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Restoring Biological Harmony for Patients with Debilitating Disease

Phase 1 Trial Evaluating MRG-106, a Synthetic Inhibitor of microRNA-155, in CTCL Patients

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Abstract #76272

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Abstract

Objectives:

MRG-106 is an oligonucleotide inhibitor of miR-155, a microRNA with a strong mechanistic link to CTCL. The objectives of this first-in-human Phase 1 study are to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of MRG-106 in patients with mycosis fungoides (MF).

Methods:

The trial employs a dose-escalation design to evaluate MRG-106 given systemically. Intralesional injection was evaluated in a separate cohort. Subjects must have biopsy-proven stage I-III MF with plaque and/or tumor lesions. Subjects were permitted to remain on concurrent stable CTCL therapy.

Results:

27 patients (19M/8F, median age 63 yrs) have been in the study for up to 12 months (as of 10/11/2017). MRG-106 was given via intralesional, subcutaneous or intravenous administration (SC/IV, ≤ 900 mg/dose). For subjects treated with SC/IV administration, 6 doses were given in the first 26 days followed by weekly doses for those who continued beyond the first cycle. Four subjects received only intralesional doses (75 mg/dose); two subjects were enrolled into both the intralesional and SC/IV cohorts. 21 subjects received only SC injections or IV administration of MRG-106. 27/29 subjects completed the first treatment cycle per protocol. Two subjects discontinued: one due to progressive disease found shortly after enrollment, and one due to an adverse event of worsening pruritus (Grade 3), judged as a dose-limiting toxicity at 900 mg SC. The pruritus may have been a symptom of disease flare after 3 doses of MRG-106 that resolved after 3 weeks. The drug was otherwise well-tolerated: of the other 46 drug-related AEs, all were Grade 1 or 2. The MTD has not yet been reached.

28/29 subjects (97%) showed improvement in either the individually treated lesion (intralesional cohort) or total skin disease (SC/IV cohorts) as measured by maximal change in either Composite Assessment of Index Lesion Severity (CAILS) or modified Severity Weighted Assessment Tool (mSWAT). CAILS and mSWAT are the internationally-accepted lesion and total skin disease scoring methods.

In the SC/IV cohorts, 22 of the 23 subjects had an improvement in mSWAT score; 11/23 subjects (48%) had ≥ 50% reduction in mSWAT score. Of the 13 subjects who received > 1 cycle, 69% achieved a ≥ 50% reduction in mSWAT score, suggesting that longer treatment periods may provide greater benefit. Improvements in mSWAT scores were observed as early as Study Day 19 (the first post-treatment assessment).

Conclusions:

These results suggest that MRG-106 is well-tolerated and has meaningful clinical activity as indicated by CAILS and mSWAT assessments. These encouraging data support the continued investigation of MRG-106 in MF patients. The study has also expanded to include enrollment of patients with other hematological malignancies in which miR-155 has been reported to be elevated and relevant.

Clinical Trial Objectives and Design

Primary Objective:

The primary objective of the study is to investigate the safety and tolerability of multiple intralesional (Part A) and subcutaneous or intravenous administrations (Part B) of MRG-106 in subjects with CTCL, MF sub-type.

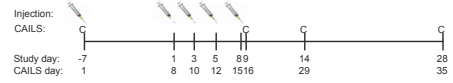
Secondary Objective:

Characterize the pharmacokinetic profile of MRG-106 (results presented in abstract #76271)

Exploratory Objectives:

- Characterize the pharmacodynamic (PD) profile of MRG-106
- Evaluate changes in histopathology of biopsied tissue
- Determine the effect of MRG-106 on skin assessment scores using the Composite Assessment of Index Lesion Severity (CAILS) and the modified Severity Weighted Assessment Tool (mSWAT) [mSWAT for Part B subjects only]
- Investigate the effects of MRG-106 on immunity, in Part B

Part A (intralesional injection):



Part B (SC or IV), first 27 days of study:

After the first 27 days of treatment, subjects can continue MRG-106 dosing with the first dosing being given 1 to 4 weeks after the Day 26 dose. Doses thereafter are administered weekly. Per investigator discretion, doses can be given less frequently than weekly, but not less than monthly.

Subject Characteristics

Parameter	Part A Intralesional, N=6	Part B Systemic, N=23	Total N=29
Sex			
Female	1	7	8
Male	5	16	21
Age			
Median (range)	61	63	63
Race			
Asian	0	1	1
African American	1	1	2
Not reported	1	0	1
Other	0	1	1
Caucasian	4	20	24
Disease Stage at Diagnosis			
Stage IA	0	4	4
Stage IB	1	7	8
Stage IIA	2	2	4
Stage IIB	3	6	9
Stage IIIA	0	2	2
Stage IIIB	0	1	1
Unknown	0	1	1
Baseline mSWAT			
N	3	23	26
Median (range)	22.5 (3 - 96)	42.7 (2 -180)	34.9 (2 -180)
Prior Systemic CTCL Therapies			
Median (range)	3 (1 - 4)	2 (0 - 9)	2 (0 - 9)
Concomitant Systemic CTCL Therapies			
Median (range)	1 (0 - 2)	1 (0 - 3)	1 (0 - 3)

	Mean miR-155 copy number from lesional skin biopsy (range)
Part A, Intralesional, N=6	744 (109,3154)
Part B, Systemic, N=5	554 (NQ,912)
Total, N=11	690 (NQ,3154)

Normal skin miR-155 = Not Quantifiable (N/Q)

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MRG-106 Has a Favorable Safety Profile

Most common AEs by preferred term, N (%)	Any grade	Grade 3-4
Injection site pain (Intralesional & S.C.)	6 (21)	0
Fatigue	6 (21)	0
Nausea	4 (14)	0
Pruritus	4 (14)	1
Erythema	4 (14)	0

