TITLE PAGE

SYNOPTIC CLINICAL STUDY REPORT

Study 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
Product Name or Number:	Cobomarsen (MRG-106)
Protocol Number:	MRG106-11-201
Developmental Phase:	2
Indication Studied:	Cutaneous T-Cell Lymphoma, Mycosis Fungoides Subtype
First Subject, First Visit	02APR2019
Last Subject, Last Visit:	01DEC2020
Data Cutoff	12OCT2020
Study Sponsor:	miRagen Therapeutics, Inc. 6200 Lookout Road Boulder, CO 80301 USA
Sponsor's Responsible Medical Officer:	Diana M. Escolar, MD, FAAN
Type of Report:	Synoptic Clinical Study Report
Date of Report:	31DEC2020

Quality Assurance Statement

This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and International Conference on Harmonization (ICH) Guidelines.

Confidentiality Statement

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1. ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Specialist Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
CI	Confidence interval
CPK	Creatine phosphokinase
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
ECG	Electrocardiogram
FDA	Food and Drug Administration
EOT	End of treatment
GGT	Gamma-glutamyl transferase
ITT	Intent to treat
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
MRG-106	Cobomarsen
mSWAT	Modified Severity Weighted Assessment Tool
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate (sum of CR plus PR)
ORR1	Objective response lasting at least 28 days
ORR4	Objective response in skin of at least 4 months duration
PD	Progressive disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change

Abbreviation/Specialist Term	Definition
PGIS	Patient Global Impression of Severity
PR	Partial response
Q1	25th percentile
Q3	75th percentile
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal

2. STUDY OBJECTIVES

The primary objective of this study was to evaluate the efficacy of cobomarsen in subjects with mycosis fungoides (MF).

Secondary objectives included assessing the safety and tolerability of cobomarsen in subjects with MF and characterizing the population pharmacokinetics of cobomarsen in subjects with MF.

3. METHODOLOGY

This Phase 2 randomized (1:1 ratio), open-label, parallel-group, active-comparator, multicenter study was conducted to assess the efficacy and safety of cobomarsen compared with vorinostat in subjects with MF. Subjects were enrolled at 21 clinical sites in Belgium, Canada, France, Italy, Spain, the United Kingdom, and the United States.

Subject participation was estimated to be up to 365 days or longer (including 28-day screening, active treatment, and follow-up for progression). Subjects remained on their assigned study treatment until confirmed disease progression, defined as either:

Confirmed progression in skin

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

b. Clinical progression in other compartments, documented by assessments (flow cytometry and/or computerized tomography [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 the modified Severity Weighted Assessment Tool (mSWAT) score (Olsen et al. 2011) that is greater than the sum of nadir plus 50% baseline score.

d. Subject met one of the other treatment discontinuation criteria described in the protocol (Appendix A).

3.1. Number of Subjects (Planned and Analyzed)

Although the study was planned to involve approximately 126 subjects, enrollment was stopped after 37 subjects were enrolled.

3.2. Test Product

Cobomarsen was administered by intravenous 2-hour infusion at a dose of 282 mg of the active moiety (equivalent to 300 mg of the active pharmaceutical ingredient or sodium salt form) on Days 1, 3, 5, 8, and weekly thereafter.

3.3. Reference Therapy

Vorinostat (400 mg [4x100 mg capsules]) was administered orally once daily with food, at approximately the same time each day. Subjects with abnormal alanine aminotransferase/ aspartate aminotransferase (ALT/AST) (> upper limit of normal [ULN]) or bilirubin (> 1.0 × ULN) at screening were to start vorinostat dosing at 300 mg (three 100-mg capsules) once daily with food, at approximately the same time each day, per dosing guidelines.

4. CRITERIA FOR EVALUATION

4.1. Efficacy

The primary efficacy endpoint was the proportion of subjects achieving a confirmed objective skin response (complete response [CR] or partial response [PR]) of at least 4 months duration (overall response rate [ORR4]) using the mSWAT scoring. In the original protocol, objective response was assessed by the criteria of Olsen et al. (2011), including response in the skin, nodes, blood, and viscera. Protocol Amendment v4.0 narrowed the response criteria to include skin response only in this population of patients that did not have abnormal nodes, viscera or blood involvement at screening (exclusion criteria). The secondary efficacy endpoint was progression-free survival (PFS), defined as the time from randomization to the earliest date of documented progression in the skin, or death due to any cause. Patient-reported outcomes were also assessed in subjects enrolled under protocol v3.0 and earlier. The impact of skin disease on quality of life was assessed by daily and weekly pain and pruritus assessments, change from baseline in pruritus medication utilization, weekly assessment of the Patient Global Impression of Change (PGI-C) scale and the Patient Global Impression of Severity (PGI-S) scale, and the Skindex-29 questionnaire (Chren et al. 1996). The Skindex-29 instrument is a validated measure of the effects of skin disease on quality of life and includes a total score as well as subdomain scores addressing symptoms, and emotional and functional impacts. The Skindex-29 questionnaire was completed at Screening, Day 1, and every 4 weeks thereafter.

4.2. Safety

Safety was assessed by incidence and severity of treatment-emergent adverse events (TEAEs), including Grade 3 and 4 adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), AEs requiring discontinuation, as well as physical examination findings, changes in electrocardiograms (ECGs), changes in laboratory parameters, and changes in vital signs.

5. STATISTICAL CONSIDERATIONS

The study planned for an interim analysis for futility (low likelihood to show superiority to the control should the study continue) based on ORR4 after approximately 40 subjects were followed for a minimum of approximately 6 months. Enrollment was halted after 37 subjects were randomized and followed for at least 6 months. A decision was then made to stop the trial after enrollment was halted, so that the interim analysis based on these 37 subjects became the final analysis for the study. The study was adequately powered for the planned futility analysis but was not powered for superiority or equivalence based on this sample size. The decision to halt the study prematurely was made for business reasons and not for reasons of safety or futility.

