Cobomarsen as a Therapy for Mycosis Fungoides
Content

- miR-155 and Cobomarsen Mechanism Overview
- Phase I Data in Mycosis Fungoides
- Phase I Data in ATLL
- Cobomarsen Phase II Overview (SOLAR)
miR-155 and Cobomarsen Mechanism Overview
**microRNAs Regulate Network Biology to Maintain Homeostasis**

- microRNAs have been evolutionarily selected to regulate networks of genes
- microRNAs are dysregulated in many diseases
- Dysregulation of microRNAs is associated with alteration of downstream gene networks and disease
- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes
- microRNA therapeutics are particularly suited for complex, multigenic disorders

**Conventional Therapies**
(Small molecules, Antibodies, siRNA, etc)
Single molecule as target

**microRNA-based Therapies**
Network (pathway) as target
miR-155 Regulates Disease Gene Pathways Implicated in Mycosis Fungoides

**Upregulation of miR-155**

- Multiple survival and immune pathways activated
  - ✓ Proliferation
  - × Apoptosis
  - ✓ T-cell activation

**Conventional Therapy (e.g., idelalisib)**

- One survival pathway inactivated
  - ✓ Proliferation
  - × Apoptosis
  - ✓ T-cell activation

**Cobomarsen**

- Multiple survival and immune pathways inactivated
  - × Proliferation
  - ✓ Apoptosis
  - × T-cell activation
miR-155 is Increased in Multiple Hematologic Malignancies

MIR-155 EXPRESSION

Number of copies of miR-155 per cell
miR-155 Expression is Linked to Multiple Hematologic Malignancies

**THE HOST GENE FOR miR-155 (BIC)**
was identified as a proto-oncogene for virally-induced B-cell lymphomas

- **EXPRESSION OF miR-155 IS SUFFICIENT** to drive B-cell expansion and formation of B-cell lymphoma

**miR-155 IS HIGHLY EXPRESSED** in multiple hematologic malignancies

- **ELEVATED miR-155** expression correlates with poor prognosis

**miR-155 IS REGULATED** by NF-kB, PI3K/AKT, and JAK/STAT, and functions in a feedback loop with these survival pathways

- **THERAPEUTIC INHIBITION OF miR-155** reduces proliferation and increases apoptosis in hematologic cancer cell lines
Cobomarsen Affects Pathophysiology of Multiple Hematological Malignancies

+ **Cobomarsen is a miR-155 inhibitor** that inactivates multiple disease-relevant pathways

+ Cobomarsen can enable **induction of pro-apoptotic and anti-proliferative pathways** in these cancer cells while not causing global immunosuppression

+ Cobomarsen may provide long term benefit with few potential resistance mechanisms by **affecting multiple signaling pathways** in cancer cells
miR-155 is Increased in Mycosis Fungoides Lesions

+ miR-155 is upregulated in MF
+ miR-155 expression correlates with lesion severity*
+ miR-155 upregulation was confirmed in miRagen’s Phase 1 Clinical Trial in MF

**COBOMARSEN IS A MIR-155 INHIBITOR**

*In collaboration with Madeleine Duvic (MD Anderson)*
Cobomarsen Reverses the Disease Gene Signature in Mycosis Fungoides

+ T cell activation, survival signaling, and cytokine signaling genes ↑ in MF lesions
  - REDUCED by cobomarsen

+ Cell cycle checkpoint genes ↓ in MF lesions
  - INCREASED by cobomarsen
Cobomarsen Reduces Proliferation and Increases Apoptosis in Cell Lines Derived From CTCL Patient

+ Cobomarsen ↓ proliferation = bexarotene
+ Cobomarsen ↑ apoptosis > bexarotene
+ Potential for additivity/synergy with bexarotene and other therapeutics for CTCL
Cobomarsen Clinical Program in Hematological Malignancies

Dose, Schedule Optimization and Response Durability in CTCL

Ph 1 CTCL → mPoC → cPoC → PART A SYSTEMIC

Ph 1 CTCL → Part A LOCAL

Parallel Indication Expansion in Ph1

ATLL → DLBCL → CLL

Ph 2 CTCL → Futility Analysis

Ph 2 in NHL / Leukemia

CTCL MYCOSIS FUNGOIDES

MIR-155-HIGH NON-HODGKINS LYMPHOMA (NHL)/LEUKEMIA
Cobomarsen Shows Favorable Tolerability

