Topical siRNA for management of androgenic alopecia and oily skin
About Quark

- Founded in 1993; privately held
- Late stage pharmaceutical company with 2 Phase 3 programs, 5 Phase 2 programs and rich pipeline with POC in non-clinical efficacy models
- Headquarters: Fremont, CA – preclinical and clinical development
- Fully owned subsidiary, QBI Enterprises Ltd: Ness Ziona, Israel – platform development, drug discovery
- JV in China - with Suzhou Ribo Life Science – Kunshan RiboQuark Pharmaceutical Technology Co, Ltd

Focus: discovery and development of siRNA-based therapeutics
siRNA-Based Drugs Act Through Specific Inhibiting Gene Expression via RNA Interference

- **RNA interference (RNAi)** is a universal biological mechanism within living cells (mammalian, plants, fungi, bacteria) that controls which genes are active and how active they are via targeting specific mRNAs to degradation.

- **siRNA therapeutic molecules** are produced synthetically using well-established solid-phase synthesis processes and mimic endogenous RNAi triggers upon cell entry.

- Use of **specific chemical modifications** in siRNA compounds ensures:
  - Stability against body exonucleases and endonucleases
  - High activity and specificity
  - Strong attenuation of pro-inflammatory effects typical for exogenously delivered oligonucleotides

**siRNA-Based Drugs Act Through Specific Inhibiting Gene Expression via RNA Interference**

- siRNA targets mRNA degradation
- siRNA targets mRNA cleavage
- NO PROTEIN

**Target mRNA cleavage**
**Target mRNA degradation**
Therapeutic Hypothesis:

• Increased androgen production or increased androgen receptor (AR) sensitivity to androgens in the hair follicles bulbs and sebaceous glands leads to

  1. Hair follicle miniaturization and pattern scalp balding (androgenic alopecia)
  2. Excessive sebum production and acne development (acne vulgaris)

• A siRNA therapeutic designed to downregulate AR activity may result in prevention / treatment of these conditions
Quark’s Novel Topical Formulation for Management of Male and Female Pattern Hair Loss and Excessive Skin Sebum Production

- **Active Ingredient:** *synthetic siRNA formulated in liposomes for topical delivery specifically to hair follicle bulb and to sebaceous glands*
  - Does not penetrate into the dermis
  - No transdermal systemic absorption
  - Once or twice a week application
  - New IP
Detection of Synthetic siRNA in Human Male Scalp Skin Explants 24 Hours After Topical Application in the Novel Formulation

RNA is visible as black dots (by in situ hybridization technique)
siRNA Dose-Dependent Reduction of AR mRNA Levels in Human Male Scalp Skin Explants 24 Hours After Topical Application of the Formulation

AR mRNA expression levels (fold of vehicle control)

RLM-RACE analysis confirms the expected cleavage site of AR mRNA in human male scalp skin

Positive Control (transfected cells)
Decrease of AR Protein Levels in Human Skin Explants 24 Hours After Topical Application of the Formulation

**Immunohistochemistry analysis in male skin**

<table>
<thead>
<tr>
<th>Comparison vs. vehicle group</th>
<th>Quark’s Novel Topical Formulation</th>
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<tbody>
<tr>
<td>Dermis</td>
<td></td>
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<tr>
<td>Infundibulum</td>
<td></td>
</tr>
<tr>
<td>Upper root sheet</td>
<td></td>
</tr>
<tr>
<td>Bulge (Close to sebaceous glands)</td>
<td></td>
</tr>
<tr>
<td>Lower root sheet</td>
<td></td>
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<tr>
<td>Bulb</td>
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**Immunoblotting analysis in female skin**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>“naked” siRNA</th>
<th>Novel Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td></td>
<td></td>
<td>100kDa</td>
</tr>
<tr>
<td>Tubulin</td>
<td></td>
<td></td>
<td>55 kDa</td>
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</tbody>
</table>

Densitometry of the immunoblot above:

- No Variation
- Slight decrease
- Moderate decrease
- Quite clear decrease
- Clear decrease
Lack of Skin Inflammation Following Repeated Topical Application of the Liposome-Formulation on Depilated Mouse Skin

Absence of infiltrating immune cells or edema following repeated applications of the liposome formulated RNA

Formulated siRNA

Ctrl Saline

Treated- Mouse 1

Treated- Mouse 2

Treated- Mouse 3
No Absorption Through Human Skin Explants (ex vivo) in Franz Diffusion Cells

Apical application of formulated siRNA for 24 hours

No siRNA was detected in the receptor fluid
Demonstration of siRNA efficacy in alleviating alopecia in animal models

• There are currently no robust animal models of AGA or acne vulgaris.

• A well-established chemotherapy-induced alopecia (CIA) model in mice was used as a surrogate model of AGA. In this model, the cells in the hair bulb die due to chemotherapy administration.

• Quark used topically delivered siRNA targeting p53 in its proprietary formulation in this surrogate model of hair loss model for POC efficacy studies. P53 gene was selected as a target due to the fact that P53 KO mice do not lose hair in the CIA model.
Efficacy of Quark’s Liposome-Formulated p53 siRNA in the Mouse Model of Chemotherapy-Induced Alopecia

Control

siRNA formulated in the liposomes

Accelerated hair regrowth

Darker hair growth (melanocyte preservation)

d21

d29
Summary

Following topical application on human male and female skin explants, the liposome-formulated siRNA targeting AR:

- Distributes to hair follicle including bulb and sebaceous glands
- Significantly reduction in AR mRNA levels
- Significantly reduction in AR protein levels
- No evidence of transdermal absorption

Following topical application on mouse skin in vivo, the liposome-formulated siRNA targeting AR leads to:

- No transdermal absorption into systemic circulation
- No skin irritation

Following topical application on mouse skin in vivo, the liposome-formulated siRNA targeting AR leads to:

- Significantly accelerated regrowth of more pigmented hair in the model of chemotherapy-induced alopecia

Based on these data further exploration of other diseases of hair follicles and sebaceous glands including AGA and acne is feasible.
Thank you!

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