No interim analysis was planned for the secondary efficacy endpoint, PFS. However, since the interim analysis became the final analysis, a Kaplan-Meier analysis was performed to compare PFS between the cobomarsen and vorinostat treatment groups.

Other outcomes that reported aggregate data with statistical analysis included the number of subjects achieving an objective response lasting at least 28 days (ORR1) and the duration of response among subjects in each treatment group who achieved a PR or CR. Additional outcomes that reported aggregate data without statistical analysis included the results of patient-reported outcomes over time for quality of life (based on the Skindex-29 total score), pain and pruritus (based on daily and weekly questionnaires), and pruritus medication utilization (based on concomitant medication reporting). Results of Skindex-29 subdomain scores, PGI-C and PGI-S assessments were not analyzed.

The safety population included all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat).

TEAEs, treatment-emergent serious adverse events (TESAEs), and treatment-related AEs, were coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. SAEs, discontinuations due to AEs, and Grade 3 or 4 AEs were summarized. Severity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. Relationship to study treatment was based on investigator's attribution.

6. DISPOSITION AND BASELINE/DEMOGRAPHIC CHARACTERISTICS

6.1. Subject Disposition (All Enrolled Subjects)

The first date of informed consent for any subject enrolled on study was 02APR2019 and the first date of dosing was 24APR2019. As of 31JAN2020, 37 subjects were enrolled in the study.

At this time, enrollment was halted in order to perform the planned interim analysis with the data from these patients. Subsequently, the decision was made to stop the trial in September 2020. The interim analysis thus became the final analysis for the study. The data cutoff for the results presented in this clinical study report is 12OCT2020. Data collected for subjects remaining on study treatment from 12OCT2020 through the last subject visit (01DEC2020) are not included in this report.

As displayed in Table 1, the most common reason for discontinuing treatment in both groups was progressive disease (PD) (4 subjects [21.1%] for cobomarsen versus 8 subjects [44.4%] for vorinostat). One subject (5.3%) in the cobomarsen group stopped treatment because of an AE (Day 72, Grade 1 lactate dehydrogenase [LDH] increase, not related, and ongoing) versus 5 subjects (27.8%) in the vorinostat group.

Table 1: Disposition of Subjects (All Enrolled Subjects)

	Cobomarsen (N = 19)	Vorinostat (N = 18)	Total (N = 37)
Subjects randomized	19 (100%)	18 (100%)	37 (100%)
Safety population[1]	19 (100%)	18 (100%)	37 (100%)
ITT population[2]	19 (100%)	18 (100%)	37 (100%)
Ended treatment			
Yes	13 (68.4%)	15 (83.3%)	28 (75.7%)
No	6 (31.6%)	3 (16.7%)	9 (24.3%)
Primary reason for end of treatment			
Progressive disease	4 (21.1%)	8 (44.4%)	12 (32.4%)
Adverse event	1 (5.3%)	5 (27.8%)	6 (16.2%)
Non-compliance/protocol violation	0	0	0
Sponsor's decision	0	0	0
Physician decision	1 (5.3%)	1 (5.6%)	2 (5.4%)
Lost to follow-up	0	0	0
Consent withdrawn	4 (21.1%)	0	4 (10.8%)
Death	0	0	0
Other	3 (15.8%)	1 (5.6%)	4 (10.8%)

ITT = intent to treat

[1] The safety population includes all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat). Assignment of subjects to treatment group is based on the treatment actually received.

[2] The ITT Population includes all randomized subjects who received at least one dose of study treatment (cobomarsen or vorinostat) and had at least one post-baseline assessment. Assignment of subjects to treatment group is based on the planned treatment assignment.

Sources: Table 14.1.1.1 and Listing 16.2.1

6.2. Demographic Characteristics (Safety Population)

The demographic characteristics were similar in the two treatment groups and were representative of the characteristics of the study population. Prognostic indicators, including baseline LDH level, age > 60, and the presence of tumors was similar between both arms, with the cobomarsen arm having a slightly higher number of subjects with skin tumors at screening and elevated LDH at diagnosis (Table 2).

Table 2: Demographic Characteristics (Safety Population)

	Cobomarsen (N = 19)	Vorinostat (N = 18)	Total (N = 37)
Age (years)[1]			
n	19	18	37
Mean (SD)	58.5 (15.58)	56.0 (16.42)	57.3 (15.82)
Median (Q1, Q3)	60.0 (50.0, 74.0)	58.0 (44.0, 67.0)	60.0 (50.0, 68.0)
Min, max	28, 80	23, 83	23, 83
Age at diagnosis			
≤ 60	12 (63.2%)	11 (61.1%)	23 (62.2%)
> 60	7 (36.8%)	7 (38.9%)	14 (37.8%)
Sex			
Male	10 (52.6%)	11 (61.1%)	21 (56.8%)
Female	9 (47.4%)	7 (38.9%)	16 (43.2%)
Ethnicity			
Hispanic or Latino	4 (21.1%)	1 (5.6%)	5 (13.5%)
Not Hispanic or Latino	14 (73.7%)	14 (77.8%)	28 (75.7%)
Not reported	1 (5.3%)	3 (16.7%)	4 (10.8%)
Unknown	0	0	0
Race			
American Indian or Alaska Native	0	0	0
Asian	0	1 (5.6%)	1 (2.7%)
Black or African American	0	1 (5.6%)	1 (2.7%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	17 (89.5%)	13 (72.2%)	30 (81.1%)
Not reported	2 (10.5%)	3 (16.7%)	5 (13.5%)
Other	0	0	0
Skin tumor at screening			
Yes	6 (31.6%)	4 (22.2%)	10 (27.0%)
No	13 (68.4%)	14 (77.8%)	27 (73.0%)
LDH > ULN at diagnosis			
Yes	4 (21.1%)	2 (11.1%)	6 (16.2%)
No	15 (78.9%)	14 (77.8%)	29 (78.4%)
Not reported	0	2 (11.1%)	2 (5.4%)

LDH = lactate dehydrogenase; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; ULN = upper limit of normal

[1] Age at informed consent as recorded on the case report form

Sources: Table 14.1.2.1 and Listing 16.2.2

7. EFFICACY RESULTS

Full data set and sensitivity analyses were performed for ORR4 and PFS. The sensitivity analysis excluded 8 subjects who missed more than one month of consecutive dosing and/or more than one month of consecutive mSWAT assessments because of the COVID-19 pandemic.

