawn.

8.4 End of Treatment Visit

At the time of study treatment discontinuation, the End of Treatment Visit should be completed for all subjects after the last dose of study treatment, and every effort should be made to perform the procedures listed below. This visit should take place as soon as possible and ≤ 14 days after the last dose of study treatment. The date and reason for stopping the study treatment will be reported. The End of Treatment visit is not considered as the end of the study. All subjects will enter the Follow-up unless they have withdrawn their consent to do so.

- Perform CTCL disease evaluation using the mSWAT (see Appendix F).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - TSH;
  - Cobomarsen group only: PD and ADA
  - Cobomarsen group only: PK.
- Collect urine for the following:
  - Urinalysis;
  - Pregnancy test (for females of childbearing potential).
- Perform a single 12-lead ECG.
- IWRS Transaction (Discontinue the Subject in the System).
- Review and record AEs and concomitant medications.

8.5 Long-term Follow-up for Subjects Who Have Not Progressed at the Time of End of Treatment Visit

After the End of Treatment Visit, subjects who did not progress on study will be followed until progression (confirmed progression in skin, confirmed loss of response in skin or clinical progression in lymph nodes, blood or viscera assessed per investigator discretion), withdrawal of

consent, initiation of subsequent MF treatment, loss to follow-up, or death, and the subject's final disposition is documented and reviewed by the Sponsor study team.

8.5.1 Every-4-Week Assessment through Week 81, then Every-8-Week Assessments Thereafter (± 3 Days)

- Perform CTCL disease evaluation using the mSWAT (see Appendix F).
- Review and record AEs and concomitant medications.

8.6 Follow-up Visit 28 ± 5 days after the End of Treatment or Early Termination

For subjects who choose not to participate in the crossover period of the study (or delay the start of the crossover period by > 28 days) or who discontinue cobomarsen treatment, the following assessments will be performed 28 ± 5 days after the End of Treatment Visit (assuming the subject has not withdrawn consent).

- Perform CTCL disease evaluation using the mSWAT (does not need to be repeated if disease progression is already confirmed) (see Appendix F).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - TSH;
  - Coagulation;
  - Cobomarsen group only: PD and ADA.
  - Cobomarsen group only: PK.
- Collect urine for the following:
  - Urinalysis;
  - Pregnancy test (for females of childbearing potential).
- Perform a single 12-lead ECG.
- Review and record AEs and concomitant medications.

9 CROSSOVER PERIOD

9.1 Crossover Period Design

After completing the randomized period, subjects that have confirmed skin disease progression on the vorinostat arm can be assessed for eligibility for the crossover period. Eligible subjects may elect to enter this optional crossover period and must have signed a study informed consent form (corresponding to the current version of the SOLAR protocol) to proceed. Every effort will be made to perform final safety and disease assessments for subjects who withdraw from the study early.

Potential subjects will need to complete the crossover screening activities and meet the entry criteria (see Section 5.2) prior to enrollment into the crossover period.

Subjects in the randomized period of the study who withdrew consent **without confirmation of skin disease progression** are not eligible to enroll in this period. In addition, subjects who received any subsequent systemic therapy for MF following confirmed disease progression in the randomized period are not eligible for the crossover period.

Study procedures completed at the End of Treatment visit in the randomized period may be used for screening assessments in the crossover period, depending on the timing of the assessments. Subjects who initiate Screening in the crossover period > 28 days after completing the randomized period will need to complete all of the crossover Screening procedures.

Subjects will undergo Screening lasting up to 28 days from the time of the first screening procedure, followed by active treatment and follow-up for response and disease progression.

Subjects who are currently on active treatment in the **PRISM Study (MRG106-11-203)** may enter the crossover period of this protocol, once the site has received necessary IRB/IEC and regulatory approvals for the current version of the SOLAR protocol. In this case, site personnel will ensure the subject has provided written informed consent for the SOLAR crossover period. The subject will not need to be re-evaluated for the entry criteria for SOLAR crossover period and should enter the study at the next scheduled nominal study visit following the last study visit completed in the PRISM study.

9.2 Crossover Study Schedule

Before recruitment of subjects into the crossover period, written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent and any additional subject information must be obtained.

The required visits for the crossover period are listed below. The investigator can bring the subject into the clinic for an unscheduled visit at any time.

9.2.1 Crossover Screening Period (Day -28 to Day -1)

All Screening procedures to determine eligibility must be performed within the specific time windows. Eligibility is determined by results of the assessments performed prior to enrollment. Disease staging and eligibility will be confirmed by the Medical Monitor prior to enrollment (24-48 hours should be allowed for Medical Monitor review).

Subjects may be rescreened once at the discretion of the Investigator (i.e., if a subject does not meet the Inclusion/Exclusion criteria during the first Screening assessments). Individual Screening assessments may be repeated, if the subject is still within the 28-day Screening window. If a subject is outside of the 28-day Screening window, then the subject must be reconsented and all Screening procedures should be repeated. If an assessment is repeated, the result obtained closest to enrollment should be used for eligibility.

Screening may last up to 28 days from the time the first study screening procedure is completed.

During Screening, the IWRS will assign a unique subject identification number to each subject who signs informed consent for the study. Once a subject is in Screening or is enrolled into the study, s/he will only be identified by the assigned identification number throughout the crossover period.

The Investigator or designee is responsible for verifying that a subject is eligible before initiating the enrollment. Eligibility must also be confirmed by the Medical Monitor, prior to enrollment. Subjects must be treated within 3 working days of the date of enrollment.

Prior to performing study related procedures:

- Verify informed consent (including crossover procedures) of potential subject by written signature on an ICF.

From Days -28 to -3, the following evaluations will occur:

- Register the subject in the IWRS.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature) (if not obtained within 14 days prior to Day 1).
- Perform MF disease evaluation using the mSWAT (if not done within 28 days prior to Day 1) (see Appendix F).

- Record prior and concomitant medications administered from 30 days prior to the first dose of study treatment.
- Record any new MF treatments following discontinuation of vorinostat in the randomized period.
- Record ECOG performance status.
- Perform a complete physical examination (including documentation of height and weight) (if not done within 14 days prior to Day 1)
- Perform a triplicate 12-lead ECG (if not done within 14 days of Day 1).
- Collect blood for the following central laboratory analysis (if not done within 14 days of Day 1):
    - FSH (for females who are not surgically sterile as confirmation of menopause for females who last menstrual cycle was within the last year)
    - Serum pregnancy test (for females of childbearing potential);
    - Hematology;
    - Clinical chemistry;
    - TSH;
    - Coagulation.
- Collect blood for flow cytometry and a concomitant CBC (performed locally; panels must include antibodies to CD3, CD4, CD8, CD26, CD45 and CD7) (if not done within 28 days of Day 1).
- Collect urine for central laboratory analysis of urinalysis (with microscopy) (if not done within 14 days of Day 1).
- Review eligibility of medical history and laboratory measurements according to inclusion/exclusion criteria.
- Review and record AEs.

From Days -3 to -1, the following evaluations will occur:

- Confirm eligibility of medical history and laboratory measurements according to inclusion/exclusion criteria.
- Re-review and record AEs.

- Enter all Screening data in the eCRF and initiate Medical Monitor review in the IWRS (allow 24-48 for Medical Monitor review).

9.2.2 Crossover Active Treatment

Subjects will be monitored and treated in the outpatient setting. After all dosing and study procedures are completed at each study visit, subjects will return home until the next visit.

9.2.2.1 Day 1 (First Day of Study Treatment)

- Perform CTCL disease evaluation using the mSWAT (predose) (see Appendix F).
- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a complete physical examination (including documentation of weight). This examination may be performed within 2 days prior to the Day 1 visit.
- Collect blood for the following:
  - Complement C5a, Bb testing (predose and within the 10 minutes before the end of the infusion);
  - Hematology (predose; only if Screening measurement was performed > 3 days before Day 1);
  - Clinical chemistry (predose; only if Screening measurement was performed > 3 days before Day 1);
  - TSH (predose; only if Screening measurement was performed > 3 days before Day 1);
  - Coagulation (predose and at 3 hours [± 10 minutes] postdose);
  - PD and ADA (predose);
  - PK (predose, and 5 ± 5 minutes before the end of the infusion).
- Collect urine for the following:
  - Urinalysis (predose; only if Screening measurement was performed > 3 days before Day 1);
  - Pregnancy test (predose, for females of childbearing potential).

- Perform a single 12-lead ECG (predose and as soon as possible postdose, ideally within 30 minutes of the end of infusion).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion. Monitor subject in the clinic for safety for a minimum of 4 hours postdose.
- Review and record AEs and concomitant medications.

9.2.2.2 Day 2

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Collect blood for the following:
  - Complement C5a, Bb testing (24 ± 4 hours after Day 1 dosing);
  - Coagulation;
- Review and record AEs and concomitant medications.

9.2.2.3 Day 3 (+ 1 Day)

- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
- Collect urine for urinalysis (predose).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.4 Day 5 (± 1 Day)

- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.5 Day 8 (± 1 Day)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Coagulation (predose);
- Collect urine for urinalysis (predose).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.6 Day 15 (± 1 Day)

- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);

- TSH (predose);
- PD and ADA (predose).

- Collect urine for urinalysis (predose).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.7 Day 22 (± 2 Days)

- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.8 Day 29 (± 3 Days)

- Perform CTCL disease evaluation using the mSWAT (predose) (see Appendix F).
- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);
  - TSH (predose);
  - Coagulation (predose);
  - PD and ADA (predose);
  - PK (predose, and 5 ± 5 minutes before the end of the infusion).

- Collect urine for the following:
  - Urinalysis (predose);
  - Pregnancy test (for females of childbearing potential).
- Perform a single 12-lead ECG (predose and as soon as possible postdose, ideally within 30 minutes of the end of infusion).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.9 Weekly Assessments Starting at Week 6 (± 3 Days)

Starting at Week 6, the following assessments are required to be done weekly.

- Obtain predose vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- IWRS transaction (cobomarsen dispensation).
- Administer intravenous infusion of cobomarsen with vital signs performed within 15 minutes of the end of the infusion.
- Review and record AEs and concomitant medications.

9.2.2.10 Every-4-Week Assessments from Weeks 9 through 81, then Every-8-Week Assessments Thereafter (± 3 Days)

NOTE: In addition to the weekly assessments listed above, the following additional assessments are required to be done every 4 weeks from Week 9 through Week 81 and then every 8 weeks thereafter:

- Perform CTCL disease evaluation using the mSWAT (predose) (see Appendix F).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose);

- TSH (predose);
- PD and ADA (predose);
- PK (predose only through Week 81, and every 8 weeks thereafter).