- **COBOMARSEN HAS BEEN GENERALLY SAFE** and well tolerated
  - Multiple patients receiving more than a year of therapy
  - Total of 1254 cumulative doses (across 68 patients)
- **NO SIGNIFICANT LAB ABNORMALITIES** found in liver function, kidney function, thyroid function and platelet counts
- **NO EVIDENCE OF METABOLIC or HEMATOLOGICAL** toxicities
- **NO EVIDENCE OF GLOBAL IMMUNOSUPPRESSION**
- **NOVEL OLIGONUCLEOTIDE** drug class

In Total, **68 Patients** (CTCL, ATLL, DLBCL, and CLL from Ph1 and CTCL SOLAR) **Have Been Exposed To Cobomarsen For Up To 2.5 Years**

(Data Cutoff July 23, 2019)
Cobomarsen Phase I Results in CTCL

Parts A and B
Cobomarsen: Two-part Phase 1 CTCL Study

PART A
Intra-tumoral delivery of cobomarsen (75 mg dose)

PART B
Systemic SC or IV delivery to determine optimal potential dose (300, 600 and 900 mg+ dose)

OBJECTIVES
+ PRIMARY Safety and tolerability
+ SECONDARY PK
+ EXPLORATORY PD, histopathology, lesion morphology
Phase I Clinical Trial Patient Flow and Disposition

SCREENED = 51
ENROLLED = 41

PART A: INTRA-LESIONAL
ENROLLED = 6
DISCONTINUED DUE TO AE = 1

PART B: SYSTEMIC
ENROLLED = 37
TREATED = 37
RECEIVED > 6 DOSES PER AMENDED PROTOCOL = 25
EXCLUDED FROM EFFICACY ANALYSIS DUE TO SEZARY SX = 1

ONGOING = 1
COMPLETED = 9
DISCONTINUED = 25
LOST TO FOLLOW-UP = 2

SCREEN FAILURES = 8
ENROLLMENT CLOSED/MISSED DEADLINE = 1
DID NOT MEET I/E CRITERIA = 7
# Phase I CTCL

## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>PART A n (%)</th>
<th>PART B n (%)</th>
<th>TOTAL n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 (17)</td>
<td>13 (35)</td>
<td>14 (34.1)</td>
</tr>
<tr>
<td>Male</td>
<td>5 (83)</td>
<td>24 (65)</td>
<td>27 (65.9)</td>
</tr>
<tr>
<td><strong>AGE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>37</td>
<td>41(^a)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59 (6)</td>
<td>58 (14)</td>
<td>58.4 (13.1)</td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Min, Max</td>
<td>50,64</td>
<td>21,85</td>
<td>21,85</td>
</tr>
<tr>
<td><strong>RACE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (17)</td>
<td>6 (16)</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (17)</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Other, specify</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>4 (67)</td>
<td>28 (76)</td>
<td>31 (75.6)</td>
</tr>
</tbody>
</table>

\(^a\) 41 unique individuals enrolled in the study. 43 subjects total with 2 Part A subjects re-enrolled in Part B.
### Phase I CTCL

**Grade 3, 4 and SAEs in Parts A and B**

<table>
<thead>
<tr>
<th>SYSTEM ORGAN CLASS</th>
<th>ADVERSE EVENT (PT)</th>
<th>SAE</th>
<th>GRADE 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia*</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypertriglyceridaemia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypophosphataemia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypercalacemia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyponatraemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified</td>
<td>Tumor flare</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor pain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Angina pectoris</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Palpitations</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood uric acid Increased</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphocyte count decreased</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transaminases increased</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Cellulitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Acute kidney injury</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proteinuria</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Orthopnea</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>4</strong></td>
<td><strong>17</strong></td>
<td></td>
</tr>
</tbody>
</table>

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*a 41 unique individuals enrolled in the study 43 subjects total with 2 Part A subjects re-enrolled in Part B

*b Neutropenia is transient, mostly in subjects on concomitant medications that had Grade 1-2 neutropenia at baseline

(Data Cutoff July 23, 2019)
## Phase I CTCL

**Most Frequent AEs Reported in Parts A and B**

---

<table>
<thead>
<tr>
<th>ADVERSE EVENT (PT)</th>
<th>TOTAL (41a) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Oropharangeal pain</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Tumor flare</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (12.2)</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> 41 unique individuals enrolled in the study. 43 subjects total with 2 Part A subjects re-enrolled in Part B.

