Development and first-in-human characterization of a potent oral CCR4 antagonist for the treatment of atopic dermatitis

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Disclosures

- Laurence Cheng is a Current Employee and Shareholder of RAPT Therapeutics, Inc.
RPT193 Acts on a Well Validated Pathway in Atopic Dermatitis and Asthma

Allergen, Microbes

Skin

Alarmins: TSLP, IL33

CCL17
CCL22

RPT193
Inhibits Th2 migration into inflamed tissues

Th2 cells are recruited via CCR4 into inflamed tissues

Cytokines
- IL-5
- IL-4
- IL-13

Inflammation
Thickening
Cough/Itch

anti-IL5/RAb
anti-IL4Rα Ab
anti-IL13 Ab
CCR4 is Highly Expressed on Th2 cells and Elevated Levels of CCR4 Ligands Correlate with Disease Activity and Severity

CCR4 is predominantly expressed on Th2 over Th1 Cells

Serum CCL17 levels correlate more strongly with atopic dermatitis clinical activity and severity compared to other biomarkers

RPT193 Has Greater Potency Against Th2 Chemotaxis Than Previous CCR4 Antagonists

CCL22-Induced Human Th2 Chemotaxis

**RPT193**
IC$_{50}$ ~370nM

**AZD2098**
IC$_{50}$ ~3µM

**GSK2239633**
IC$_{50}$ ~3µM
Oral Doses of RPT193 Reduces Skin Inflammation in an Acute OVA-Induced Atopic Dermatitis Model

100 mg/kg QD oral dosing covers the mouse Th2 IC$_{90}$ for chemotaxis at trough

- Sensitize with OVA
- Right ear: OVA
- Left ear: Saline
- Days 0 7 13 14 15
- Treatment: Vehicle, RPT193, or Dex
- Measure ear thickness: delta of OVA vs. Saline
- Delta Ear Thickness (mm)

- Vehicle
- RPT193 100 mg/kg
- Dex 10 mg/kg

p < 0.01

p < 0.05

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Oral Doses of RPT193 Demonstrates Similar Efficacy to Biologics in a Therapeutic Atopic Dermatitis Model

Sensitization

Allergen Challenge

Treatment: Vehicle, RPT193, Anti-IL-4R, or Anti-IL-13

Skin Analysis

Delta Skin Thickness (mm)

Days 0 1 7 8 9 10 11 12

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RPT193 Significantly Reduces Th2 Cell Migration Into Inflamed Skin a Mouse AD Model

**Diagram:**
- Sensitization
- Allergen Challenge
- Days 0, 1, 6, 7, 8, 9, 10, 11
- Treatment: Vehicle, RPT193
- Adoptive Transfer of CD45.1+ Th2 cells

**Graph:**
- Number of Th2 cells in inflamed ear
- Vehicle QD vs. RPT193 QD
- p < 0.0001
RPT193: Seamless Phase 1 Starts in Healthy Volunteers and Includes an AD Patient Cohort to Establish Proof of Concept

Phase 1a Single Ascending Dose (SAD) Cohorts

- 50 mg
- 100 mg
- 200 mg
- 200 mg Food effect
- 400 mg

Phase 1a Multiple Ascending Dose (MAD) Cohorts

- 50 mg
- 100 mg
- 200 mg
- 400 mg

Phase 1b Atopic Derm

- 7-Day Exposure, once daily dosing
- Single dose level, 28-Day Exposure

- Healthy Volunteer SAD and MAD Cohort Design
  - Double-blind, randomized study with 8 subjects per cohort (6 receiving oral RPT193 and 2 receiving placebo)
  - Effect of high-fat meal on pharmacokinetics tested after single 200 mg dose
  - Endpoints: PK, PD, Safety
Phase 1a Healthy Volunteer Data Support Once-Daily Dose

Dose-proportional Oral PK With Mean Terminal Half-life Of ~25 Hours Across All Dose Levels

Concentration of RPT193 in Plasma (ng/mL)

- 50 mg QD
- 100 mg QD
- 200 mg QD
- 400 mg QD

Final dose
Minimal Effect of Food Observed on Pharmacokinetics of a Single 200 mg Oral Dose of RPT193
RPT193 Exhibits Concentration-Dependent Target Occupancy Predicted to Inhibit CCR4-mediated Th2 Migration

Targeting 90% inhibition of Th2 chemotaxis
Targeted CCR4 Inhibition is Achieved with Repeated 50 mg Daily Dosing

Inhibition at day 8 across the dose levels

6 dosed / 2 placebo subjects per cohort
Analysis for some subjects did not pass QC, resulting in fewer than 8 points per cohort
Blinded Safety Data Indicate RPT193 has been Well Tolerated

SAD/MAD Safety Summary

• For the SAD and MAD, 64 subjects in total have been dosed with RPT193 or Placebo
• No Serious Adverse Events (SAEs)
• All (n=87) but one TEAE were mild in nature (single count of moderate headache in the MAD)
• No apparent increase in intensity or number in a dose-related fashion
• No ECG or lab related findings of note, including hematologic indices
RPT193: Seamless Clinical Trial Design to PoC and Beyond

RPT193 Phase 1a/1b Healthy Volunteer/Atopic Dermatitis Trial

- Phase 1a SAD
- Phase 1a MAD
- Phase 1b Atopic Dermatitis
  - Mod-Severe AD
  - Readout 4 weeks
  - Placebo-controlled 2:1
  - Single Dose Level, 28-day Exposure
  - ~30 AD Patients

Primary Endpoints: Safety, PK
Exploratory Endpoints: Clinical, Patient Reported, and Biologic Assessments

RPT193 Phase 2 Trials

- Phase 2b Atopic Dermatitis
- Phase 2a Asthma and Other Allergic Diseases
RPT193 has Demonstrated Promising Preclinical Efficacy and Early Clinical Data in Healthy Volunteers

- Therapeutic effects comparable to anti-IL4R alpha and anti-IL13 in mouse models of allergic skin inflammation
  - RPT193 blocks Th2 migration via targeting of CCR4
- Clean safety profile and well tolerated after single dose and multiple doses for 7 days of 50-400 mg in healthy volunteers
  - In addition, RPT193 GLP toxicology studies show a safety profile favorable for chronic, allergic disease indications
- Pharmacokinetics data support once daily oral dosing
  - Dose proportional exposure with low intra-subject variability
  - Minimal food effect
- Achieved target CCR4 inhibition in 100% of subjects at multiple doses of 50 mg and above
- A Phase 1b randomized, double-blind, placebo-controlled cohort enrolling moderate to severe AD patients is ongoing
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