- Collect urine for the following:
  - Urinalysis (predose);
  - Pregnancy test (performed every 4 weeks while on study treatment), for females of childbearing potential.
- Perform a single 12-lead ECG (predose).
- Review and record AEs and concomitant medications.

9.2.3 End of Treatment Visit

At the time of study treatment discontinuation, the End of Treatment Visit should be completed for all subjects after the last dose of study treatment, and every effort should be made to perform the procedures listed below. This visit should take place as soon as possible and ≤ 14 days after the last dose of study treatment. The date and reason for stopping the study treatment will be reported. The End of Treatment visit is not considered as the end of the study. All subjects will enter Follow-up unless they have withdrawn their consent to do so.

- Perform CTCL disease evaluation using the mSWAT (see Appendix F).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - TSH;
  - PD and ADA
  - PK.
- Collect urine for the following:
  - Urinalysis;

- Pregnancy test (for females of childbearing potential).

- Perform a single 12-lead ECG.
- IWRS transaction (discontinue the subject in the system).
- Review and record AEs and concomitant medications.

9.3 Long-term Follow-up for Subjects Who Have Not Progressed at the Time of End of Treatment Visit

After the End of Treatment Visit, subjects who did not progress on study will be followed until progression (confirmed progression in skin, confirmed loss of response in skin or clinical progression in lymph nodes, blood or viscera assessed per investigator discretion), withdrawal of consent, initiation of subsequent MF treatment, loss to follow-up, or death, and the subject's final disposition is documented and reviewed by the Sponsor study team.

9.3.1 Every-4-Week Assessment through Week 81, then Every-8-Week Assessments Thereafter (± 3 Days)

- Perform CTCL disease evaluation using the mSWAT (see Appendix F).
- Review and record AEs and concomitant medications.

9.3.2 Follow-up Visit 28 ± 5 days after the End of Treatment or Early Termination

For subjects who discontinue treatment, the following assessments will be performed 28 ± 5 days after the End of Treatment Visit (assuming the subject has not withdrawn consent).

- Perform CTCL disease evaluation using the mSWAT (does not need to be repeated if disease progression is already confirmed) (see Appendix F).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - TSH;
  - Coagulation;

- PD and ADA
- PK.

- Collect urine for the following:
  - Urinalysis;
  - Pregnancy test (for females of childbearing potential).
- Perform a single 12-lead ECG.

  Review and record AEs and concomitant medications.

10 ASSESSMENT OF SAFETY

10.1 Specification of Safety Parameters

Safety will be evaluated through continuous monitoring of AEs, vital signs, physical examinations, clinical laboratory measurements, and ECGs.

Management of Infusion-related adverse events:

Allergic events and/or infusion-related toxicities should be managed according to institutional guidelines. If institutional guidelines are not available, the following recommendations apply.

Rash, pruritus, urticaria and wheezing due to an infusion-related AE, may be treated with diphenhydramine hydrochloride and/or steroids as clinically appropriate. Anaphylaxis or anaphylactoid signs or symptoms may be treated with steroids and/or epinephrine as clinically indicated. Any concomitant therapies used must be recorded in the eCRF. The Medical Monitor should be consulted prior to the use of steroids whenever possible. Subjects should be treated in a facility equipped for cardiopulmonary resuscitation. Infusion-related reactions (fever, rigors) should be treated per institutional guidelines but may be treated with acetaminophen and diphenhydramine hydrochloride.

10.2 Dose Modifications Interruptions and Stopping Rules

More than 4 missed consecutive doses of cobomarsen, or a dose interruption of > 14 consecutive days of vorinostat, due to an AE or clinically significant laboratory abnormality, or other significant noncompliance with study treatment administration should result in permanent discontinuation of study treatment, unless it is judged by the Investigator and Sponsor Medical Monitor or designee to be in the best interest of the subject to continue treatment. Regardless of

study treatment administration, subjects should continue to follow the study procedure schedule outlined in Section 8 and Section 9.

10.2.1 Cobomarsen Interruptions or Permanent Discontinuations

There are no dose reductions allowed for the cobomarsen infusion.

Infusion-related Adverse Events:

- If any grade 2 infusion-related AE(s) are observed/reported at any time during the infusion, the infusion rate should be decreased by one-half and supportive care medications/procedures should be initiated as appropriate. Upon resolution of the AE, the infusion rate should be increased to the rate used prior to the infusion-related AE. If the AE does not resolve prior to the completion of the infusion, the current infusion rate should be used with subsequent study treatment administration. Subjects who had grade 2 infusion-related reactions may receive premedication with subsequent infusions.
- If any grade 3 infusion-related AE(s) are observed/reported at any time during the infusion, the infusion should be temporarily interrupted, and supportive care medications/procedures should be initiated as appropriate. Once the symptoms decrease to baseline, the infusion may be resumed at one-half the rate and maintained at this rate for the remainder of the current infusion and subsequent infusions should be administered with premedication. If a grade 3 infusion-related reaction re-occurs, the subject should be permanently discontinued.
- If grade 4 infusion-related AE(s) are observed/reported at any time during the infusion, the infusion will be immediately discontinued, supportive care will be provided as needed, and no additional investigational product will be administered to the subject.

Specific Grade 2 Renal Adverse Events of interest and Grade 3 and 4 Adverse Events of Interest (Hematological, Hepatic, TSH, and Constitutional)

- **If any renal grade 2 AE(s) of interest** (e.g., creatinine elevation > 1.5 x baseline and above the ULN) a repeat serum creatinine level will be performed. If the repeat creatinine level is still > 1.5 x baseline and above the ULN, and no other cause is identified for this elevation, study drug will be interrupted until the level returns to baseline. Once the AE has decreased to baseline level, the infusion may be resumed. If the grade 2 AE re-occurs, the subject should be permanently discontinued.

- **If any grade 3 AE(s) of interest** are ongoing at the time of the planned infusion, the infusion should be delayed, and supportive care medications/procedures should be initiated as appropriate. Once the AE has decreased to baseline, the infusion may be resumed. If the grade 3 AE re-occurs, the subject should be permanently discontinued.
- **If a grade 4 AE is observed/reported** at any time and is felt to place the subject at life threatening risk, cobomarsen will be immediately discontinued, and the Medical Monitor should be contacted. No additional investigational product will be administered to that subject.

Other Grade 3 and 4 Adverse Events

- **If any clinically significant (symptomatic, requiring intervention) grade 3/4 AE(s)** or laboratory abnormalities are ongoing at the time of the planned infusion, the infusion should be delayed, and supportive care medications/procedures should be initiated as appropriate. Once the AE resolves or symptoms decrease to baseline, the infusion may be resumed. If the grade 3/4 AE re-occurs, the subject should be permanently discontinued.
- **If any non-clinically significant (asymptomatic, not requiring an intervention) grade 3/4 AE(s)** or laboratory abnormalities are observed/reported at any time, the infusion may be temporarily interrupted based on the investigator's opinion (in consultation with the Medical Monitor), and supportive care medications/procedures should be initiated as appropriate. Once the symptoms decrease to baseline, the infusion may be resumed.

10.2.2 Vorinostat Dose Modifications, Interruptions, or Permanent Discontinuations

In general, doses of vorinostat should not be adjusted, reduced or interrupted for grade 1 AEs, but treatment may be instituted to control symptoms.

Vorinostat dose interruption or dose reduction may be considered if it is felt to be necessary (e.g., for AEs ≥ grade 2) (PDR 2018).

- **Dose Reduction 1:** If vorinostat therapy intolerance occurs and dose reduction is deemed appropriate, the dose may be reduced to 300 mg orally once daily with food.
- **Dose Reduction 2:** If intolerance continues, the dose may be reduced to 300 mg once daily with food for 5 consecutive days each week.
- No re-escalation of vorinostat dose or schedule is allowed during the study.

Grade 3 and 4 Adverse Events

- **If any clinically significant (symptomatic, requiring intervention) grade 3/4 AE(s) or laboratory abnormalities** occur, the dose should be delayed, and supportive care medications/procedures should be initiated as appropriate. Once the AE resolves or symptoms decrease to baseline, vorinostat may be resumed. If the grade 3/4 AEs re-occurs, the subject should be permanently discontinued.
- **If any non-clinically significant (asymptomatic, not requiring an intervention) grade 3/4 AE(s)** or laboratory abnormalities are observed/reported at any time, vorinostat may be temporarily interrupted based on the investigator's opinion and supportive care medications/procedures should be initiated as appropriate. Once the symptoms decreased to baseline, vorinostat may be resumed.

QT/QTc Prolongation Adverse Events

Vorinostat is known to cause QT/QTc prolongation in patients. Please use the following criteria in the management of vorinostat patients on the clinical study.

- **If any clinically significant QT/QTc interval prolongation of ≤ 500 msec** is observed/reported at any time, vorinostat dosing should be interrupted and investigations about possible causes (electrolyte imbalance, concomitant medications, etc.), supportive care medications/procedures should be initiated. If other cause is found, once the QTc is documented to be back into normal range, a re-challenge with vorinostat could be considered, based on the investigator's discretion.
- **If any QT/QTc interval prolongation of > 500 msecs** is observed, vorinostat should be permanently discontinued. Consultation with a cardiologist is required and the subject should have continuous ECG monitoring until released by the cardiologist.

If vorinostat is not tolerable and therapy must be discontinued, study assessments will be continued on an every-4-week visit schedule to follow the subject until confirmed progression, if the subject consents to continued follow-up visits.

Whenever possible, additional therapies for MF should not be initiated until disease progression is documented. Subjects will not be eligible for the crossover period of the study unless:

- Skin disease progression is confirmed;
- No additional systemic therapies for MF have been initiated.

10.3 Definition of Adverse Events

10.3.1 Adverse Event

An AE is any untoward medical occurrence whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Please note that disease progression is not considered an AE. However, a primary adverse event associated with disease progression that meets the criteria for an SAE should be reported.

10.3.2 Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

10.3.3 Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.3.4 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE (see Section 10.3.3);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

10.3.5 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘unexpected’’:

- If it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed, or
- If it is not consistent with the risk information described in the general investigational plan, or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents.

‘‘Unexpected,’’ as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

10.3.6 Adverse Events of Special Interest

Adverse events of special interest are those that have been identified in preclinical studies, as well as known AEs from oligonucleotides as a drug class and those from the cobomarsen emerging AE profile from the Phase 1 study. These AEs of interest will be closely monitored, and specific dose interruption rules have been established. These include:

- Hematological: neutropenia, lymphopenia;
- Hepatic: increase transaminases, gamma-glutamyl transferase (GGT), bilirubin consistent with hepatic involvement;

- Renal: increase serum creatinine, blood urea nitrogen (BUN) and hematuria, proteinuria, consistent with kidney involvement;
- Increased TSH;
- Constitutional symptoms: acute fever, chills, myalgias, fatigue.