7.1. Primary Efficacy Endpoint (Objective Response Lasting 4 Months)

Response to treatment (ORR4) was similar in the two groups (Table 3), with three subjects achieving ORR4 in each treatment arm. The results were also similar in the sensitivity analysis for ORR4, with two subjects achieving ORR4 in each treatment arm (Table 14.2.2.2).

Table 3: Best Response and Rate of Objective Skin Response of at Least 4 Months Duration (ITT Population)

	Cobomarsen (N=19)		Vorinostat (N=18)		
Best response achieved	n (%)	95% CI[1]	n (%)	95% CI[1]	P-value[2]
Complete response (CR)	0 (0.0%)	0.0, 0.2	1 (5.6%)	0.0, 0.3	
Partial response (PR)	6 (31.6%)	0.1, 0.6	5 (27.8%)	0.1, 0.5	
Stable disease (SD)	13 (68.4%)	0.4, 0.9	11 (61.1%)	0.4, 0.8	
Unconfirmed progressive disease (PDu)	0 (0.0%)	0.0, 0.2	1 (5.6%)	0.0, 0.3	
Progressive disease (PD)	0 (0.0%)	0.0, 0.2	0 (0.0%)	0.0, 0.2	
Relapse	0 (0.0%)	0.0, 0.2	0 (0.0%)	0.0, 0.2	
Missing or not evaluated	0 (0.0%)	0.0, 0.2	0 (0.0%)	0.0, 0.2	
Rate of objective skin response of at least 4 months duration (ORR4)	3 (15.8%)	0.0, 0.4	3 (16.7%)	0.0, 0.4	0.9539

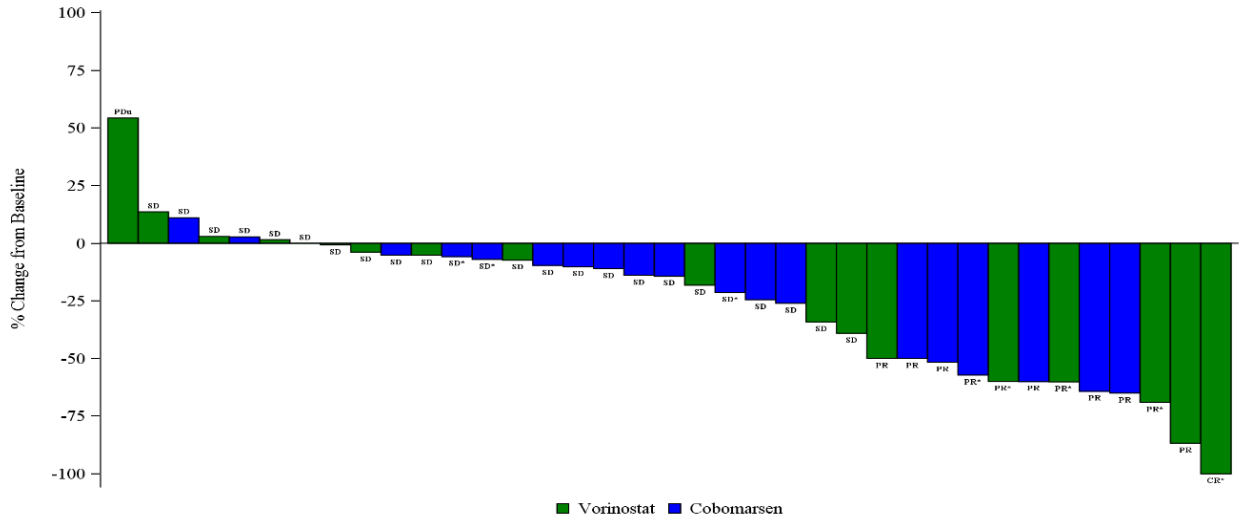
CI = confidence interval; CR = complete response; ITT = intent to treat; LDH = lactate dehydrogenase; mSWAT = modified Severity Weighted Assessment Tool; ORR4 = rate of objective skin response of at least 4 months duration; PD = progressive disease; PDu = unconfirmed progressive disease; PR = partial response; SD = stable disease; ULN = upper limit of normal
[1] Exact binomial (Clopper-Pearson) confidence intervals
[2] P-value comparing the treatment groups is based on a Cochran-Mantel-Haenzels test controlling for the number of tumors at screening (at least one tumor at screening versus no tumors at screening) and number of prognostic factors (0-1 prognostic factors versus 2 prognostic factors). Prognostic factors include age at diagnosis > 60 years and LDH level > ULN at diagnosis.

Note: Objective response rate is defined as subjects with CR or PR in mSWAT for 4 consecutive months confirmed by repeat assessments no less than 28 days (±3 days) later.

Sources: Table 14.2.1.1 and Listings 16.2.3.1 and 16.2.3.2

The waterfall plot of best response in skin as measured by change (increase or decrease) in mSWAT scores is presented in Figure 1. The percentage change from baseline is the maximum percentage decrease (or minimum increase if no decrease) in the mSWAT score across all post-baseline visits. There was no clear difference between the treatment arms.