<sup>b</sup> Neutropenia is transient, mostly in subjects on concomitant medications that had Grade 1-2 neutropenia at baseline.

(Data Cutoff July 23, 2019)
# Phase I CTCL

## Most Frequent AEs Reported in Monotherapy and Combination Therapy Patients

- **a** 41 unique individuals enrolled in the study 43 subjects total with 2 Part A subjects re-enrolled in Part B
- **b** Neutropenia is transient, mostly in subjects on concomitant medications that had Grade 1-2 neutropenia at baseline

### Adverse Events in ≥ 10% of Subjects

<table>
<thead>
<tr>
<th>PREFERRED TERM</th>
<th>MONO (15) n (%)</th>
<th>COMBO (26) n (%)</th>
<th>TOTAL (41) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4 (26.7)</td>
<td>7 (26.9)</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (6.7)</td>
<td>7 (26.9)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (26.7)</td>
<td>4 (15.4)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6.7)</td>
<td>6 (23.1)</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (13.3)</td>
<td>4 (15.4)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2 (13.3)</td>
<td>3 (11.5)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (20.0)</td>
<td>2 (7.7)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (13.3)</td>
<td>3 (11.5)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Oropharangeal pain</td>
<td>2 (13.3)</td>
<td>3 (11.5)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Tumor flare</td>
<td>2 (13.3)</td>
<td>3 (11.5)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (13.3)</td>
<td>3 (11.5)</td>
<td>5 (12.2)</td>
</tr>
</tbody>
</table>

(Data Cutoff July 23, 2019)
Cobomarsen Reverses the Disease Gene Signature And Reduces Malignant Cell Clonality in Mycosis Fungoides Patients
Phase I CTCL Thirty-three of Thirty-six Patients (92%) Treated Systemically with Cobomarsen Have Shown mSWAT Score Improvement

<table>
<thead>
<tr>
<th>STAGE</th>
<th>1A</th>
<th>2A</th>
<th>1B</th>
<th>2B</th>
<th>1A</th>
<th>2B</th>
<th>1B</th>
<th>1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE mSWAT</td>
<td>6</td>
<td>103</td>
<td>43</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>DOSES</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best Change in mSWAT Score (%)</th>
<th>300 mg</th>
<th>600 mg</th>
<th>900 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>357</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>560</td>
<td>148</td>
<td>393</td>
<td></td>
</tr>
<tr>
<td>495</td>
<td>214</td>
<td>582</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>68</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

* treatment ongoing

(Data Cutoff January 9, 2019)
Phase I CTCL

Patients Treated with Cobomarsen Administered as a 300 mg IV-infusion Achieved a PR

63%

Reached ORR4

50%

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

Change in mSWAT Score (%)

-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10

300 mg IV-inf *Treatment ongoing

ORR4 ORR4 ORR4 ORR4

NE 148 393 * 582 214
Phase I CTCL Cobomarsen Substantially Reduces Lesion Severity Following IV Administration

C1D1 Pretreatment
CAILS: 12

C3D1
CAILS: 3

C6D1
CAILS: 0

C12D1
CAILS: 0
Phase I CTCL
Cobomarsen Shows Similar Efficacy When Administered as Monotherapy or in Combination with stable regimens of other CTCL systemic therapies

<table>
<thead>
<tr>
<th>CONCOMITANT MEDICATION</th>
<th>Bexarotene (N=12)</th>
<th>Interferon-alfa (N=2)</th>
<th>Methotrexate (N=2)</th>
<th>Other* (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Other medications include single patients on pralatrexate, methoxsalen, brentuximab, gemcitabine, gamma interferon or romidepsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Greatest mSWAT score improvement of systemically-treated subjects (N=36)

% change from baseline

concomitant systemic med for CTCL

300 mg
600 mg
900 mg

n=13
n=23

none
≥ 1 tx
Phase I MF
Quality of Life Improved as Measured by Skindex-29 Total Score

