Preclinical Data on RP-A501, the First Gene Therapy to Treat a Monogenic Heart Failure Syndrome

Company Webcast
November 26, 2018
Speakers
• Gaurav Shah, M.D., Chief Executive Officer & President
• Lead collaborator and clinical investigator for AAV program
• Claudine Prowse, Ph.D., Senior Vice President, Corporate Strategy & IR Officer

Q&A Participants
• Jonathan Schwartz, M.D., Chief Medical Officer & Head of Clinical Development
• Kinnari Patel, PharmD, MBA, Chief Operating Officer & Head of Development
• Annihita Keravala, Ph.D., Associate Vice President, AAV Program
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Various statements in this presentation concerning Rocket’s future expectations, plans and prospects, including without limitation, Rocket’s expectations regarding the safety, effectiveness and timing of product candidates that Rocket may develop, including in collaboration with academic partners, to treat Danon Disease, Fanconi Anemia (FA), Leukocyte Adhesion Deficiency-I (LAD-I), Pyruvate Kinase Deficiency (PKD) and Infantile Malignant Osteopetrosis (IMO), and the safety, effectiveness and timing of related pre-clinical studies and clinical trials, may constitute forward-looking statements for the purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995 and other federal securities laws and are subject to substantial risks, uncertainties and assumptions. You should not place reliance on these forward-looking statements, which often include words such as "believe", "expect", "anticipate", "intend", "plan", "will give", "estimate", "seek", "will", "may", "suggest" or similar terms, variations of such terms or the negative of those terms. Although Rocket believes that the expectations reflected in the forward-looking statements are reasonable, Rocket cannot guarantee such outcomes. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including, without limitation, Rocket’s ability to successfully demonstrate the efficacy and safety of such products and pre-clinical studies and clinical trials, its gene therapy programs, the preclinical and clinical results for its product candidates, which may not support further development and marketing approval, Rocket’s ability to commence a registrational study in FA and Danon disease within the projected time periods, the potential advantages of Rocket’s product candidates, actions of regulatory agencies, which may affect the initiation, timing and progress of pre-clinical studies and clinical trials of its product candidates, Rocket’s and its licensors ability to obtain, maintain and protect its and their respective intellectual property, the timing, cost or other aspects of a potential commercial launch of Rocket’s product candidates, Rocket’s ability to manage operating expenses, Rocket’s ability to obtain additional funding to support its business activities and establish and maintain strategic business alliances and new business initiatives, Rocket’s dependence on third parties for development, manufacture, marketing, sales and distribution of product candidates, the outcome of litigation, and unexpected expenditures, as well as those risks more fully discussed in the section entitled “Risk Factors” in Rocket’s Annual Report on Form 10-K for the year ended December 31, 2017. Accordingly, you should not place undue reliance on these forward-looking statements. All such statements speak only as of the date made, and Rocket undertakes no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.
RP-A501 Program Highlights

• **Disease Target**
  - Monogenic multi-organ disorder with early mortality primarily due to heart failure
  - Highly penetrant and X-linked dominant
  - No effective therapies

• **RP-A501: Rocket’s First-In-Class Investigational Gene Therapy (GTx)**
  - Improvements in survival rate and correction of molecular, structural, and phenotypic hallmarks of the disease observed in preclinical studies
  - No toxicities observed in mice and monkeys
  - Strong IP; exclusive and broad rights with REGENXBIO and UCSD
  - IND studies to commence in 1H2019
  - Largest market opportunity of all Rocket programs: ~15K-30K prevalence in US+EU
Most Patients Present with Hypertrophic Cardiomyopathy (HCM)

- Unexplained left ventricular wall thickness and electrophysiological abnormalities
- Disease onset during childhood and adolescence followed by rapid progression to end-stage heart failure and death
- \textit{LAMP2} mutation recently identified in patients with HCM
Danon Disease: Newly Discovered with Growing Attention

Recent Clinical and Scientific Progress Has Increased Disease Understanding...
- **1981**: Danon Disease first described\(^1\)
- **2000**: \(LAMP2\) mutation identified\(^2\)
- **2011-2013**: \(LAMP2\) inclusion in HCM commercial gene panels\(^3\)
- **2018**: Over 75 unique \(LAMP2\) mutations identified in literature\(^4\)

...But Danon Disease Is Still Underdiagnosed and Poorly Recognized
- Nonspecific clinical presentation
- Infrequent genetic testing of HCM patients
  - Expensive and not broadly reimbursed
  - No therapeutic reasons for testing
  - Relatively new
- Cardiologist unfamiliarity with disorders of autophagy
- Inaccurate description of \(LAMP2\) mutation sequelae in early publications

Danon Disease Prevalence: ~15-30K in the US+EU

Hypertrophic Cardiomyopathy (HCM)
- US HCM Prevalence: 600K-1MM+ \(^1\)
- 1-4% of HCM patients consistently identified with \textit{LAMP2} mutations in multiple studies with >1000 subjects evaluated\(^2\)
- Danon Disease Patients with HCM\(^3\)
  - 85% of males
  - 30% of females

Dilated Cardiomyopathy (DCM)
- Danon Disease Patients with DCM\(^3\)
  - 15% of males
  - 50% of females