Figure 1: Best Overall Response in Skin (ITT Population)



CR = complete response; ITT = intent to treat; PD = progressive disease; PR = partial response; SD = stable disease
* Denotes a subject excluded from the sensitivity analysis because of the COVID-19 pandemic

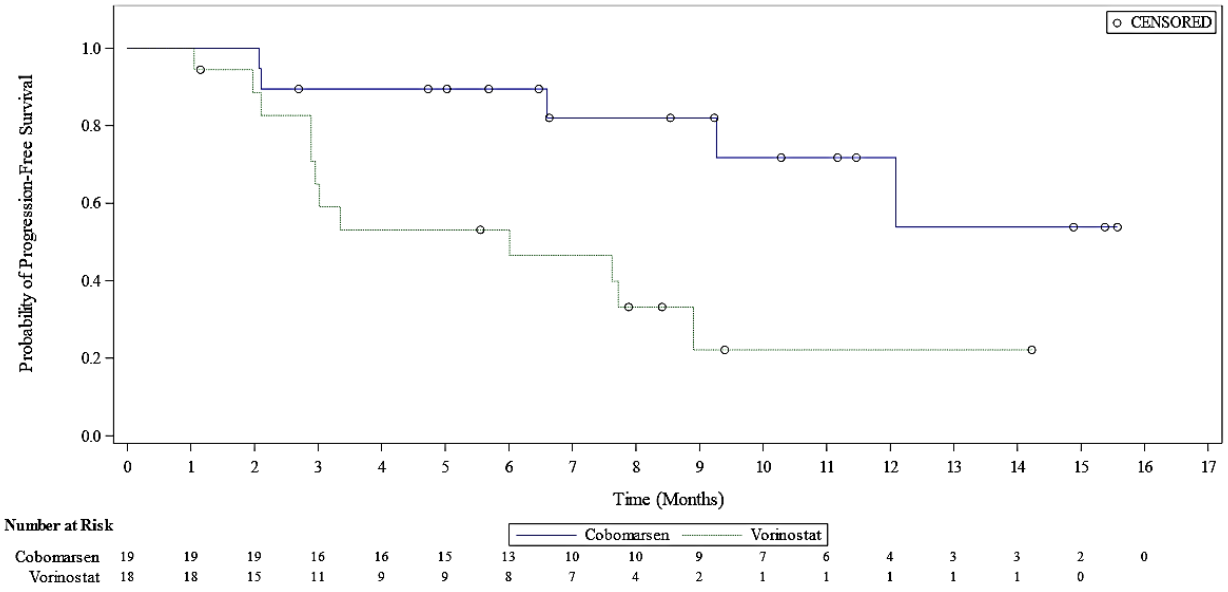
Sources: Figure 14.4.5 and Listings 16.2.3.1, 16.2.3.2, and 16.2.3.3

7.2. Secondary Efficacy Endpoint (Progression-free Survival)

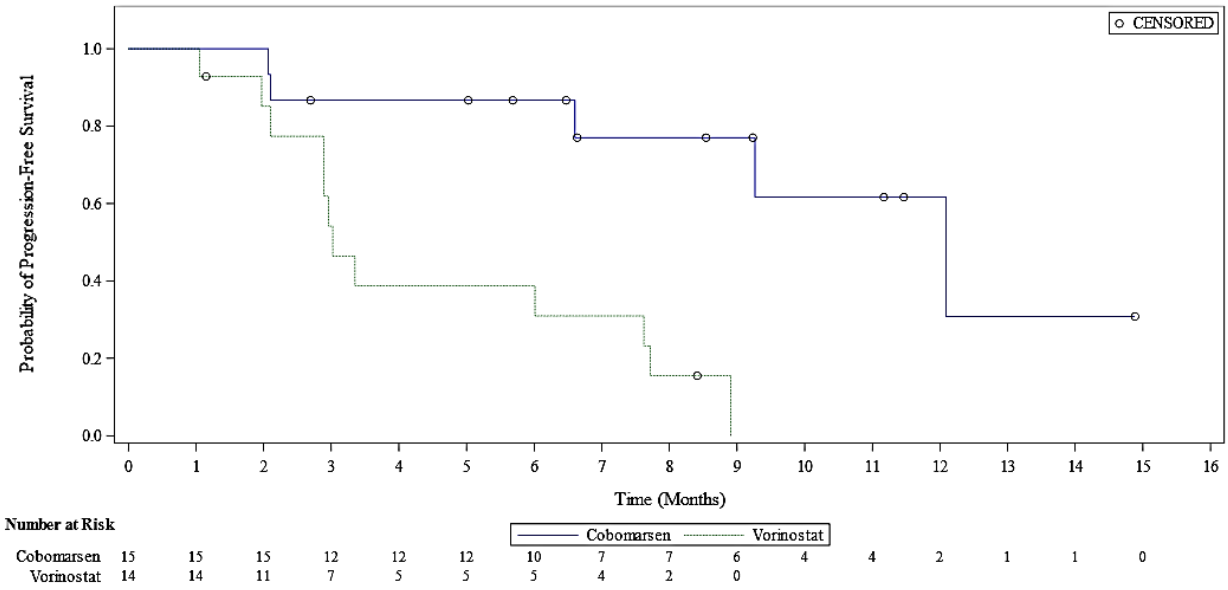
PFS (defined as the time from randomization to the date of earliest documented progression or death) was significantly longer ($p < 0.011$) with cobomarsen than with vorinostat. The results were similar in the sensitivity analysis (Figure 2).

Figure 2: Kaplan-Meier Plot of Progression-free Survival (ITT Population)

Full data set: p = 0.011



Sensitivity ana1ysis: p = 0.003



ITT = intent to treat

Note: Progression-free survival was defined as the time from randomization to the date of earliest documented progression or death. The duration of progression-free survival was censored at the date of the last mSWAT assessment if the subject was alive and had no documented progression.