10.4 Adverse Event Classification

10.4.1 Relationship to Study Treatments

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE.

- Not related: The AE is clearly not related or is unlikely to be related to the study treatment. The temporal relationship of the onset of the AE relative to administration of the product is not reasonable, or the AE can be explained by another cause such as an underlying medical condition or other concomitant therapy, or the AE has no plausible relationship to study therapy.
- Related: The AE is related to the study treatment. The temporal relationship of the AE to administration of the product is reasonable and there is no other cause to explain the event. AEs should be classified as related if the Investigator feels the event may reasonably be regarded as caused by, or probably caused by, the study treatment.

10.4.2 Severity

All AEs entered into the eCRF will be graded for severity using the NCI CTCAE, version 5.0. If an AE is not listed in the CTCAE version 5.0, then the Investigator will use the terms: Mild, Moderate, Severe, or Life-threatening to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

Severity	Definition
Grade 0	No change from Normal or Reference Range
Grade 1 (Mild)	No limitation of usual activities.
Grade 2 (Moderate)	Some limitation of usual activities.
Grade 3 (Severe)	Inability to carry out usual activities.
Grade 4 (Life-threatening)	Immediate risk of death.
Grade 5 (Death)	Resulting in death

10.5 Collection and Reporting of Adverse Events

10.5.1 Reporting of Adverse Events

Subjects will be evaluated and questioned generally to identify AEs during the course of the study. Any AEs occurring prior informed consent will be recorded on the Medical History eCRF. All AEs from the time of informed consent, including those deemed to be related to a study procedure, should be reported on the Adverse Event eCRF. All AEs, including SAEs, will be reported from the time of informed consent. All events occurring after administration of the first dose of study treatment or those that increase in severity or frequency will be considered treatment-emergent adverse events (TEAEs). Adverse events that occur from the time of informed consent up to and including 60 days after the last dose of study treatment, regardless of causality to study treatment, must be reported. Any treatment related AE reported by a subject during the clinical study, even if it occurs later than 60 days after the last dose of study treatment, should be reported in the eCRF.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the Adverse Event eCRF. Clinically significant changes in vital signs and clinically significant findings on physical examination will be recorded as AEs.

Any clinically significant change in laboratory assessments or other clinical findings, as assessed by the Investigator, is considered an AE and must be recorded on the Adverse Event eCRF. In addition, an abnormal test finding will be classified as an AE if one or more of the following criteria are met:

- The test finding is accompanied by clinically significant symptoms;
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including additional concomitant drug treatment or other therapy. Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE;
- The test finding leads to a change in study treatment dosing or discontinuation of subject participation in the clinical research study;
- The test finding is considered an AE by the Investigator.

Wherever possible, a specific disease, diagnosis or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom

is not associated with a documented disease or syndrome, the sign or symptom should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus rather than hyperglycemia).

10.5.2 Follow-up of Adverse Events

All AEs considered to be related to study treatment will be followed until resolution or stabilization.

10.6 Collection and Reporting of Serious Adverse Events

10.6.1 Initial Serious Adverse Event Reports

All SAEs that occur from the time of informed consent up to and including 60 days after the last dose of study treatment must be reported by the Investigator to the Sponsor or Sponsor's designated representative immediately, and in no circumstances later than 24 hours after gaining awareness of the event by submission of a SAE Notification Form. Investigators must report to the Sponsor or the Sponsor's designated representative any SAE, whether or not considered drug related, including those listed in the protocol or Investigator's Brochure. The initial report must contain at a minimum a subject identifier code, an event term, and an assessment of causality. The SAE Notification Form should be faxed or e-mailed to:

[redacted]

If the Investigator is unable to complete and send the SAE Notification Form within the timeframe required, the SAE must be reported via phone call to the Medical Monitor (see contact sheet in the study reference binder) and [redacted].

An Investigator may be requested by the Sponsor or the Sponsor's designated representative to obtain specific follow-up information in an expedited fashion. This information may be more detailed than that captured on the Adverse Event eCRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject

death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or the Sponsor's designated representative.

10.6.2 Follow-up of Serious Adverse Events

All SAEs should be followed up until resolution or stabilization. The timelines and procedure for follow-up reports are the same as those for the initial report.

New information regarding an SAE that becomes available after the submission of the initial SAE Notification Form must be reported by the Investigator to the Sponsor or the Sponsor's designated representative by completion of a SAE Follow-up Report Form or through other written documentation (e.g., laboratory tests, discharge summary, postmortem results). Follow-up reports and/or written documentation must be provided to the Sponsor or the Sponsor's designated representative immediately, and no later than 24 hours after the Investigator's receipt of the information.

10.7 Post-Trial Adverse Events

Any AE that occurs outside of the protocol-specified observation or after the end of the trial but is considered to be caused by the study treatment must be reported to the Sponsor or the Sponsor's designated representative.

10.8 Pregnancy Reporting and Follow-up

Pregnancy in a female clinical trial subject is not an SAE per se. Complications of such pregnancies, for example, spontaneous abortion, may qualify as an SAE and should be reported as an SAE even if they occur after the SAE reporting period has ended.

The Investigator must notify the Sponsor via telephone or e-mail immediately, and no later than 24 hours after awareness of a pregnancy in a study subject and must complete the Pregnancy Notification Form and submit it to the Sponsor within 2 working days of being notified. The subject will not receive any further doses of their assigned study treatment and will be permanently discontinued from study treatment. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended. Information regarding the course of the pregnancy, including perinatal and postnatal offspring outcome up to 8 weeks of age should be reported as follow-up information on the Pregnancy Notification Form.

Male study subjects will be instructed to notify the Investigator if a female partner becomes pregnant during the study. The Investigator must notify the Sponsor immediately and no later than 24 hours via telephone or e-mail and must complete the Pregnancy Notification Form and submit it to the Sponsor within 2 working days of being notified. The Investigator should obtain informed consent from the subject's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the subject's partner provides informed consent, the Investigator should follow the pregnancy until outcome as described above for female study subjects and report the follow-up information on the Pregnancy Notification Form.

10.9 Study Termination

The Sponsor may suspend enrollment or terminate the study at any time for safety concerns or other reasons.

10.10 End of Study Definition

The end of the study is defined as the timepoint when all study subjects meet at least one of the following criteria:

1. Confirmed progression in the randomized period for subjects randomized to cobomarsen
2. Confirmed progression in the randomized period for subjects randomized to vorinostat who choose not to participate in the crossover period
3. Confirmed progression in the crossover period
4. Full withdrawal of consent or lost to follow-up
5. Death
6. Duration on the study (from randomization) of at least 3 years.

or, the study is terminated early by the Sponsor.

10.11 Emergency Sponsor Contact

In a medical emergency (i.e., an event that requires immediate attention regarding operation of the clinical study and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor (see contact sheet in the study reference binder) or the designated Sponsor representative, as indicated in Section 1 of this protocol.

11 TRIAL-SPECIFIC COMMITTEES

11.1 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be responsible for reviewing safety data at regular intervals as well as to perform the interim analysis. A separate DMC Charter will be established that outlines DMC membership, precisely what data will be reviewed, along with the timing and frequency of the reviews. DMC recommendations will be provided to the Sponsor in compliance with the DMC Charter.

11.2 Steering Committee

The study Steering Committee (SC) will be appointed by the Sponsor prior to the initiation of the study. The SC will include principal investigators from the study and Sponsor representatives. The SC will be involved in the oversight of the study and will ensure transparent management of the study according to the protocol through recommending modifications as circumstances require. Details on the role of the SC and working procedures will be defined in the SC Charter.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical and Analytical Plans

Final statistical analysis will be completed after the last subject completes or discontinues the study and the study database has been cleaned, verified, and locked. Based on timing of the primary and secondary endpoints, additional interim database locks may occur, before the final database lock.

A statistical analysis plan (SAP) will be completed prior to the database lock. This document will provide a technical and detailed description of the data analysis methods and procedures.

The results of the final analysis will be presented in the clinical study report. Any deviations from planned statistical analyses will be presented in the clinical study report.

12.2 Study Hypotheses

The primary endpoint is objective response in skin of at least 4 months duration (ORR4). Response to cobomarsen will be compared to the control group using a Cochran-Mantel-Haenzel (CMH) statistic incorporating the stratification factors from the randomization.

The randomization will be stratified based on subjects with at least one skin tumor at Screening vs. no skin tumors at Screening. Subjects will also be stratified based on prognostic factors (age at diagnosis > 60 years and LDH level > ULN at diagnosis) (Scarisbrick et al. 2015). Subjects will be stratified based on having 0-1 vs 2 of these prognostic factors.

There is only one primary and one key secondary endpoint (PFS) for analysis; a one-sided p=0.025 for response by CMH will establish statistical significance. The study hypothesis is that response to cobomarsen is superior to the control group. The null hypothesis (Ho) is that N (%) of responders to cobomarsen and N (%) of responders to control do not differ; the alternative hypothesis (Ha) is that N (%) of responders to cobomarsen is superior to N (%) of responders to control. A step-down procedure will be used to assess the statistical significance of PFS, such that a statistically significant difference in PFS will be confirmatory of a treatment effect only if the analysis of the primary endpoint is statistically significant at the one-sided 0.025 level of significance.

12.3 Analysis Datasets

Assignment of subjects to analysis sets will be done prior to database lock. The following analysis sets will be defined: the Intent to Treat analysis set (ITT), the Safety set, the Per Protocol Set (PPS), and the PK Analysis Set (PKAS).

12.3.1 Intent to Treat Analysis Set (ITT)

The ITT will include all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat) and had at least one post-baseline assessment.

12.3.2 Safety Set

The Safety set will include all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat).

12.3.3 Per Protocol Set (PPS)

The PPS will consist of all subjects randomized to the study, who received study treatment, and completed assessments necessary for the evaluation of the primary endpoint with no major protocol deviations that would affect endpoint analysis.

12.3.4 Pharmacokinetic Analysis Set (PKAS)

The PKAS will consist of subjects randomized to cobomarsen who received at least one dose of cobomarsen and had at least one post baseline PK sample taken and analyzed.

12.4 Statistical Methods and Sample Size Justification

12.4.1 General Approach

All statistical analyses will be performed using SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be presented. For continuous variables, the sample size (n), mean, median, standard deviation, minimum and maximum values will be presented. Missing data will not be imputed unless otherwise stated.

12.4.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline disease characteristics will be summarized by treatment group.

12.4.3 Analysis of the Primary Efficacy Endpoint

The analysis of the primary efficacy endpoint is the proportion of subjects in the randomized period achieving an ORR4 in skin using mSWAT assessments. ORR4 is the proportion of subjects with a CR or PR for 4 consecutive months confirmed by repeat assessments no less than 28 days (± 3 days) later (Olsen et al. 2011).