- **No SAEs attributed to MRG-106**
- **No Grade 4 Adverse Events attributed to MRG-106**
- **One Grade 3 worsening pruritus attributed to MRG-106 (Dose-Limiting Toxicity)**

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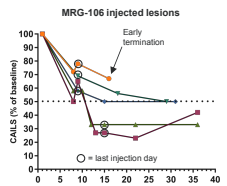
All Grade 3 or 4 Adverse Events

	Part A (Intra-lesional)	Part B (Subcutaneous)			Part B (IV, 2 hr infusion)			Part B (IV Bolus)	
System Organ Class *Preferred Term*	75mg (6)	300mg (3)	600mg (3)	900mg (3)	300mg (3)	600mg (3)	900mg (3)	300mg (5)	Total (29)
Metabolism and nutrition disorders	**1 (16.7%)**	**1 (33.3%)**							**3 (10.3%)**
Hypercalcemia	1 (16.7%)								1 (3.4%)
Hyponatremia		1 (33.3%)							1 (3.4%)
Hypophosphatemia					1 (33.3%)				1 (3.4%)
Blood and lymphatic system disorders	**1 (16.7%)**		**1 (33.3%)**	**1 (33.3%)**					**3 (10.3%)**
Leukopenia				1 (33.3%)					1 (3.4%)
Neutropenia			1 (33.3%)	1 (33.3%)					2 (6.9%)
Lymphopenia	1 (16.7%)								1 (3.4%)
Laboratory findings	**1 (16.7%)**							**1 (20.0%)**	**2 (6.9%)**
Blood CPK increased	1 (16.7%)								1 (3.4%)
Uric acid increased								1 (20.0%)	1 (3.4%)
Infections	**1 (16.7%)**								**1 (3.4%)**
Cellulitis	1 (16.7%)								1 (3.4%)
Skin and subcutaneous tissue disorders				**1 (33.3%)**					**1 (3.4%)**
Pruritus				1 (33.3%)					1 (3.4%)
Vascular disorders				**1 (33.3%)**					**1 (3.4%)**
Hypertension				1 (33.3%)					1 (3.4%)

Improvement of CAILS with Intralesional Injection of MRG-106 (Part A)

Patient	# of Doses	Study Days with Drug Injection	MRG-106 Treated: CAILS Score (Max/Min)	MRG-106 Treated: Maximal % Reduction in CAILS
107-001	3	-7, 1, 2	18 → 12	33%
102-001	5	-7, 1, 3, 5, 8	26 → 6	77%
101-001	5	-7, 1, 3, 5, 8	12 → 4	67%
105-001	4	1, 3, 5, 8	16 → 8	50%
102-003	4	1, 3, 5, 8	12 → 6	50%

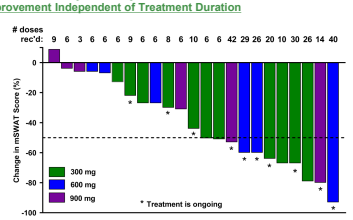


All lesions injected with MRG-106 showed improvement in the CAILS score. A reduction in CAILS score of ≥ 50% (consistent with the definition of clinical response) was observed in the MRG-106 treated lesions in all four evaluable subjects who completed dosing. The MRG-106 injected lesion responses were maintained to the End of Study visit (either 28 days or 35 days after the first dose).

22 of 23 (96%) Patients Treated Systemically with MRG-106 have mSWAT Score Improvement Independent of Treatment Duration

- 19 subjects were eligible for > 1 month of treatment
- 13 subjects chose to continue with additional months of treatment

Data suggest that increased dosing duration may continue to increase improvement in mSWAT score.



6 doses = initial cycle
4 doses in subsequent cycles

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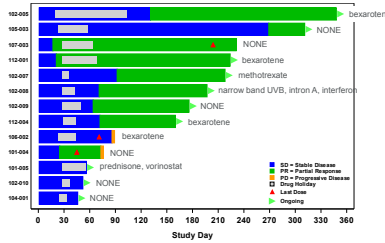
9 of 13 (69%) Patients Treated for > 1 Month Show ≥ 50% mSWAT Score Improvement

Subjects permitted to continue CTCL therapy if stable dose ≥ 4 weeks prior to MRG-106 administration



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Conclusions

- MRG-106 is generally well-tolerated to date.
- No SAEs or Grade 4 AEs deemed related to study drug.
- One subject had a Grade 3 AE deemed potentially related to study drug: pruritus.
- Intralesional injection of MRG-106 led to encouraging therapeutic improvements in cutaneous lesions, based on CAILS scores.
- 9 of 13 (69%) patients treated for > 1 month with systemic administration of MRG-106 have ≥ 50% mSWAT score reduction.
- mSWAT improvement is durable in all patients, who continued on treatment .
- Magnitude of mSWAT improvements appeared to correlate with time on MRG-106 treatment.
- Efficacy appears similar across dose range tested (300-900 mg/dose).
- The study in patients with CTCL is on-going.
- The role of MRG-106 is being investigated in other hematological malignancies, including ATLL, CLL and DLBCL in which miR-155 is dysregulated.

Disclosures: Authors of this presentation have the following possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Anita Seto, Linda Pestano, Judy Ruckman, Michele Landry, Gilad Gordon, Paul Rubin, and William Marshall are employees or consultants of miRagen Therapeutics, Inc.

Christiane Querfeld, Francine Foss, Lauren Pinter-Brown, Pierluigi Porcu, Basem William, Youn Kim, and Herbert Eradat have received honoraria from miRagen Therapeutics, Inc.

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