Sources: Figures 14.4.1 and 14.4.2, Table 14.2.3.1 and Listing 16.2.3.1

7.3. Secondary Efficacy Endpoint (Duration of Response in Skin)

Duration of response in the skin is summarized in Tables 14.2.5.1 and 14.2.5.2.

7.4. Patient-reported Outcomes

7.4.1. Skindex-29

For both treatment arms, the Skindex-29 total score showed some improvement in quality of life (Figure 3). After the end of treatment and follow-up, subjects who completed the questionnaire showed a worsening of quality of life, as measured by this instrument. Over time, fewer subjects completed the questionnaires, limiting their interpretability. Subdomains of the Skindex-29 questionnaire were not analyzed separately, but the data are provided in Listing 16.2.3.4.

Figure 3: Skindex-29 Change from Baseline by Treatment

EOT = end of treatment

Source: Table 14.2.7.1 and Listing 16.2.3.4

7.4.2. Pruritus and Pain

Pruritus and pain were each measured daily and weekly by asking subjects to rate their worst itch or their worst pain over the last 24 hours using an 11-point scale ranging from 0 (no itch/pain) to 10 (worst imaginable itch/pain). Mean daily pruritus score and mean daily pain score are shown in Figure 4 and Figure 5, respectively, for study days on which more than 3 subjects could be evaluated.

The vorinostat arm was superior to the cobomarsen arm in terms of reduction in daily pain and pruritus scores (Figure 4 and Figure 5). However, subjects treated with cobomarsen had a 73.7% reduction in pruritus medication use versus 38.9% for vorinostat (Table 14.2.6.1).

Although scores on the PGI-S and PGI-C scales for both pain and pruritus were collected during the study, they were not evaluated for the final analysis but are available in the final datasets.

Figure 4: Pruritus Mean Daily Score (by Study Day n>3)[a]

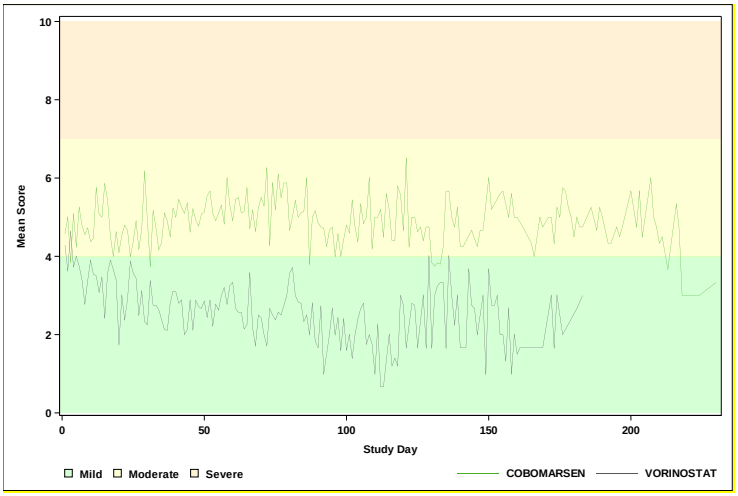
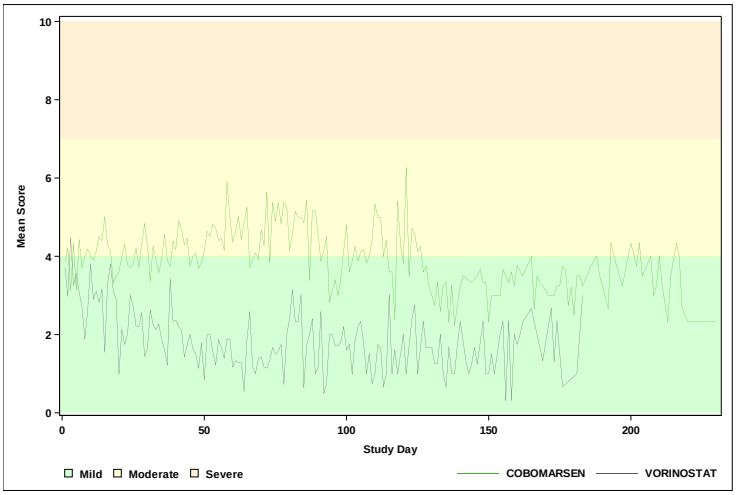


Figure 5: Pain Mean Daily Score (n>3)[a]



[a]Mild, moderate, and severe designations were defined by the sponsor

Source: Listing 16.2.3.5

8. SAFETY RESULTS

8.1. Extent of Exposure (Safety Population)

Duration of treatment was longer for cobomarsen than for vorinostat (Table 4). However, the exposure data for the vorinostat arm were based on entries in the daily vorinostat diaries and compliance in completing the diaries was uneven.

Table 4: Duration of Treatment (Safety Population)

	Cobomarsen (N = 19)	Vorinostat (N = 18)
Duration of exposure (days)[1]		
n	19	18
Mean (SD)	247.9 (133.66)	140.8 (106.91)
Median (Q1, Q3)	246.0 (134.0, 351.0)	111.5 (78.0, 208.0)
Min, max	72, 477	10, 428
Total dose received (mg)[2]		
n	19	18
Mean (SD)	9231.8 (4187.85)	25761.1 (23223.09)
Median (Q1, Q3)	8460.0 (6204.0, 12972.0)	21600.0 (4800.0, 32800.0)
Min, Max	3666, 18048	700, 75900

SD = standard deviation; Q1 = 25th percentile; Q3 = 75th percentile;
[1] For subjects randomized to cobomarsen, the duration of exposure was calculated as the date of last cobomarsen infusion minus the date of first cobomarsen infusion + 1. For subjects randomized to vorinostat, the duration of treatment was the date of last vorinostat dose minus the date of first vorinostat dose + 1.
[2] For subjects randomized to cobomarsen, the total dose received is based on the administration case report form. For subjects randomized to vorinostat, the total dose received is based on the administration and daily diary case report forms.