12.4.4 Analysis of the Secondary Endpoints

The secondary endpoint of progression-free survival is defined as the time from randomization to the date of the earliest documented progression or death due to any cause.

Time to event analyses (Kaplan-Meier) will be done for PFS, time to ≥ 50% mSWAT improvement, time to maximal effect in skin, duration of maintaining response in skin, CRR, and TTP. For responding subjects, duration of response and duration of ≥ 50% improvement will be displayed.

Summary statistics for change from Baseline for mSWAT scores will be presented by treatment and visit.

The percent of subjects achieving ≥ 50% improvement in mSWAT scores will be presented by treatment for:

- ≥ 50% improvement for at least 28 days;
- ≥ 50% improvement at 4 months;
- ≥ 50% improvement at 28 days.

The N (%) of complete responses will be presented by treatment.

P-values generated from secondary analyses are supportive only. The mean change from baseline in use of pruritus medication will be presented by treatment and visit.

12.4.5 Safety Analyses

Treatment-emergent AEs will be coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA®) and summary tables for all AEs will be generated for the Safety Population. Incidence rates and percentages will be summarized by preferred term and system organ class. Additional summary tables will be generated for the following population subsets: subjects with SAEs, subjects with treatment related AEs, subjects who discontinue due to AEs, and subjects with grade 3 or 4 AEs. Severity will be assessed according to the NCI CTCAE version 5.0 and relationship to study treatment will be attributed by investigator.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD; March 2015 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

12.4.5.1 Laboratory Data

All hematology, chemistry, TSH, coagulation, and urinalysis results will be listed by subject for each assessment and descriptive statistics may be tabulated for select criteria. Changes from baseline may be summarized by treatment.

12.4.5.2 Physical Examination

Clinically significant changes in vital signs and clinically significant findings on physical examination will be recorded as AEs. Incidence of subjects with changes from normal physical examination findings at baseline to abnormal during the study may be generated.

12.4.5.3 Twelve-lead ECG

Information on ECGs will be presented in listings. The incidence of subjects with changes from normal ECG findings at baseline to abnormal during the study will be generated as appropriate. Summary of mean/median changes in ECG intervals may be generated on a data-driven basis.

12.4.6 Pharmacokinetic Analysis

The concentration-time data will be used to prepare a population PK model for cobomarsen in subjects. The actual elapsed time from dose will be used in the final PK modeling and parameter calculations. The PK/PD analysis of the study will be used to describe the cobomarsen and its metabolite(s) (if applicable) concentration time profile(s) and exposure/response relationships with respect to PD/clinical/safety endpoints by means of modeling and simulation. Full details of the relevant population PK modeling work (including objectives, relevant endpoints, methodology, software etc.) will be defined in a separate data analysis plan or the study integrated analysis plan. The results of these analyses will be described in a separate report from the clinical study report.

The exact date/time of sample collections (and dosing events) should be recorded (in the eCRF). Although every effort should be made to collect PK blood samples according to the Schedule of Events, blood samples collected outside of the planned window are not to be considered protocol deviations as long as the actual collection date and time is recorded, with the exception of the predose sample, which will be considered a deviation if it is not collected predose.

12.4.7 Planned Interim Analyses

An interim analysis will be performed after approximately 40 subjects are followed for a minimum of approximately 6 months to allow assessment for a 4-month duration of response (ORR4) from the date of initial objective response. A decision to stop the study at interim analysis for superiority will be considered if the one-sided test statistic p-value is < 0.01 (Pocock, et al. 1977). The number of skin ORR4 events required to demonstrate superiority at the interim analysis are shown in Table 6.

Table 6: ORR4 Events Required to Demonstrate Superiority in Skin Objective Response for Interim Analysis ($p < 0.01$)

Vorinostat (N = 18)	Cobomarsen (N = 18)
0/18	6/18
1/18	8/18
2/18	10/18
3/18	11/18
4/18	12/18
5/18	13/18
6/18	14/18
7/18	15/18
8/18	16/18
9/18	17/18
10/18	18/18
11/18	18/18
12/18	18/18

Enrollment will be halted if data from this study or other cobomarsen studies conclusively demonstrate that cobomarsen does not have significant activity in MF.

12.5 Sample Size Determination

12.5.1 Primary Endpoint Sample Size

A sample size of 126 subjects (63 per group) provides greater than 80% power to detect a difference between cobomarsen and vorinostat, after accounting for the alpha spend at the interim analysis (interim alpha = 1%, one sided). This power statement assumes a response rate of 35% in the cobomarsen group and 10% in the vorinostat group, using a one-sided, two sample binomial test of proportions at the adjusted final one-sided alpha of 1.5% (total alpha = 2.5%, one sided). The planned primary analysis will account for all randomized subjects. Power was computed using the normal approximation method. When the normal approximation method is used to compute power for Fisher's Exact Test, the results are based on the pooled, continuity-corrected Chi-Square test (i.e. Z-Test C.C. (Pooled)). (Kim et al. 2017).

12.5.2 Key Secondary Endpoint Sample Size

The null hypothesis is that there is no difference in progression free survival (PFS) between cobomarsen and vorinostat. A sample size of 126 subjects (63 per group; 66 events) provides at least 80% power to detect a difference between vorinostat and cobomarsen, assuming a median PFS of 4 months for vorinostat and 8 months for cobomarsen. This calculation is based on a one-sided, logrank test at the 0.025 level of significance, assuming 15 months of recruitment, 6 months of follow-up, and 17% censoring. No interim analysis is planned for PFS.

12.6 Measures to Minimize Bias

12.6.1 Randomization Procedures

The randomization will be stratified based on subjects with at least one skin tumor at Screening vs. no skin tumors at Screening. Subjects will also be stratified based on prognostic factors (age at diagnosis > 60 years and LDH level > ULN at diagnosis) (Scarisbrick et al. 2015). Subjects will be stratified based on 0-1 vs 2 of these prognostic factors.

12.6.2 Evaluation of Success of Blinding

Not applicable

12.6.3 Breaking the Study Blind

Not applicable

13 DATA HANDLING AND RECORD KEEPING

13.1 Study Files and Subject Source Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include the subject's clinical source documents and Investigator's Study Files.

Subject clinical source documents may include, but are not limited to, hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, radiograph, pathology and special assessment reports and consultant letters.

The investigator will ensure the Study Files are maintained, including the eCRFs and query forms, protocol/amendments, IRB/IEC and regulatory approvals with associated correspondence, signed ICFs, study treatment records, staff curriculum vitae and authorization forms, all

correspondence and other appropriate documents. Such data shall be secured in order to prevent loss.

The investigator will allow personnel authorized by the Sponsor access to all study data at any time.

13.2 Data Collection Methods

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. An eCRF must be completed for each person who signs informed consent, regardless of the duration of their trial participation.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. Documents (including laboratory reports, hospital records subsequent to SAEs, etc.) transmitted to the CRO or the Sponsor should include the assigned subject identifier but should not include the subject's name in order to ensure confidentiality.

Electronic CRFs will be provided for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and maintained in the subject's official electronic study record. The Investigator should consult the eCRF completion guidelines for comprehensive instructions for completing the eCRF.

Clinical data will be entered into a 21 CFR Part 11-compliant electronic data capture system, unless otherwise specified. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.3 Retention of Records

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified.

Investigators may need to retain documents longer if required by applicable regulatory requirements or if requested by the Sponsor. The investigator must notify the Sponsor prior to destroying any clinical study records. Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and miRagen to securely store the documents in an off-site storage location so that they can be returned to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for off-site storage.

13.4 Protocol Deviations

The investigator and the study site staff are responsible for ensuring the study is conducted in accordance with the schedule of procedures and assessments described in this protocol and in accordance with Good Clinical Practice (GCP). The site must use continuous vigilance to identify and document any deviations that occur. All deviations must be reviewed by the investigator to assess whether the safety of study participants or study integrity has been affected by the deviation.

Intentional deviations from the protocol shall not be made except in a medical emergency, when the intent is to reduce immediate risk to the subject. In such cases, the Sponsor, CRO, the IRB/IEC and regulatory authorities, as appropriate, should be notified, in accordance with local requirements. In all other cases, the nature of the deviation, the justification for the deviation, and prior written approval of the Sponsor must be documented.

Under no circumstance should the investigator contact the Sponsor or designee monitoring the study, to request approval of a protocol deviation, as no authorized deviations are permitted.

Changes to the protocol may be made only when a written substantial protocol amendment has been approved by the Sponsor and submitted to the IRB/IEC and applicable regulatory agencies in accordance with local requirements. Appropriate approval(s) must be obtained before changes can be implemented.

14 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control procedures will be implemented beginning with the data entry system, and data quality control checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Sponsor (or designee) is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded in the eCRFs by assigning CRAs to each site. The CRA is responsible for reviewing the eCRFs at regular intervals throughout the study, verifying adherence to the protocol, assuring completeness, consistency and accuracy of the data, and reviewing study files and drug accountability. The data will be verified against the original medical records and laboratory results as part of source document verification to ensure validity of the data. The investigator's responsibility is to ensure that any issues detected in the course of a monitoring visit are resolved.

To ensure compliance with GCP and all applicable regulatory requirements, a quality assurance audit may be conducted by the Sponsor or the Sponsor's designee. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its designees, and/or regulatory agencies (see Section 13.3). In signing this protocol, the investigator understands and agrees to give access to the necessary documentation and files.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

This Section 15 of the Clinical Trial Protocol is subject to the terms of the Clinical Trial Agreement between miRagen Therapeutics, Inc. and the study centers. In the event of a discrepancy between the Clinical Trial Agreement and this Clinical Trial Protocol, the terms of the Clinical Trial Agreement shall control.

15.1 Ethical Conduct of the Study

This study will be conducted in compliance with the ICH GCP guidelines, US regulations for the ethical conduct of clinical studies under 21 Code of Federal Regulations (CFR; Parts 50, 56 and 312), the European Clinical Trials Directive 2001/20/EC and implementing national regulations, the European Clinical Trials Regulation No. 536/2014, the Declaration of Helsinki, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). This study will also adhere to all FDA, state and local regulatory requirements, and requirements for data protection.

15.2 Institutional Review Board/Independent Ethics Committee Review

Before trial initiation, the investigator and institution must have written and dated approval from an accredited IRB/IEC for the study protocol, written ICF, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/IEC approved prior to implementing the change; a determination will be made regarding whether previously consented subjects need to be re-consented using the amended form.

Appropriate reports on the progress of the study will be made by the investigator to the IRB/IEC and the Sponsor in accordance with applicable regulations. All correspondence with the IRB/IEC should be retained in the investigator's Study File. Copies of IRB/IEC approvals should be forwarded to miRagen or its designee.