+ 15 out of 17 (88%) patients saw an improvement in their mean Skindex-29 score

+ Improvements mostly occurred in patients that received > 6 doses of cobomarsen
Phase I MF Clinical Trial of Cobomarsen

Investigators

Francine M. Foss
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Palo Alto, CA

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Theresa Pacheco
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Aurora, CO

Bradley Haverkos
University of Colorado
Aurora, CO

Jennifer DeSimone
Inova
Fairfax, VA

Pierluigi Porcu
Sidney Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA

Ahmad Halwani
Huntsman Cancer Center
Salt Lake City, UT
Cobomarsen Phase I Results in ATLL

Part F
Epidemiology of Adult T-cell Leukemia/Lymphoma

+ Adult T-cell leukemia/lymphoma (ATLL) is a mature peripheral T-cell neoplasm caused by human T-cell leukemia virus type 1 (HTLV-1)
+ HTLV-1 establishes lifelong latency in human T-cells (50-70 years) before development of ATLL
+ Malignant transformation leading to ATLL occurs in HTLV-1–infected individuals with a cumulative lifetime risk of 2.1% for women and 6.6% for men
+ The median survival time for acute ATLL patients is reported from 4.1 to 8.3 months, approximately 10 months for lymphomatous ATLL and 27 to 67 months for chronic unfavorable ATLL
ATLL has a High Expression of miR-155
The Role of miR-155 in ATLL

+ miR-155 upregulation has been reported in HTLV-1 cell lines and ex vivo tumor cells from ATLL patients
+ Increased expression of miR-155-5p enhances the growth of HTLV-1 infected T-cells

Yeung et al, Cancer Res 2008
Cobomarsen Reduces Proliferation and Induces Apoptosis in a Dose-Dependent Manner in an HTLV-1+ CTCL Cell Line

+ miR-155 expression is increased in HuT102 cells (HTLV-1+ CTCL line)
+ Cobomarsen inhibits cellular proliferation and induces apoptosis \textit{in vitro}
Cobomarsen Clinical Experience in ATLL

PART F:
Open-label, dose-ranging, multiple dose trial of cobomarsen in ATLL

OBJECTIVES
- PRIMARY: Safety and tolerability
- SECONDARY: PK
- EXPLORATORY: PD, histopathology, lesion morphology

OVERALL TRIAL DESIGN
- INCLUSION CRITERIA
  - Acute, lymphomatous, chronic, and smouldering subtypes
  - Relapsing or in PR/CR after prior therapy
  - Progressed on, or refractory to, at least one prior therapy
- DOSING AND DURATION
  - SQ or IV
  - 3 loading doses the first week
  - Weekly dosing thereafter
  - Discontinue if subject becomes intolerant, develops clinically significant side effects, or progresses
### Subject Characteristics and Disposition