Sources: Table 14.3.3.1 and Listings 16.2.5.1 and 16.2.5.2

With cobomarsen, only a few subjects had treatment interruptions, suggesting that there was good compliance with drug administration (Listing 16.2.5.2).

For one subject (3201-0005), the Week 29 infusion (Day 199) was interrupted for over 2 hours because of Grade 2 allergic pruritus (infusion-related reaction). The AE lasted from Day 199 to Day 205 and was considered related to study treatment.

With vorinostat, dosage was reduced in 7 subjects because of side effects (Listing 16.2.5.1).

8.2. Adverse Events

AEs collected through the data cutoff date of 12OCT2020 are summarized in this report. Any SAEs reported between 12OCT2020 and 01DEC2020 or after the last study visit through the end of 2020 will be reported as per protocol and Good Clinical Practice. All other AEs reported between 12OCT2020 and 01DEC2020 will be included in the final AE dataset.

8.2.1. Summary of Adverse Events (Safety Population)

The number of subjects with TEAEs was similar in both treatment groups (Table 5) though the number of related TEAEs was lower in the cobomarsen arm (12 subjects [63.2%]) than in the vorinostat arm (17 subjects [94.4%]). There were no Grade 4 TEAEs in the cobomarsen arm versus 1 (5.6%) in the vorinostat arm.

No subject discontinued treatment with cobomarsen because of a TEAE, while 6 subjects (33.3%) discontinued treatment with vorinostat because of a TEAE (Table 5).

Table 5: Summary of Adverse Events (Safety Population)

	Cobomarsen (N = 19)	Vorinostat (N = 18)
Total number of TEAEs	204	162
Number (%) of subjects reporting at least one:		
TEAE	18 (94.7%)	17 (94.4%)
TEAE by CTCAE Grade[1]		
Grade 1	3 (15.8%)	1 (5.6%)
Grade 2	13 (68.4%)	9 (50.0%)
Grade 3	2 (10.5%)[2]	6 (33.3%)
Grade 4	0	1 (5.6%)
Grade 5	0	0
TEAE by relationship[3]		
Not related	6 (31.6%)	0
Related	12 (63.2%)	17 (94.4%)
TEAE leading to discontinuation of study drug	0	6 (33.3%)
TEAE requiring dose interruption of study drug	3 (15.8%)	3 (16.7%)
TEAE requiring dose reduction of study drug	0	2 (11.1%)
TEAE requiring dose rate reduction of study drug	0	1 (5.6%)
TEAE causing death	0	0
Total number of TESAEs	3	1
Number (%) of subjects reporting at least one:		
TESAE	2 (10.5%)	1 (5.6%)
TESAE by CTCAE Grade[1]		
Grade 1	0	0
Grade 2	1 (5.3%)	0
Grade 3	1 (5.3%)	1 (5.6%)
Grade 4	0	0
Grade 5	0	0
TESAE by relationship[3]		
Not related	2 (10.5%)	1 (5.6%)
Related	0	0

CTCAE = common terminology criteria for adverse events; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[1] Subjects reporting more than one adverse event are counted only once using the highest severity

[2] Listing 16.2.4.2 (Grade 3/4 AEs) shows 3 subjects receiving cobomarsen having Grade 3/4 AEs, whereas the table above and Table 14.3.1.1 show 2. The third subject (0102-0054) shown in Listing 16.2.4.2 with a Grade 3 AE is not included in the summary tables because the AE (squamous cell carcinoma) was not treatment-emergent, occurring as it did on 03JAN2020, while the subject started treatment on 22JAN2020.

[3] Subjects reporting more than one adverse event are counted only once using the closest relationship to study drug

Sources: Table 14.3.1.1 and Listings 16.2.4.1 and 16.2.4.2

In both treatment arms, the system organ class with the highest rate of TEAEs was gastrointestinal disorders (52.6% for cobomarsen and 72.2% for vorinostat), with diarrhea and nausea being the most frequent TEAE for both: 36.8% for both diarrhea and nausea for cobomarsen and 38.9% and 33.3%, respectively, for vorinostat. Overall, there were no notable differences in the rate of AEs occurring in ≥ 10% of subjects between the 2 treatment groups (Table 6).

Table 6: Treatment-Emergent Non-serious AEs Occurring in ≥ 10% of MF subjects treated with Cobomarsen or Vorinostat