15.3 Informed Consent Process

An ICF template will be provided by the Sponsor to the investigator for submission to the IRB/IEC. Any site-specific changes to the ICF must be approved by the Sponsor prior to its submission to the IRB/IEC. The ICF must be approved by the IRB/IEC prior to being presented to potential study subjects.

Individuals may agree to participate in the clinical trial only after the risks and possible benefits of their participation have been explained and extensively discussed. The investigator will explain the purposes, procedures, and potential risks of the research study in terms suited to their comprehension, as well as their rights as a research subject. Subjects will have the opportunity to carefully review the written ICF, discuss the study with their surrogates, and ask questions prior to signing. Written informed consent must be obtained from each study subject or his/her legally acceptable representative prior to conducting any study-related procedures.

The investigator must use the most current IRB/IEC-approved ICF for documenting written consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally acceptable representative and by the person obtaining consent. The site must retain the original signed ICF and provide a copy to the subject.

15.4 Confidentiality of Information

Individual subject medical information obtained as a result of this study is considered confidential. The investigator and the study center will adhere to all applicable laws relating to the protection of subject information. To assure that subject confidentiality is maintained, subject data will be identified only by a study-assigned number on any Sponsor forms, reports, publications, or in any other disclosures, except where required by law.

All personnel of miRagen Therapeutics, Inc. and its designees with access to the primary study data will handle subject data in a confidential manner in accordance with applicable regulations governing clinical research. Subject records will be inspected only in connection with this research project. Information generated as a result of a subject's participation in this study may be disclosed to third parties for research, regulatory, and other purposes in any country as determined by miRagen Therapeutics, Inc. However, subjects will not be individually identified but will be referred to by the study-assigned number.

15.5 Future Use of Stored Specimens

Laboratory data collected for this study will be analyzed and stored at the central laboratory.

With the subject's approval and as approved by local IRBs, de-identified biological samples will be stored at the central laboratory for up to 2 years after the completion of the study. These samples could be used for future research performed by miRagen or its collaborators into the causes of MF, its complications, and other conditions for which individuals with MF are at increased risk, and to improve treatment.

16 PUBLICATION POLICY

Publication and/or disclosure of information or data related to this Clinical Trial Protocol is subject to and governed by the Clinical Trial Agreement between miRagen Therapeutics, Inc. and the study center to which the Principal Investigator is a signatory.

After conclusion of the study, investigators in this study may make oral presentations of study results or publish such results in scientific journals or other scholarly media without prior written approval from miRagen Therapeutics, Inc., only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of miRagen Therapeutics, Inc. in an abstract, manuscript or presentation forum;
- The investigator has complied with the terms of the Clinical Trial Agreement and all requests from miRagen Therapeutics, Inc. to delete any references to its confidential information (other than study results);
- The study has been completed at all study sites for at least 1 year.

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18 LIST OF APPENDICES

Appendix A. Schedule of Events (Screening, Randomized Period)

Study Procedure or Assessment (completed after obtaining informed consent from the patient).	**Screening [a]**	
Weeks Prior to Randomization	**-4**	**Time of Randomization**
Study Day Prior to Randomization	**-28 to -3**	**Day -3 to -1**
Registration in Interactive Web Response System	X	X [i]
Modified Severity Weighted Assessment Tool (mSWAT)	X	
Medical History and Concomitant Medications [b]	X	
Report Prior CTCL Treatments	X	
ECOG Performance Status	X	
Vital Signs	X	
Complete Physical Examination Including Weight and Height	X	
Triplicate 12-lead Electrocardiogram [c]	X	
Radiological Imaging (CT/MRI Scans) [d]	X	
HIV, Hepatitis B, Hepatitis C Screening [e]	X	
Follicle-stimulating Hormone [e, f]	X	
Serum Pregnancy Test [e]	X	
Hematology, Chemistry, Coagulation and TSH [e]	X	
Urinalysis with Microscopy [e]	X	
Flow Cytometry and CBC (performed by the local laboratory) [g]	X	
Review Inclusion/Exclusion Criteria	X	X (RECONFIRM)
Confirm CTCL Staging based on Screening Assessments		X
Initiate Medical Monitor Review after all Screening Data are Entered in the eCRF [h]		X
Adverse Events	Review on an ongoing basis	

Abbreviations: CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; HIV = human immunodeficiency virus; IWRS = Interactive Web Response System; MRI = magnetic resonance imaging; mSWAT = Modified Severity Weighted Assessment tool; TSH = thyroid-stimulating hormone

a) Subjects who do not meet the inclusion/exclusion criteria may rescreen once at the discretion of the Investigator.

b) All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of the study should be recorded on the eCRF.
c) Triplicate 12-lead ECGs (3 serial ECGs conducted within approximately 5-10 minutes total time).
d) CT/MRI scans collected by the local site and sent to the Central Laboratory for confirmation.
e) Collected by the clinical site, processed and sent to the central laboratory. Coagulation includes prothrombin time, partial thromboplastin time, and international normalized ratio.
f) Only for women who are not surgically sterile as confirmation of menopause (for subjects whose last menstrual cycle was within the last year).
g) Flow cytometry and CBC performed by the site's local laboratory. Panels must include antibodies to CD3, CD4, CD8, CD26, CD45 and CD7.
h) To occur prior to initiating randomization procedures in IWRS.
i) Randomization in IWRS will occur after Medical Monitor approval.

Appendix B. Schedule of Events (On Treatment and Post-Treatment Follow-up – Cobomarsen Group)

Study Procedure or Assessment	On Treatment Visits										Follow-Up and End of Treatment			
Study Week	**1**				**2**	**3**	**4**	**5**	**Weekly Visits from Week 6 through End of Treatment (±3 days)**	**Q4W Visits from Weeks 9 through 81 then Q8W thereafter (±3 days)**	**End of Treatment Visit**	**Follow-up visit: 28 (±5) Days after End of Treatment Visit [a]**	**Follow-up for Response and Progression [b]**	
Study Day	**1[c]**	**2**	**3 (+1)**	**5 (±1)**	**8 (±1)**	**15 (±1)**	**22 (±2)**	**29 (±3)**						
IWRS Transaction (Study Treatment Dispensation)	X		X	X	Weekly starting at Week 2 until End of Treatment Visit						X[t]			
mSWAT [d]	X							X		X	X	X	X[r]	
Vital Signs [s]	X	X	X	X	Weekly starting at Week 2 until End of Treatment Visit						X	X		
Physical Examination [e]	X				X	X		X		X	X	X		
Weight	X							X		X	X	X		
Complement (C5a, Bb)[f]	X	X												
Urine Pregnancy Test	X							X		X[u]	X	X		
Single 12-lead ECG [g]	X							X		X	X	X		
Laboratory Assessments [h]	X		X		X	X		X		X	X	X		
Coagulation [i]	X	X			X			X				X		
Sample for PD and ADA (predose)	X					X		X		X	X	X		
Adverse Events [j]	Review on an ongoing basis												X	
Prior and Concomitant Medications [k]	Review on an ongoing basis												X	
Blood PK Sample	X[l]	X[m]	X[n]	X[n]	X[o]	X[n]		X[l]		X[p]	X	X		

Study Procedure or Assessment	On Treatment Visits										Follow-Up and End of Treatment			
Study Week	1				2	3	4	5	Weekly Visits from Week 6 through End of Treatment (±3 days)	Q4W Visits from Weeks 9 through 81 then Q8W thereafter (±3 days)	End of Treatment Visit	Follow-up visit: 28 (±5) Days after End of Treatment Visit [a]	Follow-up for Response and Progression [b]	
Study Day	1[c]	2	3 (+1)	5 (±1)	8 (±1)	15 (±1)	22 (±2)	29 (±3)						
Cobomarsen Infusion [q]	X		X	X	Infusions performed weekly starting at Week 2 until End of Treatment Visit									

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; CR = complete response; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECG = electrocardiogram; eCRF = electronic case report form; INR = international normalized ratio; IWRS = Interactive Web Response System; MRI = magnetic resonance imaging; mSWAT = Modified Severity Weighted Assessment tool; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PR = partial response; PT = prothrombin time; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event;; TSH = thyroid-stimulating hormone

a) Follow-up visit assessments to be performed 28 days after the last dose of study treatment and for subjects who discontinue treatment early (if the subject has not withdrawn consent).
b) Subjects who did not progress on study will continue to be followed for response and progression every 4 weeks through Week 81, then every 8 weeks.
c) Day 1 refers to the first dosing day.
d) mSWAT assessment will be completed prior to dosing when applicable, at the indicated visits. The Day 1 evaluator should conduct all subsequent mSWAT evaluations.
e) Complete physical examination on Day 1 or within 2 days prior to the Day 1 visit; brief physical examination at all subsequent time points.
f) To be collected on Day 1 (predose and within the 10 minutes before the end of the infusion) and on Day 2 (24 ± 4 hours after Day 1 dosing).
g) To be performed predose and as soon as possible postdose (ideally within 30 minutes of the end of the infusion) on Days 1 and 29, and predose on indicated study days, and at the follow-up visit. If the subject has an elevated QTcF during study treatment defined as (QTcF > 450 msec for males or > 470 msec for females or > 480 msec for subjects with bundle branch block, please see section 7.2.3 for additional guidance.
h) Hematology, clinical chemistry, TSH and urinalysis (including microscopy) as indicated in the protocol will be collected predose on each of the indicated study days. Laboratory assessments do not need to be performed on Day 1 if Screening laboratory measurements were performed within 3 days prior to Day 1.
i) Coagulation assessments (PT, aPTT, and INR) are to be performed on Day 1 predose and at 3 hours (± 10 minutes) postdose; on Day 2; on Day 8 predose; on Day 29 predose; and at the follow-up visit.
j) All AEs, including SAEs, will be reported from the time of informed consent up to and including 60 days after the last dose of study treatment. Treatment-related AEs ongoing at the end of treatment or follow-up visits should be followed to resolution or until the investigator considers them “chronic” or “stable.”
k) All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of the study should be recorded on the eCRF.
l) On Day 1 and Day 29, plasma for PK will be drawn at (pre-dose, 60 ± 5 minutes after the start of the infusion, 5 ± 5 minutes before the end of the infusion, and 4 hours [± 10 minutes] after the end of the infusion).
m) On Day 2, plasma for PK will be drawn 24 ± 4 hours after Day 1 dosing.
n) A single PK sample will be drawn predose.
o) Plasma for PK will be drawn at predose and 5 ± 5 minutes before the end of the infusion.

p) Plasma for PK will be drawn at predose and 5 ± 5 minutes before the end of the infusion though Week 25. Plasma for PK will be drawn predose only from Week 29 through 81 and every 8 weeks thereafter.
q) Subjects randomized to cobomarsen will undergo intravenous infusions on Days 1, 3, and 5, and weekly thereafter starting at Week 2. On Day 1, subjects will be monitored for 4 hours postdose.
r) mSWAT performed at Every-4-Week Assessments through Week 81, then Every-8-Week Assessments Thereafter (± 3 days).
s) Vital signs performed predose and within 15 minutes of the end of the cobomarsen infusion.
t) Discontinue the subject in the IWRS.
u) Urine pregnancy test to be completed every 4 weeks through end of treatment.

