**MicroRNA-29b Mimic (MRG-201) Reduces Fibroplasia and Inhibits Collagen Expression in Skin Incisions in Normal Healthy Volunteers**

**OBJECTIVE/PURPOSE:** Cutaneous scars, including hypertrophic scars and keloids, can arise from dermal injuries or surgery and represent a major unmet medical need, for which no approved drug therapies exist. MicroRNA-29b is well recognized as an anti-fibrotic miRNA that inhibits the expression of multiple collagens and other extracellular matrix genes in many tissues. miR-29 expression is reduced in cutaneous scars and keloids and expression of the miR-29 target genes COL1A1, COL1A2, and COL5A1 (collagens) are increased in those scars and in fibroblasts derived from those scars. Therefore, restoration of miR-29 expression in a skin wound or at the site of an excised scar is anticipated to lead to a therapeutic benefit by reducing scarring and/or preventing scar retraction. The objective of this study was to test the safety and pharmacodynamics of such a miR-29-based therapy in normal healthy volunteers.

**DESIGN:** A novel oligonucleotide mimic of miR-29b (MRG-201) was evaluated in a Phase 1 placebo controlled double-blinded, anti-fibrotic randomized, single and multiple dose escalation clinical trial in 34 normal healthy volunteers with and without skin incisions. Safety, tolerability, pharmacokinetics and pharmacodynamics, including the effect of MRG-201 on skin histology and target engagement, were evaluated following intradermal administration of MRG-201.

**RESULTS:** MRG-201 was generally well tolerated at all dose levels, the maximum tolerated dose (MTD) was not reached. Local tissue exposure of MRG-201 was well above endogenous miR-29 levels while systemic exposure was low, supporting its favorable safety profile. Assessment of pharmacodynamic biomarkers demonstrated target engagement and restoration of collagen mRNA expression following both single and multiple administrations of MRG-201 as compared to a placebo injected incision in the same subject. Fibroplasia was significantly reduced following multiple administrations of MRG-201 (mean placebo fibroplasia area 1.88 mm², mean MRG-201 fibroplasia area 1.13 mm², p=0.0086), and the histology and target engagement, were evaluated following intradermal injection of MRG-201.

**CONCLUSIONS:** These results demonstrate a favorable safety profile for MRG-201 and establish mechanistic proof-of-concept for MRG-201 in inhibiting collagen mRNA expression and preventing fibroplasia in skin incisions in normal healthy volunteers. These results support further investigation of MRG-201 as a novel therapeutic to inhibit cutaneous scar formation or prevent keloid or hypertrophic scar recurrence following excision.

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**MRG-201 Target Validation in vitro and in vivo**

**Dysregulation of miR-29 Family Members and MRG-201 Target Genes in Keloids and Cutaneous Scars**

<table>
<thead>
<tr>
<th>Keloids</th>
<th>Cutaneous Scars</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL1A1</td>
<td>COL3A1</td>
</tr>
<tr>
<td>COL5A1</td>
<td></td>
</tr>
<tr>
<td>L30L2</td>
<td></td>
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<tr>
<td>PCOLCE2</td>
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</tbody>
</table>

**Clinical Trial MRG201-30-001**

**Part A: Kinetics of miR-29b Expression and Pharmacodynamic Gene Expression in Normal Healthy Volunteers with Sutured Skin Incisions**

- **Pathway:** ECM metabolism
- **Gene:** COL1A1, COL1A2, COL5A1, COL3A1, COL1A2, COL1A2, COL5A1, COL3A1

**Genes significantly regulated in inflammation**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Regulation</th>
</tr>
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<tbody>
<tr>
<td>IL-1β</td>
<td>Upregulated</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Upregulated</td>
</tr>
<tr>
<td>IL-6</td>
<td>Upregulated</td>
</tr>
</tbody>
</table>

**Target Genes in Keloids and Cutaneous Scars**

- **miR-29b and MRG-201 Target Genes are Reciprocally Regulated With Skin Injury**

**MRG-201 Treatment Significantly Blunts Fibroplasia in Human Incised Skin**

**MRG-201 Pharmacokinetics and Tissue Biodistribution**

- **Low systemic exposure**
- **Plasma accumulation with repeated dosing**
- **No evidence of plasma accumulation with repeated dosing**
- **Tissue levels not substantially higher after repeated dosing compared to single dosing**

**Validation of MRG-201 Pharmacodynamic Biomarkers**

- **In vivo assessments**

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**Evidence of Pharmacodynamic (PD) Activity and Mechanistic Proof (Concept mPoC) After Single Administration of MRG-201**

**Clinical Trial MRG201-30-001**

**Part B-D: Safety, Tolerance, Pharmacokinetics and Pharmacodynamics Assessment of MRG-201 Administered intradermally in NHVs**

**Part B**

- **Single Ascending Dose**
  - 0.5 – 14 mg Administered to Intact Skin
  - 19 Subjects
  - Within-subject randomized double-blinded, placebo controlled trial: MRG-201 vs. saline
  - 8 x 25 μL injections evenly spaced on both sides of a 1.5 cm line or incision
  - MRG-201 is generally well tolerated at all doses. 11 injection site reactions of moderate severity in 47 subjects (130 doses)
  - Injection site reactions not correlated with dose level or number of doses per subject
  - Possibly related AEs: Headache (1), chills (1), fatigue (2), weakness (1), microscopic hematuria (1), sensation of warmth/bloating (2), pain at injection site (1) – all of mild severity (grade 1) and resolved
  - **Maximum Tolerated Dose not determined. Maximal deliverable dose = 14 mg / 200 μL**

**Part C**

- **Single Ascending Dose**
  - 4, 7, 14 mg Administered to Skin Incision
  - 9 Subjects

**Part D**

- **Multiple Ascending Dose**
  - 4, 7, 14 mg Administered M.W,F,M,W,F to Skin Incision
  - 19 Subjects

**Conclusions**

- MRG-201 is well-tolerated in intact and incised skin
- No safety or injection site reaction concern, no inhibition of wound healing
- No adverse histologic findings
- Maximum tolerated dose not defined; maximum deliverable dose = 14 mg / 200 μL
- Demonstrated mPoC for MRG-201 in human incised skin
- Fibrosis-associated pharmacodynamic biomarkers that are up-regulated following incision are down-regulated by MRG-201
- Magnitude of target engagement (repression of collagens and other factors) appears dose-proportional with single administration
- Within a subject, MRG-201 target engagement correlates with the impact on fibroplasia following multiple administrations