System Organ Class *Preferred Term*	Cobomarsen (N = 19)	Vorinostat (N = 18)	Total (N = 37)
Gastrointestinal disorders	10 (52.6%)	13 (72.2%)	23 (62.2%)
Diarrhoea	7 (36.8%)	7 (38.9%)	14 (37.8%)
Nausea	7 (36.8%)	6 (33.3%)	13 (35.1%)
Constipation	2 (10.5%)	2 (11.1%)	4 (10.8%)
Vomiting	0	3 (16.7%)	3 (8.1%)
Abdominal pain upper	0	2 (11.1%)	2 (5.4%)
General disorders and administration site conditions	8 (42.1%)	10 (55.6%)	18 (48.6%)
Fatigue	7 (36.8%)	6 (33.3%)	13 (35.1%)
Influenza like illness	1 (5.3%)	3 (16.7%)	4 (10.8%)
Pyrexia	3 (15.8%)	1 (5.6%)	4 (10.8%)
Chills	1 (5.3%)	2 (11.1%)	3 (8.1%)
Skin and subcutaneous tissue disorders	8 (42.1%)	8 (44.4%)	16 (43.2%)
Pruritus	7 (36.8%)	4 (22.2%)	11 (29.7%)
Alopecia	1 (5.3%)	5 (27.8%)	6 (16.2%)
Dry skin	2 (10.5%)	1 (5.6%)	3 (8.1%)
Infections and infestations	6 (31.6%)	4 (22.2%)	10 (27.0%)
Skin infection	4 (21.1%)	0	4 (10.8%)
Nasopharyngitis	0	3 (16.7%)	3 (8.1%)
Overgrowth bacterial	2 (10.5%)	1 (5.6%)	3 (8.1%)
Urinary tract infection	2 (10.5%)	0	2 (5.4%)
Respiratory, thoracic and mediastinal disorders	6 (31.6%)	4 (22.2%)	10 (27.0%)
Cough	3 (15.8%)	2 (11.1%)	5 (13.5%)
Dyspnoea	1 (5.3%)	2 (11.1%)	3 (8.1%)
Dysphonia	0	2 (11.1%)	2 (5.4%)
Nasal congestion	2 (10.5%)	0	2 (5.4%)
Musculoskeletal and connective tissue disorders	2 (10.5%)	6 (33.3%)	8 (21.6%)
Muscle spasms	2 (10.5%)	6 (33.3%)	8 (21.6%)
Back pain	0	2 (11.1%)	2 (5.4%)
Nervous system disorder	6 (31.6%)	2 (11.1%)	8 (21.6%)

Table 6: Treatment-Emergent Non-serious AEs Occurring in ≥ 10% of MF subjects treated with Cobomarsen or Vorinostat

Headache	5 (26.3%)	0	5 (13.5%)
Dizziness	2 (10.5%)	0	2 (5.4%)
Paraesthesia	0	2 (11.1%)	2 (5.4%)
Metabolism and nutrition disorders	3 (15.8%)	4 (22.2%)	7 (18.9%)
Decreased appetite	1 (5.3%)	4 (22.2%)	5 (13.5%)
Hyperuricaemia	2 (10.5%)	0	2 (5.4%)
Vascular disorders	3 (15.8%)	4 (22.2%)	7 (18.9%)
Hypertension	3 (15.8%)	4 (22.2%)	7 (18.9%)
Blood and lymphatic system disorders	0	3 (16.7%)	3 (8.1%)
Lymphopenia	0	2 (11.1%)	2 (5.4%)
Thrombocytopenia	0	2 (11.1%)	2 (5.4%)
Investigations	2 (10.5%)	0	2 (5.4%)
Weight increased	2 (10.5%)	0	2 (5.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (10.5%)	0	2 (5.4%)
Tumour pain	2 (10.5%)	0	2 (5.4%)
Psychiatric disorders	2 (10.5%)	0	2 (5.4%)
Depression	2 (10.5%)	0	2 (5.4%)

AEs = adverse events

Source: Table 14.3.1.3

With cobomarsen, 2 subjects had Grade 3 TEAEs and none had Grade 4 AEs (Table 5). One of these Grade 3 AEs (urticaria) was considered related to treatment (Table 7).

With vorinostat, 6 subjects had Grade 3 TEAEs and one had a Grade 4 TEAE (creatine kinase increased) (Table 5). The Grade 3 TEAEs considered related to treatment included creatine phosphokinase (CPK) increased, AST increased, hepatocellular injury, cholestasis, and thrombocytopenia (Table 7). The CPK increased and AST increased were in one subject (0123-0021), who was discontinued because of the Grade 4 CPK increase.

Table 7: Treatment-Emergent Related Grade 3-4 Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class ***Preferred Term***[1]	Cobomarsen (N = 19)	Vorinostat (N = 18)
Subjects reporting at least one related Grade 3-4 TEAE	1 (5.3%)	3 (16.7%)
Blood and lymphatic system disorders	0	1 (5.6%)
Thrombocytopenia	0	1 (5.6%)
Hepatobiliary disorders	0	1 (5.6%)
Cholestasis	0	1 (5.6%)
Hepatocellular injury	0	1 (5.6%)
Investigations	0	1 (5.6%)
Aspartate aminotransferase increased	0	1 (5.6%)
Blood creatine phosphokinase increased	0	1 (5.6%)
Skin and subcutaneous tissue disorders	1 (5.3%)	0
Urticaria	1 (5.3%)	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event are counted only once.
[1] Adverse events are coded to system organ class and preferred term using MedDRA, version 21.1

Sources: Table 14.3.1.2 and Listings 16.2.4.1 and 16.2.4.2

8.2.2. Serious Adverse Events

There were 3 SAEs in 2 subjects treated with cobomarsen and 1 SAE in 1 subject treated with vorinostat (Table 8). All these events were deemed serious because they resulted in hospitalization or prolongation of hospitalization. None of the SAEs in either group were considered related to treatment.

Table 8: Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

Subject ID	System Organ Class[1] / *Preferred Term*[1] / Verbatim Term	Start Date/Time (Study Day[2])	End Date/Time (Study Day[2])	CTCAE Grade	Relationship to Investigational Product	Action Taken	Outcome
Cobomarsen							
0130-0012	**Infections and infestations** / *Skin infection* / Skin Infection	22JUL2019 (8)	17AUG2019 (34)	Grade 2	Not related	Drug interrupted; antibiotic treatment	Recovered /Resolved
3201-0005	**Infections and infestations** / *Superinfection* / Superinfection of Skin Lesions	06FEB2020 (289)	11FEB2020 (294)	Grade 3	Not related	Dose not changed; medication	Recovered /Resolved
3201-0005	**Infections and infestations** / *Superinfection* / Superinfection of Skin Lesions	04MAY2020 (377)	15JUN2020 (419)	Grade 3	Not related	Dose not changed	Recovered /Resolved
Vorinostat							
0135-0017	**Injury, poisoning and procedural complications** / *Infusion related reaction* / Infusion Related Reaction (**To A New Study Drug**)	23DEC2019 12:35 (106)	25DEC2019 (108)	Grade 3	Not related	Not applicable	Recovered /Resolved

CTCAE = Common Terminology Criteria for Adverse Events
[1] Adverse events are coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1.
[2] Time (days) relative to date of first dose of study drug

Source: Table 14.3.2.2

8.2.3. Deaths

There were no deaths in the study (Table 14.3.2.1).

