DISCOVERY & PRECLINICAL VALIDATION FOR TWO THERAPEUTIC LEADS WITH NOVEL MOAS IDENTIFIED USING ARIA’S PROPRIETARY AI-PLATFORM

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AGENDA

• Background

• Discovery with Aria’s proprietary AI-platform

• *In vivo* efficacy study

• Summary
BACKGROUND
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
### IDIOPATHIC PULMONARY FIBROSIS (IPF)

**MARKET**
- **3 MILLION** cases worldwide
- **3-5 YEARS** - life expectancy after diagnosis
- **NINTEDANIB & PIRFENIDONE** standards of care: slow disease progression

**SPEED AND SUCCESS**
- **↑ 10 OF 20 MOLECULES ADVANCED** from hit prediction to *in vivo*
- **12 WEEKS** from program start to *in vivo* results

**LEAD MOLECULE TXR-1002 & TXR-1007 IN VIVO HIGHLIGHTS:**
- **2 NOVEL MOAs** in IPF
- Significant **REDUCTION** of collagen in lung tissue - comparable to nintedanib
- **LOWERS** lung infiltration of neutrophils – lower than nintedanib
- **LOWERS** lung infiltration of lymphocytes – comparable to nintedanib
- **GOOD TOLERABILITY** – Minimal body weight changes.
- TXR-1002, TXR-1007 clinically investigated mechanisms
DISCOVERY WITH ARIA’S PROPRIETARY AI-PLATFORM
OUR PROCESS SAVES YEARS IN DEVELOPMENT WITH 30X SUCCESS RATE

TRADITIONAL APPROACH

- Pathogenesis analysis
- Target identification
- Bioassay development
- High throughput screening

Limitations:
- Single MOA hypothesis
- Creation of de novo NCE risky

1% - 2% success

ADVANCED APPROACH

- Advantages
  - Multiple MOAs examined
  - NCE based on known chemistry

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

30% success

0-6 MONTHS
DISCOVERY PROCESS IDENTIFIES TXR-1002 AND TXR-1007 IN 12 WEEKS

**AI-Driven Discovery**
Diverse Data, Methods:
- 32 data sources
- 65 methods
- 2M+ molecule chemistry library

50K Molecules

**AI-Assisted Review**
Novelty and Safety:
- Novel MOA
- Safety profile
- ADME properties

87 Molecules

**Hit Diligence**
PhD-led Deep Dive:
- MOA relevance
- MOA safety
- IP development path

20 Molecules

**Preclinical**
Optimal Disease Models:
- Test diverse MOAs
- CRO availability
- Rapid in vivo efficacy

10 Molecules
IN VIVO EFFICACY STUDY
IN VIVO EFFICACY STUDY DESIGN

**C57/BL6 Male mice**

Body weight measurement 3 times weekly

- Bleomycin Oral Aspiration
- Drug Dosing Start

In-life

Sample Collection
- BALF*
- Lung

Efficacy Measures
- Lymphocyte counts
- Neutrophil counts
- Collagen staining

Post-life

- Bleomycin-induced lung injury in male mice
- Proof-of-concept model for initial drug candidate evaluation
- Standard of care nintedanib (PDGFR, FGFR, and VEGFR inhibitor) used as reference therapy
- Additional lung fibrosis models available for further candidate investigation; e.g., TGF-β overexpression and/or a treatment paradigm instead of prophylaxis

* BALF - Bronchoalveolar lavage fluid
EXCELLENT TOLERABILITY FOR TXR-1002 & TXR-1007

- Weight profile better than nintedanib
**IN VIVO EFFICACY COMPARABLE TO STANDARD OF CARE**

- TXR-1002 & TXR-1007 significantly reduce collagen staining in lung tissue (comparable to nintedanib)
- TXR-1002 & TXR-1007 lowers lung infiltration of neutrophils (TXR-1002 better than nintedanib)
  - Directional – inflammation markers measured at day 21**

**Lung Collagen**

<table>
<thead>
<tr>
<th>Masson Trichrome Scores</th>
<th>No Vehicle</th>
<th>Vehicle Only</th>
<th>Nintedanib</th>
<th>TXR-1002</th>
<th>TXR-1007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collagen Fibrosis Score</strong></td>
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</tr>
<tr>
<td>0 = 0%</td>
<td>1 = 1-5%</td>
<td>2 = 6-15%</td>
<td>3 = 16-40%</td>
<td>4 = 41-70%</td>
<td>5 = 71-100%</td>
</tr>
</tbody>
</table>

**Lung Neutrophils**

<table>
<thead>
<tr>
<th>Score</th>
<th>No Vehicle</th>
<th>Vehicle Only</th>
<th>Nintedanib</th>
<th>TXR-1002</th>
<th>TXR-1007</th>
</tr>
</thead>
</table>

- n=10 mice per group
- *p< 0.05
- **Typical study protocol is to measure earlier to capture peak inflammation**
IN VIVO EFFICACY COMPARABLE TO STANDARD OF CARE

- TXR-1002 & TXR-1007 lowers lymphocytes (comparable to nintedanib)
- Directional – inflammation markers measured at day 21*

*Typical study protocol is to measure earlier to capture peak inflammation
n=10 mice per group
TXR-1002 & TXR-1007 SUMMARY

TXR-1002 & TXR-1007 DEMONSTRATE POSITIVE INITIAL EFFICACY WITH A NEW MECHANISM FOR IPF

GOOD TOLERABILITY – clinically investigated mechanism

LUNG INFLAMMATION HISTOLOGY – decrease infiltrating neutrophils and lymphocytes

LUNG FIBROSIS HISTOLOGY – decreased fibrosis (key efficacy measure)
**STUDY SUMMARY AND CONTINUED DEVELOPMENT OF NOVEL MOA FOR IPF**

**APPROACH**

- **Prediction Hits**
- **In Vivo Screening**
- **Lead Optimization**
- **IND-enabling Studies**

**Time (weeks)**
- 4
- 8

### APPROACH

- **Current Position**
- **Candidate Selection**

- **Rapid Progression through hit validation and lead optimization**
  - 10 MOAs selected and evaluated in an *in vivo* screening study
  - 2 leads/hits TXR-1002 & TXR1007 discovered from *in vivo* screen (different MOAs)
  - Positive results in bleomycin-induced IPF mouse model
  - Currently lead optimization activities ongoing for TXR-1002, with novel MOA
    - Well tolerated mechanism in clinical trials
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