Discovery & Preclinical Validation of Therapeutic Leads with Novel MOAs for CKD
March 4, 2021
ABOUT ARIA PHARMACEUTICALS

First-in-class small molecules

Over 18 diseases in our pipeline

Generating a 30X Hit Rate at in vivo efficacy milestones

Saves years in drug development
ARIA CHRONIC KIDNEY DISEASE (CKD) PROGRAM OVERVIEW

Pathophysiology
Unmet Needs & Opportunity

Aria Discovery AI- Platform

In vivo Efficacy

TXR-1208 & TXR-1210 Discovery

Continued Development/ Conclusions
CHRONIC KIDNEY DISEASE (CKD)

MARKET
700 MILLION cases worldwide
35% - 5 year survival rate
DIABETIC NEPHROPATHY THERAPIES - standard of care: does not stop disease progression

SPEED AND SUCCESS
3 OF 10 MOLECULES ADVANCED from hit prediction to in vivo
12 WEEKS from program start to in vivo results
LEAD MOLECULE TXR-1208 & TXR-1210 IN VIVO HIGHLIGHTS:
NOVEL MOAs in CKD
Significant DECREASE of kidney fibrosis and inflammation compared to TGFbeta mAb
Minimal body weight changes – GOOD TOLERABILITY

1 Pharmaceutical Intelligence Services, GlobalData LLC
Discovery Process and Results

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OUR PROCESS SAVES YEARS IN DEVELOPMENT WITH 30X SUCCESS RATE

TRADITIONAL APPROACH

- Pathogenesis analysis
- Target identification
- Bioassay development
- High throughput screening
- Lead discovery
- Lead optimization
- IND-enabling studies

1 YEAR
2 YEARS
3 YEARS
4 YEARS

1%-2% success

Limitations
• Single MOA hypothesis
• Creation of de novo NCE risky

ARIO
PHARMACEUTICALS

APPROACH

- Efficacy predictions
- Lead discovery
- Lead optimization
- IND-enabling studies

0-6 MONTHS
30% success

Advantages
• Multiple MOAs examined
• NCE based on known chemistry
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TRADITIONAL APPROACH

Pathogenesis analysis → Target identification → Bioassay development → High throughput screening → Lead discovery → Lead optimization → IND-enabling studies

1 YEAR 2 YEARS 3 YEARS 4 YEARS

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APPROACH

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0-6 MONTHS 30% success
DISCOVERY PROCESS IDENTIFIES TXR-1210 IN 12 WEEKS

AI-Driven Discovery

Diverse Data, Methods:
- System Biology Data
- Disease Specific Data
- Chemistry Library
- ~65 methods

50K Molecules (known chemistry)

AI-Assisted Review

Novelty and Safety:
- Novel MOA
- Safety profile
- ADME properties

87 Molecules

Hit Diligence

PhD-led review, Safety:
- MOA relevance
- MOA safety
- IP development path

25 Molecules

Preclinical

Optimal Disease Models:
- Test diverse MOAs
- CRO execution
- Rapid in vivo efficacy

10 Molecules
Discovery Process and Results

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PRECLINICAL IN VIVO CKD EFFICACY STUDY – MOUSE UNILATERAL URETERAL OBSTRUCTION (UUO) MODEL

Drug dosing start

D-5

D0

D9

• Unilateral Ureteral Obstruction
• Control Tx (TGF-β1 mAb) dosing start

Sample collection

• Kidney

Efficacy Measures

• H & E staining
• α-SMA staining
• Collagen staining (PSR)
• Hydroxyproline

• Renal injury and fibrosis caused by obstruction of urine flow
• Benchmark POC model for initial drug candidate efficacy evaluation
EXCELLENT OVERALL TOLERABILITY OF PREDICTION HITS

- All test molecules are well tolerated during once-daily dosing for 14 days
- Body weight greater than vehicle treated animals with TXR1208 and TXR1210
Efficacy assessed by collagen (PSR and hydroxyproline) and myofibroblast activation (α-SMA) markers

- TXR-1208, TXR-1209, and TXR-1210 significantly decrease α-SMA with a trend of decreased collagen deposition (PSR)
- TXR-1210, TXR-1209, TXR-1208, and TXR-1202 decrease picrosirius red collagen marker without achieving p<0.05 significance
- PSR collagen and TIL results generally agree with α-SMA
- α-SMA and TIL results generally agree with PSR

**Myofibroblasts: α-SMA**

**Collagen: Picrosirius Red**

**Collagen: Hydroxyproline**
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- In vivo Efficacy With Prediction Hits/ novel MOAs
- TXR-1208 & TXR-1210 Discovery Leads
- Continued Development & Conclusions
TXR-1210 & TXR-1208 SIGNIFICANTLY DECREASED KIDNEY FIBROSIS AND INFLAMMATION

- TXR-1210, TXR-1208: p<0.001
- High statistical significance

- TXR-1208, TXR-1210: p<0.01
- \(\alpha\)-SMA, collagen results generally agree with T cells

Myofibroblasts: \(\alpha\)-SMA

Infiltrating T Cells: H&E

N=10 mice per group
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- In vivo Efficacy with Prediction Hits/novel MOAs
- TXR-1208 & TXR-1210 Discovery
- Conclusions & Continued Development
**TXR-1208 & TXR-1210: IN VIVO EFFICACY SUMMARY**

- **In vivo Fibrosis**
  - Significantly decreased myofibroblast activation
  - Decreased collagen deposition without achieving significance of p<0.05

- **Inflammation**
  - Significantly decreased infiltrating T cells

- **Tolerability**
  - Excellent tolerability assessed by body weight

- Significant efficacy in the UUO model
- Efficacy comparable to TGFβ mAb and superior to vehicle
STUDY SUMMARY AND CONTINUED DEVELOPMENT OF NOVEL MOAs FOR CKD

### Approach

#### Time (weeks)
- 4: Prediction Hits
- 8: In Vivo Screening
- Lead Optimization
- IND-enabling Studies

#### Current Position
- Candidate Selection

#### Candidate Selection
- Rapid Progression through hit validation and lead optimization
- 10 MOAs selected and evaluated in an *in vivo* screening study
- 4 weeks to complete predictions, select hits, and begin in vivo screening
- 2 discovery leads/hits discovered from *in vivo* screen (different MOAs) to have evidence of efficacy
- Attractive starting points for lead optimization
- Establish PK/PD Efficacy relationships
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