**9 Patients Enrolled** 89% Black, 67% Male; Median Age of 49 Years

<table>
<thead>
<tr>
<th>SUBJECT ID</th>
<th>ATLL TYPE AT DIAGNOSIS</th>
<th>ATLL PRESENTATION AT SCREENING</th>
<th>RELAPSE OR PARTIAL REMISSION</th>
<th>% ABNORMAL LYMPHOCYTES AT SCREENING</th>
<th>LYMPH NODES AT SCREENING CT SCAN/PET</th>
<th>DOSE (mg)</th>
<th>DAYS SINCE LAST TX</th>
<th>DURATION OF COBOMARSEN TX (DAYS)</th>
<th>DISPOSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>101-008</td>
<td>Acute</td>
<td>Acute</td>
<td>Partial Remission</td>
<td>9%</td>
<td>Normal</td>
<td>600</td>
<td>21</td>
<td>500</td>
<td>Ongoing</td>
</tr>
<tr>
<td>101-010</td>
<td>Lymphomatous</td>
<td>Lymphomatous</td>
<td>Partial Remission</td>
<td>14%</td>
<td>Normal</td>
<td>600</td>
<td>46</td>
<td>465</td>
<td>Ongoing</td>
</tr>
<tr>
<td>101-012</td>
<td>Lymphomatous</td>
<td>Lymphomatous</td>
<td>Partial Remission</td>
<td>10%</td>
<td>Normal</td>
<td>600</td>
<td>108</td>
<td>186</td>
<td>Ongoing</td>
</tr>
<tr>
<td>101-014</td>
<td>Lymphomatous</td>
<td>Lymphomatous</td>
<td>Partial Remission</td>
<td>15%</td>
<td>Normal</td>
<td>600</td>
<td>28</td>
<td>136</td>
<td>Discontinued</td>
</tr>
<tr>
<td>119-001</td>
<td>Chronic Unfavorable</td>
<td>Chronic unfavorable</td>
<td>Partial Remission</td>
<td>None</td>
<td>Abnormal</td>
<td>600</td>
<td>450</td>
<td>274</td>
<td>Ongoing</td>
</tr>
<tr>
<td>101-011</td>
<td>Lymphomatous</td>
<td>Lymphomatous</td>
<td>Relapsing</td>
<td>Not Done</td>
<td>Abnormal</td>
<td>600</td>
<td>219</td>
<td>10</td>
<td>Discontinued</td>
</tr>
<tr>
<td>102-012/102-015</td>
<td>Acute</td>
<td>Lymphomatous transformation, mostly skin</td>
<td>Relapsing</td>
<td>9%</td>
<td>Not Done</td>
<td>600</td>
<td>21</td>
<td>92</td>
<td>Discontinued</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26%</td>
<td>Normal</td>
<td>600</td>
<td>30</td>
<td>43</td>
<td>Discontinued</td>
</tr>
<tr>
<td>118-001</td>
<td>Smouldering</td>
<td>Aggressive, LCT, mostly skin</td>
<td>Relapsing</td>
<td>0.3%</td>
<td>Abnormal</td>
<td>600</td>
<td>31</td>
<td>24</td>
<td>Discontinued</td>
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<tr>
<td>119-002</td>
<td>Chronic Unfavorable</td>
<td>Acute</td>
<td>Relapsing</td>
<td>45%</td>
<td>Abnormal</td>
<td>900</td>
<td>469</td>
<td>18</td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

(Data Cutoff March 15, 2019)
Safety Summary of Cobomarsen in ATLL Cohort

Data Cutoff March 15, 2019

+ **NO DEATHS** while on cobomarsen treatment

+ **NO DOSE LIMITING TOXICITIES** (maximum tolerated dose not yet established) and **NO DISCONTINUATION FROM TRIAL** due to related AEs

+ **4 SAEs** in 3 subjects **DUE TO DISEASE PROGRESSION** (unrelated to drug)

+ **NO RELATED GRADE 3 OR GRADE 4 AEs**

+ **NO SIGNIFICANT HEMATOLOGICAL EVENTS**

+ **MOST COMMON** (in more than 2 subjects) **RELATED AEs** (all grade 1 and 2) were **DIARRHEA** and **NAUSEA**
Cobomarsen Allows For Rapid Bone Marrow Recovery Following Chemotherapy in 4 Subjects

**Example – Subject 101-008**

- **Subject 101-008** received EPOCH 21 days prior to cobomarsen treatment
- During Cycle 1 cobomarsen treatment, immature B cells populate the periphery as transitional B cells
- B cells mature into naïve B cells over the next few cycles

(Data Cutoff March 15, 2019)
Subject 101-008 Acute ATLL in Partial Remission

- Diagnosed Dec 2016 with acute ATLL
- Relapsed after treatment with zidovudine, interferon α-2b, lenalidomide and EPOCH chemotherapy
- Cobomarsen monotherapy initiated Nov 2017
  - Stable abnormal ATL cells for > 16 mo
  - Normalization of residual enlarged lymph node after chemotherapy (1.0 to 0.8 cm), which remained normal as of last imaging Nov 2018
  - Reduction in biomarkers of cell activation and proliferation (Ki67, CD69 and HLA-DR)
- Subject remains on treatment and has completed Cycle 18, missing only 1 dose due to sciatic pain

(Data Cutoff March 15, 2019)
Subject 101-008 Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells in ATLL

### Flow Cytometric Assessment of Activation and Proliferation Biomarkers' Expression in Circulating ATLL Cells

<table>
<thead>
<tr>
<th>Activation Markers</th>
<th>C1D1</th>
<th>C1D5</th>
<th>C1D27</th>
<th>C2D22</th>
<th>C6D22</th>
<th>C14D22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>71%</td>
<td>67%</td>
<td>56%</td>
<td>53%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>MFI</td>
<td>2880</td>
<td>2148</td>
<td>1264</td>
<td>1129</td>
<td>1283</td>
<td>1179</td>
</tr>
</tbody>
</table>

