The RNAi Compound RXI-109 Reduces Connective Tissue Growth Factor (CTGF), a Key Component of Dermal Scarring, at Incision Sites in a First-in-Human Phase 1 Clinical Trial

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RXI-109 Background

- There are currently no drugs approved to prevent hypertrophic scar or keloid formation
- RXI-109 targets and reduces CTGF, a key regulator of the dermal scarring pathway
- RXI-109 is an sd-rxRNA® that works through an RNA interference (RNAi) mechanism
  - sd-rxRNAs are small interfering RNAs (siRNA) designed with RXi’s proprietary technology
  - sd-rxRNAs are efficiently taken up by cells
- RXI-109 is delivered locally to the incision/scar site
- Early treatment with RXI-109 may reduce hypertrophic scarring and keloid formation
- Two Phase 1 safety trials have been completed
  - RXI-109-1201, an ascending dose, single dose study is presented here
  - RXI-109-1202, an ascending dose, multi-dose study is presented in Poster #8225
  - Phase 2 trials have been initiated
- Additional related work presented at AAD 2014:
  - Preclinical data: Poster #8326
Study RXI-109-1201: Overview

A Phase 1 Single Center, Randomized, Double-Blind, Ascending Dose, Within-Subject Controlled Study of RXI-109 for the Treatment of Incision Scars Made in the Pannus of Healthy Women Who Will Later Undergo Elective Abdominoplasty

Parameters evaluated:
- Safety & side effect assessment versus placebo
- Histological comparison of the scar sites versus placebo
- Pharmacokinetic parameters after local intradermal injection
- CTGF protein & mRNA levels
- Photographic comparison versus vehicle
RXI-109-1201: Study Design and Abdominal Incision Layout

RXI-109-1201
Single dose at each incision site
5 dose cohorts, 3 subjects each
Dose range 1-10 mg per incision site
Abdominoplasty and biopsies on Day 84

• Pre-treatment at four (4) sites was made by intradermal injection on the abdomen of healthy volunteers according to a predetermined randomization pattern for each subject.
• Four incisions (2 cm in length) were made at the treated sites 24 hours post treatment.
• Incisions were spaced at least 4 cm apart.
• Randomized treatment to one side with RXI-109, one side with placebo.
• Safety assessments were made throughout the 3-month study.
RXI-109-1201: Safety Results

Conclusions:

• No significant side effects nor toxicity were observed.
• Treatment did not delay healing on the active or the placebo side, i.e. no negative effect on wound healing/closure.
• Maximum blood level of RXI-109 is only approximately 5% of intradermally administered dose

Monitored for side effects, safety and toxicity in the 7 days post injection, and regularly afterwards for up to 3 months. Parameters monitored included:

• ECG
• Blood Biochemistry
• Blood Count
• Urinalysis and LFTs
• Complement and Coagulation
• Clinical Assessments of Incisions by Physician & Subjects
• RXI-109 in Systemic Circulation after Intradermal Injection
RXI-109-1201: Skin Assessments

**RXI-109 Treatment**
- Erythema
- Induration
- Tenderness
- Pain

**Placebo Treatment**
- Erythema
- Induration
- Tenderness
- Pain

Cohort 1
- Erythema-Placebo
- Tenderness-Placebo
- Induration-Placebo
- Pain-Placebo

Cohort 2
- Erythema-RXI
- Tenderness-RXI
- Induration-RXI
- Pain-RXI

Cohort 3
- Erythema-RXI
- Tenderness-RXI
- Induration-RXI
- Pain-RXI

Cohort 4
- Erythema-RXI
- Tenderness-RXI
- Induration-RXI
- Pain-RXI

Cohort 5
- Erythema-RXI
- Tenderness-RXI
- Induration-RXI
- Pain-RXI
RXI-109-1201: Safety Conclusions

- Number and severity of local side effects are similar (RXI-109 vs. placebo)
  - On Days 1 and 2 side effects were unilateral
    - Mostly mild erythema
  - After Day 3, side effects were bilateral

- Majority of the adverse events (30/35) were unrelated to drug
  - AEs were generally mild and resolved without sequelae
  - No immunological reactions
  - No changes noted in liver function tests, urinalysis, kidney function parameters, cardiovascular function, complement, coagulation, hematology or blood chemistry parameters

- The single SAE was unrelated to drug
  - Occurred one week after the abdominoplasty (>4 months after the single dose)
RXI-109-1201: Histology

CTGF Protein Signal in the Scar Area

• Smaller wound area tracks with lower CTGF protein levels within the scar area
• % positive CTGF protein staining is calculated as the percent of CTGF (yellow) within the defined scar area (green) (Note: *Blue signal is anything below the threshold defined as a positive signal*)
• The numbers presented are an average of 3 histological sections from each site
RXI-109-1201: Histological Measurements of Wound Area and CTGF Protein

- Dose dependent reduction of CTGF protein with RXI-109 treatment vs. placebo 84 days after a single dose
- Statistical significance was achieved at the highest dose tested (Cohort 5) despite small cohorts (3 subjects)
- Result is consistent with the expected mechanism of action of RXI-109

The levels of CTGF protein in RXI-109 dosed sites are shown as a percent of placebo dosed sites. P values were determined by t-test. * p value ≤0.05; ** p value ≤ 0.01

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohorts 4 &amp; 5</th>
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<tbody>
<tr>
<td>% CTGF Protein Level</td>
<td>100%</td>
<td>97%</td>
<td>102%</td>
<td>87%</td>
<td>83%</td>
<td>85%</td>
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Paired t-test P-values:

- Cohort 1: 0.93
- Cohort 2: 0.47
- Cohort 3: 0.85
- Cohort 4: 0.08
- Cohort 5: 0.05
- Cohorts 4 & 5: 0.0044

The levels of CTGF protein in RXI-109 dosed sites are shown as a percent of placebo dosed sites. P values were determined by t-test. * p value ≤0.05; ** p value ≤ 0.01
Study RXI-109-1201: Conclusions

- **Safety and Pharmacokinetics**
  - Safe and well tolerated at all dose levels tested
  - No negative effect on healing in healthy volunteers with no predisposition for bad scarring
  - Maximum blood level of RXI-109 is ~5% of intradermally administered dose

- **Biomarkers**
  - **Preclinical data** demonstrate potent, dose dependent silencing of CTGF with RXI-109 in vitro and in vivo with no delay in early wound healing
  - **RXI-109-1201**
    - Statistically significant lowering of CTGF protein concentration in RXI-109 treated-incisions compared to placebo control 3 months after a single dose
    - Trend toward dose dependent reduction in CTGF protein; more pronounced effect at higher doses

- RXI-109 was also safe in a Phase 1 multi-dose study (Poster #8225)