Appendix C. Schedule of Events (On Treatment and Post-Treatment Follow-up – Vorinostat Group)

Study Procedure or Assessment	**On Treatment Visits**										**Follow-Up and End of Treatment**			
Study Week	**1**				**2**	**3**	**4**	**5**	**Weekly Visits from Week 6 through End of Treatment (±3 days) [a]**	**Q4W Visits from Weeks 9 through 81 then Q8W thereafter (±3 days)**	**End of Treatment Visit**	**Follow-up visit: 28 (±5) Days after End of Treatment Visit [b]**	**Follow-up for Response and Progression [c]**	
Study Day	**1[d]**	**2**	**3 (+1)**	**5 (±1)**	**8 (±1)**	**15 (±1)**	**22 (±2)**	**29 (±3)**						
IWRS Transaction (Study Treatment Dispensation)	X							X		X	X[p]			
mSWAT [e]	X							X		X	X	X	X[o]	
Vital Signs	X	X	X	X	X	X	X	X		X	X	X		
Physical Examination [f]	X				X	X		X		X	X	X		
Weight	X							X		X	X	X		
Complement (C5a, Bb) [g]	X	X												
Urine Pregnancy Test	X							X		X[q]	X	X		
Single 12-lead ECG [h]	X							X		X	X	X		
Laboratory Assessments [i]	X		X		X	X		X	Week 7 only [j]	X	X	X		
Coagulation [k]	X	X			X			X	Week 7 only [k]			X		
On treatment telephone contact [l]									X					
Adverse Events [m]	Review on an ongoing basis												X	
Prior and Concomitant Medications [n]	Review on an ongoing basis												X	

Study Procedure or Assessment	On Treatment Visits										Follow-Up and End of Treatment			
Study Week	1				2	3	4	5	Weekly Visits from Week 6 through End of Treatment (±3 days) [a]	Q4W Visits from Weeks 9 through 81 then Q8W thereafter (±3 days)	End of Treatment Visit	Follow-up visit: 28 (±5) Days after End of Treatment Visit [b]	Follow-up for Response and Progression [c]	
Study Day	1[d]	2	3 (+1)	5 (±1)	8 (±1)	15 (±1)	22 (±2)	29 (±3)						
Vorinostat Dosing	Taken orally once daily with food													

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CR = complete response; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECG = electrocardiogram; eCRF = electronic case report form; INR = international normalized ratio; IWRS = Interactive Web Response System; MRI = magnetic resonance imaging; mSWAT = Modified Severity Weighted Assessment tool; PR = partial response; PT = prothrombin time; Q4W = every 4 weeks; Q8W = every 8 weeks;; SAE = serious adverse event; TSH = thyroid-stimulating hormone

a) The weekly study visits for the vorinostat group can be conducted via telephone, unless the investigator feels it is in the best interest of the subject to visit the clinic.
b) Follow-up visit assessments to be performed 28 days after the last dose of study treatment for subjects who choose not to participate in the crossover period. and for subjects who discontinue treatment early (if the subject has not withdrawn consent).
c) Subjects who did not progress on study will continue to be followed for response and progression.
d) Day 1 refers to the first dosing day.
e) mSWAT assessment will be completed prior to dosing when applicable, at the indicated visits. The Day 1 evaluator should conduct all subsequent mSWAT evaluations.
f) Complete physical examination on Day 1 or within 2 days prior to the Day 1 visit; brief physical examination at all subsequent time points.
g) To be collected on Day 1 (predose and 2 hours [± 10 minutes] post dose) and on Day 2 (24 ± 4 hours after Day 1 dosing).
h) To be performed predose and at 1 ± 0.5 hours postdose on Days 1 and 29, and predose on indicated study days.If the subject has an elevated QTcF during study treatment defined as QTcF > 450 msec for males or > 470 msec for females or > 480 msec for subjects with bundle branch block, please see section 7.2.3 for additional guidance.
i) Hematology, clinical chemistry, TSH, and urinalysis (including microscopy) as indicated in the protocol will be collected predose on each of the indicated study days. Laboratory assessments do not need to be performed on Day 1 if Screening laboratory measurements were performed within 3 days prior to Day 1.
j) Hematology and clinical chemistrywill be collected at the Week 7 visit for vorinostat subjects only.
k) Coagulation assessments (PT, aPTT, and INR) are to be performed at on Day 1 predose and at 3 hours (± 10 minutes) postdose; on Day 2; on Day 8 predose; on Day 29 predose; at week 7; and at the follow-up visit.
l) Clinic visits may be scheduled instead of telephone contact, at the discretion of the investigator.
m) All AEs, including SAEs, will be reported from the time of informed consent up to and including 60 days after the last dose of study treatment. Treatment-related AEs ongoing at the end of treatment or follow-up visits should be followed to resolution or until the investigator considers them “chronic” or “stable.”
n) All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of the study should be recorded on the eCRF.
.
o) mSWAT, performed at Every-4-Week Assessments through Week 81, then Every-8-Week Assessments Thereafter (± 3 days).
p) Discontinue the subject in the IWRS
q) Urine pregnancy test to be completed every 4 weeks through end of treatment.

Appendix D. Crossover Period Schedule of Events (Screening, Crossover Period)

Study Procedure or Assessment (completed after obtaining informed consent from the patient).	**Screening [a]**	
Weeks Prior to Enrollment	**-4**	**Time of Enrollment**
Study Day Prior to Enrollment	**-28 to -3**	**Day -3 to -1**
Registration in Interactive Web Response System	X	X [b]
Modified Severity Weighted Assessment Tool (mSWAT) [c]	X	
Medical History and Concomitant Medications [d]	X	
Report Prior CTCL Treatments	X	
ECOG Performance Status	X	
Vital Signs [e]	X	
Complete Physical Examination Including Weight and Height [e]	X	
Triplicate 12-lead Electrocardiogram [e, f]	X	
Follicle-stimulating Hormone [e, g, h]	X	
Serum Pregnancy Test (for females of childbearing potential) [e, h]	X	
Hematology, Chemistry, Coagulation and TSH [e, g]	X	
Urinalysis with Microscopy [e, g]	X	
Flow Cytometry and CBC (performed by the local laboratory) [c, i]	X	
Review Inclusion/Exclusion Criteria	X	X (RECONFIRM)
Initiate Medical Monitor Review after all Screening Data are Entered in the eCRF [j]		X
Adverse Events	Review on an ongoing basis	

Abbreviations: App = application; CBC = complete blood count; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IWRS = Interactive Web Response System; MRI = magnetic resonance imaging; mSWAT = Modified Severity Weighted Assessment tool; TSH = thyroid-stimulating hormone

a. Subjects who do not meet the inclusion/exclusion criteria may rescreen once at the discretion of the Investigator.
b. Enrollment in IWRS will occur after Medical Monitor approval.
c. Does not need to be repeated if completed within the 28 days prior to Day 1.
d. All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of cobomarsen (Day 1) will be recorded on the eCRF.
e. Does not need to be repeated if completed within the 14 days prior to Day 1.
f. Triplicate ECG (3 serial ECGs conducted within approximately 5-10 minutes total time).
g. Collected by the clinical site, processed and sent to the central laboratory. Coagulation includes prothrombin time, partial thromboplastin time, and international normalized ratio.
h. Only for women who are not surgically sterile as confirmation of menopause (for subjects whose last menstrual cycle was within the last year).

i. Flow cytometry and CBC performed by the site's local laboratory. Panels must include antibodies to CD3, CD4, CD8, CD26, CD45 and CD7.
j. To occur prior to initiating enrollment procedures in IWRS.

Appendix E. Crossover Period Schedule of Events (Crossover On Treatment and Post-Treatment Follow-up)

Study Procedure or Assessment	**On Treatment Visits**										**Follow up and End of Treatment**		
Study Week	**1**				**2**	**3**	**4**	**5**	**Weekly Visits from Week 6 through End of Treatment (±3 days)**	**Q4W Visits from Weeks 9 through 81 then Q8W thereafter (±3 days)**	**End of Treatment Visit**	**Follow-up visit: 28 (±5) Days after End of Treatment Visit [a]**	**Follow-up for Response and Progression [b]**
Study Day	**1[c]**	**2**	**3 (+1)**	**5 (±1)**	**8 (±1)**	**15 (±1)**	**22 (±2)**	**29 (±3)**					
IWRS Transaction	X		X	X	Weekly starting at Week 2 until End of Treatment Visit						X		
mSWAT [d]	X							X		X	X	X [e]	X [f]
Vital Signs [g]	X	X	X	X	Weekly starting at Week 2 until End of Treatment Visit						X	X	
Physical Examination [h]	X				X	X		X		X	X	X	
Weight	X							X		X	X	X	
Complement (C5a, Bb) [i]	X	X											
Urine Pregnancy Test (for females of childbearing potential)	X							X		X[r]	X	X	
12-lead ECG [j]	X							X		X	X	X	
Laboratory Assessments [k]	X		X		X	X		X		X	X	X	
Coagulation [l]	X	X			X			X				X	
Sample for PD and ADA (predose if applicable)	X					X		X		X	X	X	
Adverse Events [m]	Review on an ongoing basis												X
Prior and Concomitant Medications [n]	Review on an ongoing basis												X
Blood PK Sample	X [o]							X [o]		X [p]	X	X	
Cobomarsen Infusion [q]	X		X	X	Weekly starting at Week 2 until End of Treatment Visit								

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CR = complete response; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; INR = international normalized ratio; IWRS = Interactive Web Response System;;