### Percent Cells Positive for Biomarkers

- **CD69**:
  - C1D1: 19%
  - C1D5: 13%
  - C1D27: 8%
  - C2D22: 8%
  - C6D22: 8%
  - C14D22: 7%

- **HLA-DR**:
  - C1D1: 19%
  - C1D5: 13%
  - C1D27: 8%
  - C2D22: 8%
  - C6D22: 8%
  - C14D22: 7%

- **Ki-67**:
  - C1D1: 35%
  - C1D5: 25%
  - C1D27: 5%
  - C2D22: 5%
  - C6D22: 7%
  - C14D22: 7%

### Change from Baseline in Biomarkers

(Data Cutoff March 15, 2019)
Subject 101-012  Acute ATLL in Partial Remission

- Diagnosed Dec 2017 with ATLL, lymphomatous sub-type
- Received 6 cycles of CHOEP (Jan-May 2018) with complete response in nodes but relapsing peripheral ATL cells
- CT scan at screening was normal
- Cobomarsen first dose Sept 2018
  - Completed Cycle 6 as of cut off date
  - CT scans have remained normal
  - LDH all within normal range
  - Reduction in biomarkers of activation (CD69) and proliferation (Ki67)

(Data Cutoff March 15, 2019)
Subject 101-010 Lymphomatous ATLL in Partial Remission

+ Diagnosed April 2017 with lymphomatous ATLL
+ Extensive and bulky lymphadenopathy reduced by 6 cycles of CHOEP (completed 5 months prior to initiation of cobomarsen)
+ Restaging
  - Resolution of adenopathy but increased splenic uptake
  - 20% of ATL cells in peripheral blood
+ Cobomarsen initiated Dec 2017
  - Stable lymph node size and peripheral blood tumor cell counts maintained for 15 months
  - CR obtained in viscera – CT scan Nov 2018 is now normal (resolution of splenic lesion)
  - Reduction in biomarkers of cell activation and proliferation (Ki67, CD69 and HLA-DR)
  - Subject has completed Cycle 16 as of cut off date
+ Rhinovirus infection Nov 2018 and concurrent increase in neutrophil count showed evidence of a normal immune response

(Data Cutoff March 15, 2019)
Subject 101-010 Cobomarsen Decreases Activation and Proliferation Status of Circulating Tumor Cells

(Data Cutoff March 15, 2019)
Cobomarsen Decreases the Activation and Proliferation of Circulating Tumor Cells

**ACTIVATION MARKERS ATL TUMOR CELLS**

- %CD69+
- %HLA-DR+

**PROLIFERATION INDEX ATL TUMOR CELLS**

- %Ki-67+

(Data Cutoff March 15, 2019)
Conclusions

+ Study continues to enroll subjects with acute and lymphomatous ATLL, relapsing and in partial or complete remission

+ Cobomarsen treatment resulted in durable clinical stabilization of all subjects with acute, lymphomatous and unfavorable chronic ATLL for up to 16 months (median = 9 months) after partial remission induced by chemotherapy

+ Biomarkers of cell activation and proliferation decrease with cobomarsen treatment underscoring the biological effect of the drug

+ Safety and tolerability profile appears benign with dose up to 600 mg – no deaths, DLTs, related SAEs, related Grade 3 or Grade 4 AEs, hematological events or discontinuation from trial due to related AEs

+ Cobomarsen therapy allows for normal bone marrow recovery after chemotherapy-induced suppression

+ The preliminary results are encouraging and supports trial continuation to explore cobomarsen for the treatment of ATLL subjects
## Phase I ATLL Clinical Trial of Cobomarsen