\(^1\)Source: J Am Coll Cardiol. 2015 Mar 31;65(12):1249-1254.
Eric Adler, MD

- Director of Cardiac Transplant and Mechanical Circulatory Support and Professor of Medicine at UC San Diego
- Principal investigator of numerous heart failure clinical trials
Danon Disease: Devastating Multisystemic Disorder with No Specific Treatments

- **95% of patients have severe cardiomyopathy**
  - Patients die from progressive heart failure
  - Males frequently die in their teens and females die in their thirties and forties

- **Other clinical manifestations**
  - Skeletal Myopathy
  - CNS manifestations
  - Liver disease manifests as elevations of liver enzymes

- **Heart transplant is not curative and is associated with considerable morbidity and mortality**

**Danon Disease Clinical Presentation and Intervention Timeline**

- Females
  - **HCM**
  - End-Stage Cardiomyopathy (CMIO)
  - Skeletal Myopathy
  - DCM
  - Implantable Electronic Cardiac Device (IECD)
  - Death/Heart Transplant (HTx)/LVAD

- Males
  - **Cog. Impairment**
  - IECD
  - Death/HTx/LVAD
Danon Disease: An Impairment in Autophagy Caused by LAMP2B Mutations

Macroautophagy

Isolation Membrane → Cytosolic Proteins and Organelles → Autophagosome → Autolysosome

LAMP2

Acid Hydrolases

Danon Disease
X-linked cardiac & skeletal myopathy
**Construct:** RP-A501 is designed to increase expression of LAMP2 in target organs

**AAV9 Capsid Has High Tropism for the Heart, Liver, CNS, and Skeletal Muscle**

- AAV9 LAMP2B transgene is 1.4 kb in length
- Entire vector is ~4.2 kb and fits nicely into the AAV construct
- AAV9 has well-characterized safety in rodents, monkeys, and humans
RP-A501 Restores Cardiac Function in KO Mice

**Dose-Dependent Improvements in Systolic and Diastolic Function in LAMP2 KO Mice**

*PBS = Phosphate Buffered Saline (Negative Control)*
RP-A501 Shows Survival Benefit at Higher Doses

Note: All mice were sacrificed at Month 10
RNA: RP-A501 Elicits Dose-Dependent Expression of hLAMP2B mRNA in Cardiac Tissue of KO Mice

*hLAMP2B = Human LAMP2B*
Protein: RP-A501 Elicits Expression of LAMP2B Protein and Autophagic Flux in Heart
**Structural:** RP-A501 Reduces Autophagic Vacuoles in All Examined Organs

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Liver: RP-A501 Improves Liver Enzymes

**Alkaline Phosphatase**

- **WT**
- **PBS**
- **1e13**
- **5e13**
- **1e14**
- **2e14**

- **AAV9.LAMP2B**
- **LAMP2 KO**

P-values: P<0.0001

**Alanine Aminotransferase**

- **WT**
- **PBS**
- **1e13**
- **5e13**
- **1e14**
- **2e14**

- **AAV9.LAMP2B**
- **LAMP2 KO**

P-values: P<0.001, P=0.019, P=0.005, P=0.04
• RP-A501 Demonstrates Phenotype Improvements:
  o Survival benefit at higher doses
  o Dose-dependent restoration of cardiac function
  o Improvement in liver enzymes

• RP-A501 Reduces Autophagic Vacuoles in All Examined Organs: Heart, Liver, Skeletal Muscle

• RP-A501 Elicits Dose-Dependent Increase in LAMP2 mRNA and Protein
RP-A501 Preclinical Safety Profile:

• No therapy-related deaths
• No significant hematologic changes
• No significant biochemical changes
• No significant clinical chemistry changes
• A mild and transient ALT elevation that self-resolved
Collaborations and Intellectual Property

• Exclusive licensee to all of UCSD’s relevant published and future patents

• Exclusive worldwide licensee to develop and commercialize a gene therapy for Danon disease using REGENXBIO’s AAV-9 capsids
  • Exclusive option for two additional AAV serotypes

• Broad filing strategy covering areas such as composition of matter, mechanism of action, and manufacturing
RP-A501 Clinical Development Plans

2019
- Initiate Phase 1 with clinical GMP AAV9 RP-A501 in patients with Danon disease
- Continue registry & patient education/identification
- Clinical retrospective database in progress

2020
- Phase 2/Registrational Study for BLA/MAA submission seeking Accelerated Approval
Near-Term Potential Clinical Value Drivers

1H19

- Danon: IND Acceptance; FPI
- FA: FPI Phase 1/2 trial (IND cleared in Nov ’18)
- FA: Additional Data from Patients Treated under “Process A”
- LAD-I: FPI for registration-enabling Phase 1/2 trial (IND cleared in Nov ’18)
- PKD: IMPD/IND acceptance; FPI

2H19

- FA: data from Patients Treated under “Process B”
- FA: FDA alignment on final endpoints for registration
- LAD-I: Phase 1/2 data
- Four programs in the clinic
Rocket’s Expanding Pipeline: Potential for Significant Value Creation Near and Long Term

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Legend:
- LVV
- AAV
Q&A