MRI = magnetic resonance imaging; mSWAT = Modified Severity Weighted Assessment tool; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PR = partial response; PT = prothrombin time; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; TSH = thyroid-stimulating hormone

a. Follow-up visit assessments to be performed 28 days after the last dose of cobomarsen for subjects who discontinue treatment early (if the subject has not withdrawn consent).
b. Subjects who do not progress on study will continue to be followed for response and progression.
c. Day 1 refers to the first dosing day.
d. mSWAT assessment will be completed prior to dosing when applicable, at the indicated visits. The Day 1 evaluator should conduct all subsequent mSWAT evaluations.
e. mSWAT evaluations do not need to be repeated if disease progression is already confirmed.
f. mSWAT performed at Every-4-Week Assessments through Week 81, then Every-8-Week Assessments Thereafter (± 3 days).
g. Vital signs performed predose and within 15 minutes of the end of the cobomarsen infusion.
h. Complete physical examination on Day 1 or within 2 days of the Day 1 visit; brief physical examination at all subsequent time points.
i. To be collected on Day 1 (predose and within the 10 minutes before the end of the infusion) and on Day 2 (24 ± 4 hours after Day 1 dosing).
j. To be performed predose and as soon as possible postdose on Days 1 and 29 (ideally within 30 minutes postdose on Day 1, predose on other indicated study days, and at the Follow-up Visit 28 ± 5 days after the End of Treatment Visit.
k. Hematology, clinical chemistry, TSH and urinalysis (including microscopy) will be collected predose on each of the indicated study days. These assessments do not need to be repeated on Day 1 if the Screening assessments were performed within 3 days prior to Day 1 and satisfied eligibility criteria.
l. Coagulation assessments (PT, aPTT, and INR) are to be performed on Day 1 predose and at 3 hours (± 10 minutes) postdose; on Day 2; on Day 8 predose; on Day 29 predose; and at the Follow-up Visit 28 ± 5 days after the End of Treatment Visit. Coagulation does not need to be repeated on Day 1 if Screening coagulation assessments were performed within 3 days prior to Day 1 and satisfied eligibility criteria.
m. All AEs, including SAEs, will be reported from the time of informed consent up to and including 60 days after the last dose of cobomarsen. Treatment-related AEs ongoing at the end of treatment or follow-up visits should be followed to resolution or until the investigator considers them “chronic” or “stable.”
n. All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of the study should be recorded on the eCRF.
o. On Day 1 and Day 29, blood for plasma PK will be drawn predose and 5 ± 5 minutes before the end of the infusion.
p. Blood for plasma PK will be drawn, predose only, every 4 weeks from Week 9 through Week 81 and every 8 weeks thereafter.
q. Subjects will undergo intravenous infusions with cobomarsen on Days 1, 3, 5, and 8 and weekly thereafter (starting at Week 2). On Day 1, subjects will be monitored in the clinic for safety for 4 hours postdose.
r. Urine pregnancy test to be completed every 4 weeks through end of treatment.

Appendix F. Modified Severity Weighted Assessment Tool and Response Criteria

Derived from Olsen E, Whittaker S, Kim Y, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011; 29(18):2598-2607.

Table F1: Modified Severity Weighted Assessment Tool

Body Region	% BSA in Body Region	Assessment of Involvement in Subject's Skin		
		Patch[a]	Plaque[b]	Tumor[c]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA x weighting factor				

NOTE: mSWAT score equals summation of each column line.
Abbreviations: BSA = body surface area; mSWAT = Modified Severity Weighted Assessment tool

a) Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
b) Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
c) Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Table F2: Response in Skin Based on mSWAT Score

Response	Definition
CR	100% clearance of skin lesions[a]
PR	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
SD	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
PD[b]	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease
a) A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.
b) Whichever criterion occurs first.

Table F3: Response Assessment in Lymph Nodes[a]

Response	Definition
SD	Fails to attain the criteria for PD
PD[b, c, d]	≥ 50% increase in SPD from baseline of lymph nodes that are proven to be N3 histologically, or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis, if 1-1.5 cm in the long axis that is proven to be N_3 histologically

Abbreviations: PD = progressive disease; SD = stable disease; SPD = sum of the maximum linear dimensions (major axis) × longest perpendicular dimension (minor axis)
a) Peripheral and central lymph nodes.
b) Whichever criterion occurs first.
c) As an alternative to histological confirmation, PET scan > 5 SUV is also considered malignant.
d) In exceptional circumstances where biopsy or PET scan cannot be done, the new enlarged node will be designated N_x and considered malignant.

Table F4: Response Assessment in Viscera

Response	Definition
SD	Fails to attain the criteria for PD
PD	New organ involvement

Abbreviations: PD = progressive disease; SD = stable disease;

Table F5: Response Assessment in Blood[a]

Response	Definition
SD	Fails to attain criteria for PD
PD	≥ 50% increase from baseline and at least 1,000 neoplastic cells/μL (B2)

Abbreviations: PD = progressive disease; SD = stable disease
a) As determined by absolute numbers of neoplastic cells/μL.

Appendix G. National Comprehensive Cancer Network (NCCN) Guidelines for Treating Mycosis Fungoides/Sézary Syndrome

Skin-Directed Therapies	Systemic Therapies
For limited/localized skin involvement (Skin-Limited/Local) • Topical corticosteroids[a] • Topical chemotherapy (mechlorethamine [nitrogen mustard]) • Local radiation (8–36 Gy) • Topical retinoids (bexarotene, tazarotene) • Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)[b] • Topical imiquimod *For generalized skin involvement (Skin-Generalized)* • Topical corticosteroids[a] • Topical chemotherapy (mechlorethamine [nitrogen mustard]) • Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)[b] • Total skin electron beam therapy (TSEBT) (12–36 Gy)[c, d]	*Category A (SYST-CAT A)* • Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13cis-retinoic acid], acitretin)[d] • Interferons (IFN-alpha, IFN-gamma) • HDAC-inhibitors (vorinostat, romidepsin)[d] • Extracorporeal photopheresis[e] • Methotrexate (≤100 mg q week) • Brentuximab vedotin[f] *Category B (SYST-CAT B)* • Preferred therapies (alphabetical order) ➢ Brentuximab vedotin[f] ➢ Gemcitabine ➢ Liposomal doxorubicin ➢ Low-dose pralatrexate • Other therapies ➢ Chlorambucil ➢ Pentostatin ➢ Etoposide ➢ Cyclophosphamide ➢ Temozolomide ➢ Methotrexate (> 100 mg q week) ➢ Pembrolizumab[g] (category 2B) ➢ Bortezomib (category 3) *Category C (SYST-CAT C)[h] (alphabetical order)* • Bortezomib (category 3) • Brentuximab vedotin[f] • Gemcitabine • Liposomal doxorubin • Low- or standard-dose pralatrexate • Romidepsin

Derived from the National Comprehensive Cancer Network Guidelines Version 1.2018.

a) Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.
b) Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with a history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.
c) It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.
d) Safety of combining TSEBT with systemic retinoids or HDAC inhibitors, such as vorinostat or romidepsin, or combining phototherapy with vorinostat or romidepsin is unknown.
e) Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).
f) A randomized phase 3 trial comparing brentuximab vedotin (BV) with physician's choice of oral bexarotene or methotrexate showed superior clinical outcome of BV in patients with CD30+ MF and pcALCL. CD30 positivity was defined as CD30 expression≥ 10% of total lymphoid cells in at least 1 of minimal 2 skin biopsies required to evaluate for eligibility. Forty-four percent of eligible patients with MF had at least 1 Screening skin biopsy with CD30 <10%. In the two previously reported investigator-initiated studies, clinical responses with BV was observed across all CD30 expression levels including in those with negligible CD30 expression.
g) Preliminary phase II data in patients with MF and SS. Disease flare is seen in some patients (especially in erythrodermic skin/SS patient) and should be distinguished from disease progression. Khodadoust et al. Blood 2016; 125:Abstract 181.
h) Patients with large cell transformed (LCT) MF and stage IV non-SS/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

Appendix H. TNMB Staging of Mycosis Fungoides

Modified ISCL/EORTC Revisions to the Staging of MF/SS				
Stage	**T**	**N**	**M**	**B**
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Derived from Olsen et al. 2011.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to full characterize histologic subcategories.

TNMB Stages	Description of TNMB
Skin[a]	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) v T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) v T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node[b]	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	< 250/µL CD4+ CD26- or CD4+ CD7-
B_1	250 to 1000/µL CD4+CD26- or CD4+ CD7-
B_2	> 1000/µL CD4+ CD26- or CD4+ CD7- with T-cell blood clone

Derived from Olsen et al. 2011 and Scarisbrick et al. 2018.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; NCI, National Cancer Institute.

[a] Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

[b] Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.

[c] The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Appendix I. Potency (Per Protocol) of Topical Corticosteroid Products

Steroid Generic Name	Trade Names	miRagen Derived Potency
Amcinonide Ointment, cream or lotion, 0.1%	CYCLOCORT, VISDERM	High
Augmented Betamethasone dipropionate , 0.05%	Diprolene Ointment / lotion / Diprolene AF Cream	High
Betamethasone butyrate propionate 0.05%	ANTEBATE, Diprosone	High
Betamethasone dipropionate (Ointment, lotion) 0.05%	DIPROLENE, Diprosone OV, Alphatrex, Beta 1 Kit, Beta Derm, Beta-Val, Betanate, Betatrex, Celestone, Del-Beta, Diprolene, Diprolene AF, Diprosone, Luxiq Foam, Maxivate, RRB Pak, Sernivo, Valisone, Taro-sone, Topisone	High
Betamethasone dipropionate 0.064%	RINDERON-DP	High
Betamethasone dipropionate Cream 0.05% + Salicylic Acid 3%	Diprosalic	High
Betamethasone dipropionate Cream, 0.05%	DIPROLENE, Diprosone, Taro-sone, Lotriderm, Maxivate, Betantate,	High
Betamethasone dipropionate glycol, 0.05%	Diprolene Glycol, Topilene Glycol	High
Betamethasone dipropionate, Lotion, 0.02%		High
Betamethasone valerate Ointment, 0.1%	Beta-val, Betaderm, Lixiq, Valisone, Betatrex, Benovate, Celestone-V, Betnovate. Celestoderm	High
Clobetasol propionate Ointment/Cream/ topical solution/gel/foam/shampoo/spray/Lotion/ Emollient cream, 0.05%	Dermovate, Dermaol cream, Dermol ointment, Clobevate, Cormax, Embeline E, Temovate -E, Ratio-Clobetasol, Excel Cream, IMPOYZ (Encore Dermatology), Embeline, CLOBEX (Galderma Laboratories), , OLUX-E (Mylan Pharmaceuticals), OLUX (Mylan Pharmaceuticals), TEMOVATE (PharmaDerm), OLUX (Prestium Pharma), OLUX-E (Prestium Pharma), IMPOYZ (Promius Pharma)	High
Desoximatasone gel, 0.05%	TOPICORT GEL	High
Desoximetasone Cream or ointment, 0.25%	Topicort, Topisone	High
Desoximetasone, 0.25%	Topicort emollient cream, oint	High
Diflorasone diacetate (Ointment / Cream), 0.05%	Diflal, Diacort, PSCORON, Apexicon, PSCORON E, Apexicon E, Florone, Maxiflor, ApexiCon E Cream,Nerisone, Nerisone C (+ Chloqunaldol 1%)	High
Diflucortolone valerate 0.1%	TEXMETEN, NERISONA, Nerisone ointment (NP)	High
Diflucortolone Valerate 0.3%	Nerisone Forte	High
Difluprednate 0.05%	MYSER	High
Fluocinolone acetonide ointment, 0.025%	SYNLAR ointment, FLUCORT	High
Fluocinonide 0.1%	VANOS CREAM	High