### Investigators

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>City, State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francine M. Foss</td>
<td>Yale Cancer Center</td>
<td>New Haven, CT</td>
</tr>
<tr>
<td>Juan Carlos Ramos</td>
<td>University of Miami</td>
<td>Miami, FL</td>
</tr>
<tr>
<td>Noah Kornblum</td>
<td>Montefiore Medical Center</td>
<td>Bronx, NY</td>
</tr>
<tr>
<td>Lauren Pinter-Brown</td>
<td>University of California</td>
<td>Irvine, CA</td>
</tr>
<tr>
<td>Christiane Querfeld</td>
<td>City of Hope</td>
<td>Duarte, CA</td>
</tr>
<tr>
<td>Alison Moskowitz</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>New York, NY</td>
</tr>
<tr>
<td>Matthew Weinstock</td>
<td>Beth Israel Medical Center</td>
<td>Boston, MA</td>
</tr>
<tr>
<td>Jasmine Zain</td>
<td>City of Hope</td>
<td>Duarte, CA</td>
</tr>
<tr>
<td>Adrienne A. Phillips</td>
<td>Weill Cornell Medicine</td>
<td>New York, NY</td>
</tr>
</tbody>
</table>
SOLAR: A Phase II Clinical Trial of Cobomarsen in Mycosis Fungoides

Protocol Overview
SOLAR Phase 2 Clinical Trial

A Randomized, Open-Label, Parallel-group, Active Comparator, Global Trial in Patients with Stage IB-III Mycosis Fungoides (MF)

Primary Endpoint
+ Overall Response Rate of Four Months (ORR4) using Global Response Criteria

Secondary Endpoints
+ Progression-free Survival
+ Patient Reported Outcomes
SOLAR Design as a Patient-centric Clinical Trial

- Detailed Patient Risk Assessment
- Travel Concierge
- Patient Reported Outcomes
- Research Home Infusion Services
SOLAR Study Participating Countries

126 Subjects at ~60 Sites
Across 11 Countries

+ Austria
+ Australia
+ Belgium
+ Canada
+ France
+ Germany
+ Italy
+ Netherlands
+ Spain
+ United Kingdom
+ United States
SOLAR Design

+ **PHASE 2 STUDY**: comparing cobomarsen to vorinostat
  - Up to 126 subjects – 1:1 randomization
  - ~60 sites in US, Canada, EU & Australia
  - Duration of study – up to 36 months

+ **STRATIFICATION FACTORS**:
  - Skin tumors (0 vs 1 or more)
  - Having 0-1 vs 2 of the following prognostic factors:
    - 60 years age at diagnosis
    - LDH level > ULN at diagnosis

+ **DURATION OF TREATMENT**: until progression or study completion
  - 28-day screening period, active treatment period, follow-up for progression and survival

+ **INTERIM ANALYSIS FOR FUTILITY**: after the first 40 subjects followed for at least 6 months

+ **LONG-TERM FOLLOW UP**: every 3 months (phone call) for survival
Selection of the Comparator

+ **REGULATORY REQUIREMENT TO HAVE ONLY ONE COMPARATOR**

+ **BEXAROTENE OR METHOTREXATE** were not selected (limited patient population naïve to these therapies)

+ **LIMITED CONTROLLED TRIALS** in CTCL to gather comparator response rates that can be utilized to calculate sample size

+ **HDAC INHIBITOR CONSIDERED A GOOD COMPARATOR** so vorinostat and romidepsin were considered; vorinostat administration is less burdensome on patients (oral medication vs. 4-hour in hospital IV infusion)

+ **VORINOSTAT EFFICACY IS SIMILAR TO OTHER CANDIDATE COMPARATORS**

### MF Patients

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>ORR4</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>7%</td>
<td>N/A</td>
<td>3.1 mos</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>16%</td>
<td>7.7%*</td>
<td>3.5 mos</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>16%</td>
<td>15.8%*</td>
<td>3.5 mos</td>
</tr>
</tbody>
</table>

Data from Mavoric and ALCANZA trials

* Includes pcALCL and MF patients
KEY INCLUSION CRITERIA

+ Stages IB, IIA, IIB, III
+ Must have received at least one prior therapy for CTCL (per NCCN guidelines for generalized skin involvement)
+ mSWAT score ≥ 10

KEY EXCLUSION CRITERIA

+ Previous enrollment in a cobomarsen study
+ Prior therapy with HDAC inhibitors or contraindication to vorinostat (or HDAC inhibitors)
+ Evidence of (current) large cell transformation (LCT)
+ Prior or current Sézary syndrome or mycosis fungoides with IIB
+ Extensive nodal involvement with complete or partial effacement of LN (i.e., N3) or visceral involvement
+ Unresolved toxicities from prior therapy
+ Other medical conditions such as bleeding diathesis, prolonged QT syndrome or previous or concurrent malignancies