8.3. Clinical Laboratory Evaluation

In the cobomarsen treatment group, there were no Grade 3/4 laboratory abnormalities and no significant trends in activated partial thromboplastin time (aPTT), gamma-glutamyl transferase (GGT), or in lymphocyte or platelet counts.

In the vorinostat group, 5 subjects had 25 instances of Grade 3 or 4 laboratory abnormalities, with Grade 1-3 platelet count decreases in 6/18 subjects (33.3%).

In addition, some laboratory abnormalities were reported as AEs (see Section 8.2.1).

8.4. Vital Signs, Physical Findings, and Other Observations Related to Safety

Blood pressure increases were recorded in both treatment groups. Over 40% of subjects in each group had a history of hypertension. The blood pressure increases were mostly mild or moderate (Grade 1 or Grade 2) (Table 14.3.4.1 and Listing 16.2.6.1).

There were no significant ECG findings or QTc prolongation in either arm (Table 14.3.4.2 and Listing 16.2.6.2).

9. CONCLUSIONS

This curtailed study found no evidence that cobomarsen is inferior to vorinostat (an FDA approved drug for CTCL) with respect to objective response rate in the skin. Cobomarsen was superior to vorinostat in providing disease stabilization, as shown by a significant prolongation in PFS, and had a better safety profile, with no patients discontinuing cobomarsen because of drug-related adverse events. Of note, the study did not include subjects with disease involvement in lymph nodes, blood, or viscera; thus, response to drug was limited to skin assessment, the compartment involved at baseline. Patient-reported outcomes and medication use for pruritus were collected among subjects enrolled prior to implementation of protocol v4.0. Based on the data collected for these subjects, vorinostat appears superior in controlling pain and pruritus, however, there was a significant decrease in pruritus medication utilization in the cobomarsen arm that was greater than in the vorinostat arm. There was no effect of cobomarsen on laboratory parameters of interest based on historical safety concerns for the drug class, including liver, renal, or hematological toxicities, and there was no indication of an effect of cobomarsen on QTc interval.

10. SPONSOR'S APPROVAL

Study 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
Protocol Number:	MRG106-11-201
Date of Report:	31 December 2020

I have read this synoptic report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

DocuSigned by:
4E486EAF26734B9...

Dec 31, 2020 | 2:06 PM PST

Diana Escolar, M.D., FAAN
Chief Medical Officer
miRagen Therapeutics, Inc.

Date

11. REFERENCES

1. Chren M, Lasek R, Quinn L, et al. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol 1996; 107(5): 707-713.

2. 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): 2598-2601.

14. TABLES, GRAPHS, AND FIGURES REFERRED TO, BUT NOT INCLUDED, IN THE TEXT

14.2 Efficacy Data

14.3 Safety Data

16. APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

Global protocol versions:

MRG-106-11-201, v1.0, 12JUN2018

MRG-106-11-201, v2.0, 16JAN2019

MRG-106-11-201, v3.0, 07JUN2019

MRG-106-11-201, v4.0, 10FEB2020

Country-specific protocol amendments available upon request.

16.1.2 Signature of Principal Investigator or Coordinating Investigator or Sponsor's Responsible Medical Officer

Refer to Section 10.

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued Subjects

Listing 16.2.1 Subject Disposition – All Enrolled Subjects

16.2.2 Protocol Deviations

Available upon request.

16.2.3 Subjects Excluded from Efficacy Analysis

Listing 16.2.3.2 Subjects Excluded from the Sensitivity Analysis – All Enrolled Subjects

16.2.4 Demographic Data

Listing 16.2.2 Demographics – All Enrolled Subjects

16.2.5 Compliance and/or Drug Concentration Data

Listing 16.2.5.1 Vorinostat Administration – All Enrolled Subjects

Listing 16.2.5.2 Cobomarsen Administration – All Enrolled Subjects

16.2.6 Individual Efficacy Response Data

Listing 16.2.3.1 Derived Efficacy Data – All Enrolled Subjects

Listing 16.2.3.3 Overall Visit Response for Modified Severity Weighted Assessment Tool (mSWAT) – All Enrolled Subjects Excluded from the Sensitivity Analysis

Listing 16.2.3.4 Patient Reported Outcomes: Skindex-29 – All Enrolled Subjects

Listing 16.2.3.5 Patient Reported Outcomes: Daily Pain and Pruritus – All Enrolled Subjects

Listing 16.2.3.6 Patient Reported Outcomes: Weekly Pain and Pruritus – All Enrolled Subjects

Listing 16.2.3.7 Patient Reported Outcomes: PGI-S/PGI-C – All Enrolled Subjects

Listing 16.2.6.3 Concomitant Pruritus Medications – All Enrolled Subjects

16.2.7 Adverse Event Listings

Listing 16.2.4.1 Adverse Events - All Enrolled Subjects

Listing 16.2.4.2 Grade 3-4 Adverse Events - All Enrolled Subjects

16.2.8 Listing of Individual Laboratory Measurements

Listing 16.2.8.1 Lab Listing

16.2.9 Electrocardiogram and Vital Sign Measurements by Subject

Listing 16.2.6.1 Vital Signs – All Enrolled Subjects

Listing 16.2.6.2 12-Lead ECG – All Enrolled Subjects

16.3 CASE REPORT FORMS FOR DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

Available upon request.

16.4 NARRATIVES OF DEATHS, OTHER SERIOUS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

Available upon request.