Steroid Generic Name	Trade Names	miRagen Derived Potency
Fluocinonide Cream, ointment, Lotion or gel, 0.05%	LIDEX, VANOS, TOPSYM, Lyderm, Lidemol (emmolient base), Topsyn, Lidex-E,	High
Flurandrenolide Tape, (4mcg per cm2)	Cordran	High
Fluticasone propionate (micro-ionized), 0.005%	CUTIVATE ointment	High
Halcinonide (Cream, Ointment, Solution) 0.1%	HALOG,Halciderm	High
Halobetasol propionate 0.05%	ULTRAVATE, Lexette Foam. Halox	High
Halobetasol propionate lotion, 0.01%	Bryhali Lotion, 0.01%	High
Hydrocortisone butyrate propionate 0.1%		High
Mometasone furoate ointment, 0.1%	ELOCON, FULMETA, ASMANEX, Novasone	High
Triamcinolone acetonide (ointment, cream), 0.5%	Cinalog, Kenalog	High
Triamcinolone acetonide, (Ointment, Cream, Lotion) 0.1%	LEDERCORT, KENACORT-A, Triaderm, Aristocort-R, Kenalog, Oxacort, Triacet	High
Triamcinolone acetonide, Ointment, 0.1% + chloroteracycline hydrochloride 3%	Aureocort Ointment	High
Triamicinolone diacetate cream/ointment, 0.1%	Aristocort, Amcort	High
Alclometasone dipropionate Cream or Ointment, 0.1%	ALMETA	Medium
Alclometasone dipropionate Ointment, 0.05%	ACLOVATE,	Medium
Beclometasone dipropionate 0.025%	QVAR, Generic Beclometasone dipropionate cream/Ointment, Propaderm	Medium
Beclomethasone dipropionate lotion, 0.025%	Propaderm	Medium
Betamethasone valerate, 0.12%	BETNEVATE, RINDERON-V, Lixiq Foam	Medium
Betamethasone valerate 0.025%	Betnovate-RD cream/Ointment	Medium
Betamethasone valerate Cream, 0.1%	Betnovate-1/2, Celestoderm-V, Celestoderm-V/2, Ectosone Mild-Lotion, Ectosone Regular-Cream, , Metaderm Regular, Novo-Betamet, Beta-Val	Medium
Betamethasone valerate Lotion or scalp lotion, 0.1%, Betamethosone valerate 0.05% lotion	Valisone, Ectosone, Betaderm, Ratio-Ectosone, Ratio-Ectosone mild, Fucicort (+ fusidic acid 2%), Bentonovate C cream (+ clonquinol), Ectosone Regular-Lotion, Ectosone Scalp Lotion, Metaderm Mild,	Medium
Betamethasone valerate Lotion, 0.05%	Ectosone Regular-Lotion, Ectosone Scalp Lotion, Metaderm Mild,	Medium
Betamethasone valerate, 0.05%	Betonvate ½ Celestone- V1/2, Betaderm, Ratio-Ectosone,	Medium
Budesonide	Paper from Belgium, Entocort C	Medium
Clobetasone butyrate, 0.05%	KINDAVATE, Eumovate (cream/ointment)	Medium

Steroid Generic Name	Trade Names	miRagen Derived Potency
Clocortolone pivalate, 0.1%	Cloderm cream	Medium
Deprodone propionate 0.3%	ECLAR	Medium
Desonide Ointment, 0.05%	Desocort, DesOwen ointment, Tridesilon	Medium
Desoximetasone Cream, 0.05%	Topicort Mild (Cream), Desoxi (cream), Topicort LP, Topicort 0.05% Emollient cream	Medium
Desoximetasone Gel, 0.05%	Topicort Gel	Medium
Dexamethasone propionate, 0.1%	METHADERM	Medium
Dexamethasone valerate, 0.12%	ZALUCS, VOALLA	Medium
Dexamethasone, 0.1%	DECADRON	Medium
Diflucortolone valerate cream, 0.1%	Nerisone Cr, Nerisone Oily, Nerisalic oily	Medium
Flucortolone, 0.25%	Ultralanum plain cream/ointment	Medium
Fludroxycortide Cream or Ointment, 0.05%		Medium
Fludroxycortide, 0.0125%	Haelan Cream/ointment	Medium
Fluocinolone acetonide Cream , 0.025%	SYNLAR cream, Fluoderm regular, Synemol	Medium
Fluocortin bultelester		Medium
Fluprednidene acetate	Decoderm, Decoderm Comp, Crinohermal fem, Candio-hermal Plus, Sali-Decoderm, Vabaderm, Decoder Micoflu,	Medium
Flurandrenolide, 0.05%	CORDORAN	Medium
Flurandrenolide ointment, 0.025%		Medium
Fluticasone propionate, 0.05%	CUTIVATE cream, CUTIVATE Lotion	Medium
Halcinonide Cream, 0.025%	Halog	Medium
Halometasone, 0.05%		Medium
Hydrocortisone buteprate, 0.1%, Hydrocortisone probutate 0.1%	PANDEL (cream, Ointment, Solution)	Medium
Hydrocortisone butyrate Cream, 0.1% / Hydrocortisone 17- butyrate, 0.1%,	LOCOID,Locoid Lipocream, Barriere-Hc, Cortate, Cort-Eze, Cortoderm Mild Ointment, Cortoderm Regular Ointment, Emo-Cort, Emo-Cort Scalp Solution, Hydrocortisone Cream, Novo-Hydrocort, Novo-Hydrocort Cream, Prevex Hc, Sarna Hc	Medium
Hydrocortisone valerate Cream or Ointment, 0.2%	WESCORT cream, WESCORT ointment, Hydroval	Medium
Methylprednisolone aceponate, 0.1%	Advantan cream/ointment	Medium
Mometasone furoate cream or lotion, 0.1%	ELOCON, Elocom	Medium
Prednicarbate, 0.1%	Dermatop (emollient cream, oint)	Medium
Prednisolone valerate acetate 0.3%	LIDOMEX	Medium
Triamcinolone acetonide , 0.05%, 0.02% -	Kenalone, Aristocort 1/2, Trianex (oint)	Medium
Triamcinolone acetonide, 0.025%	Triaderm,Aristocort,Kenalog	Medium
Alclometasone dipropionate Cream, 0.05%	ACLOVATE, LOGODERM, Modrasone cream	Low
Betamethasone valerate, 0.02%	Betnovate 1/5 Celestone-M	Low

Steroid Generic Name	Trade Names	miRagen Derived Potency
Desonide Cream/gel/Lotion/Solution/foam, 0.05%	VERDESDO, Desocort, Desonate, Desowen, Versedo Foam, Lokara	Low
Dexamethasone sodium phosphate Cream, 0.1%		Low
Fluocinolone acetonide, Cream/Solution/shampoo, 0.01%	SYNLAR solution, Capex, Derma-smooth/FS	Low
Fluocinolone acetonide, 0.00625%	Synalar 1 in 4 Dilution Cream, Capex, Derma-Smoothe/FS, and Synalar, Fluonid, Dermasmooth, Fluoderm Mild Cream, Fluoderm Mild Ointment, Fluoderm Regular Cream, Fluoderm Regular Ointment, Fluolar Mild, Fluolar Regular, Fluonide Mild-Cream, Synalar Mild, Synalar Regular, and Synamol	Low
Fluocinonide, 0.01%		Low
Flurandrenolide cream, 0.025%		Low
Hydrocortisone 2.5%, 1.85%, 1%, 0.5% (any formulation, Base or Acetate)	Dermaid Cream, Soft cream, DP Lotion-HC 1%, Skincalm, Lemnis Fatty Acid Cream, Pimafucort Cream/Ointment, A-Hydrocort, Ala-Cort, Ala-Scalp, Anucort-HC, Anumed-HC, Anusol HC, Caldecort, Cetacort, Colocort, Cordate, Cortaid, Cortaid Advanced, Cortaid Intensive Therapy, Cortderm, Cortef, Cortenema, Corticaine, Corticool, Cortifoam, Cortizone, Cortizone-10, Cortizone-10 Cooling Relief, Cortizone-10 Intensive Healing, Cortizone-10 Plus, Dermarest, Dricort, Dermarest Eczema, Dioderm, Emo-cort, Encort, First - Hydrocortisone, Gly-Cort, GRx HiCort, Hemmorex-HC, Hemorrhoidal-HC, Hemril, Hycort, Hyderm, Hydro Skin, Hydrocortisone in Absorbase, Hydrocortone, Hydroskin, Hytone, Instacort, Lacticare HC, Locoid, Locoid Lipocream, MiCort-HC, Monistat Complete Care Instant Itch Relief Cream, Neosporin Eczema, NuCort, Nutracort, NuZon, Pandel, Penecort, Preparation H Hydrocortisone, Pramosone 2.5%, Procto-Kit, Procto-Med HC, Procto-Pak, Proctocort, Proctocream-HC, Proctosert HC, Proctosol-HC, Proctozone-HC, Rectacort HC, Rectasol-HC, Rederm, Sarna-HC (camphor & menthol)Scalacort, Scalpicin Anti-Itch, Solu-Cortef, Texacort, Tucks HC, Vagisil Anti-Itch, Walgreens Intensive Healing, Westcort	Low
Hydrocortisone (+ Miconazole)	Micreme H	Low
Hydrocortisone (+ neomycin, natamycin)	Primafucort cream/ointment	Low
Hydrocortisone (alcohol or acetate) 0.5%, 1%, 2%	Cortic 0.5%, Cortaid, Derm-aid, Cortef, Egocort, Sigmacort, Squibb-HC, Analpram HC, Epifoam,	Low

Steroid Generic Name	Trade Names	miRagen Derived Potency
	Pramosone 1%, Ucort, Proctofoam HC 1%, HC-SLONE, Pediaderm HC (Lotion), Scalacort (lotion), (Cortaid, Cortef Feminine or Rectal Itch Cream, Gynecort, Lanacort, Wellcortin)	
Hydrocortisone/Urea 1%/10%		Low
Methylprednisolone		Low
Methylprednisolone acetate Cream, 0.25%		Low
Prednicarbate, 0.05%	Dermatop (emollient cream, oint)	Low
Prednisolone 0.5%	PREDONINE	Low
Tixocortol pivalate	Pivalone	Low