---

SPAIN
At least 2 prior systemic therapies

ITALY
Prior therapies, at least 1 systemic

FRANCE
Stage IIB or III only; 2 prior therapies, at least 1 systemic

Protocol V3.0
### Treatment Washout Requirements (Prior to Screening)

<table>
<thead>
<tr>
<th>5 Half Lives</th>
<th>8 Weeks</th>
<th>4 Weeks</th>
<th>Day -28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational Small Molecule Drug</td>
<td>Investigational Biologic Drug</td>
<td>Systemic corticosteroid prednisone equivalent &gt; 10 mg per day(^1)</td>
<td>Macrolide or tetracycline antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chronic use, more than 20 days total</td>
<td>Total skin electron beam (TSEB) therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• More than 3 short courses of 7 days</td>
<td>Phototherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immune therapy</td>
<td>High potency topical corticosteroids (chronic use, more than 20 days total)(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antibody-directed</td>
<td>Other topical MF treatments (chronic use, more than 20 days total)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Immunoglobulin-based</td>
<td>Previous systemic MF treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other monoclonal antibody therapies</td>
<td></td>
</tr>
</tbody>
</table>

---

\(^1\) Stable regimen of **systemic** prednisone equivalent to ≤ 10 mg per day is permitted

\(^2\) Stable doses of **low to medium potency topical** corticosteroids are permitted
## Concomitant Steroid and Anti-pruritic Agent Guidance

### Patient may continue on:
- Stable regimens of systemic prednisone equivalent to ≤10mg per day
- Stable dose of medium or low potency topical corticosteroids for the treatment of pruritus
- Stable dose of systemic anti-pruritic agents (not used for prophylaxis)
- Topical moisturizers

### Patient may start new:
- Short courses (≤ 7 days) of low- and medium-potency topical corticosteroids
- Short courses of systemic or high-potency topical corticosteroids for non-CTCL indications
- Short courses (≤ 7 days) of systemic corticosteroids for CTCL indication allowed in exceptional cases
- Short courses (≤ 7 days) of oral antihistamines for symptomatic pruritus
- Short courses of other anti-pruritic agents for symptomatic pruritus are allowed in exceptional cases

### Patients may not:
- Start new prophylactic systemic anti-pruritic agents
- Increase corticosteroid dose for CTCL-related symptoms
- Start new chronic courses of topical or systemic agents for pruritus or CTCL-related symptoms

---

NEW SYSTEMIC TREATMENT FOR CTCL WILL BE PROHIBITED DURING THE STUDY
Strategies For Management of Vorinostat Side Effects And Patient Retention Until Progression

+ **miRagen PROVIDES** patient and physician guidelines on managing vorinostat side effects

+ **MOST COMMON AEs** are gastrointestinal

+ **PRACTICAL STRATEGIES**
  o Take vorinostat before bed
  o Remind patients to stay hydrated
  o Popsicles
  o Inform patients of possible side effects of the drug

+ **OPTIONS TO MANAGE** side effects:
  o Lowering dose to 300 mg qd
  o Decreasing to 5 days per week
  o Stopping medication (but *continue with follow-up until progression*)

+ **CAN PATIENTS WITH STABLE DISEASE OR PR/CR** that discontinue for tolerability cross to PRISM?
  o **No:** patients can discontinue treatment, but they **NEED** to remain on study **UNTIL PROGRESSION** to be eligible for PRISM
PRISM Overview
Open Label PRISM Study

For patients that have progressed on the vorinostat arm in SOLAR

+ **TO BE ELIGIBLE FOR PRISM**, SOLAR patients on vorinostat must have **confirmed progression**
+ **ADDITIONAL THERAPIES** for MF should **not be initiated between SOLAR and PRISM**
+ **INCLUSION CRITERIA**: allows patients with **nodal progression** (N3)
+ **EXCLUSION CRITERIA**: patients with **blood progression** (B2)
+ **PRISM SCREENING ASSESSMENTS** will **not need to be repeated** if rolling directly from SOLAR
For the most up to date study information, please visit miRagen.com/clinicians