The Emerging Safety and Activity of TRiM™ Platform Based siRNA Drugs
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to DIA, its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. DIA and the DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.
Disclosures

Arrowhead Pharmaceuticals: Employee and Shareholder
Agenda

• Technology/Platform Introduction

• Summary pharmacodynamic data by program

• Across program platform safety data
Components:

- Stabilization chemistries
- PK enhancers as necessary
- Linker chemistries
- Targeting ligands
<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Pre-clinical</th>
<th>Pre-IND</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARO-AAT</td>
<td>Alpha-1 Liver Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARO-APOC3</td>
<td>Hypertriglyceridemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARO-ANG3</td>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARO-HSD</td>
<td>Liver Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARO-ENaC</td>
<td>Cystic Fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARO-HIF2</td>
<td>Renal Cell Carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JNJ-3989</td>
<td>Hepatitis B</td>
<td>Partnered with Janssen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMG 890</td>
<td>Cardiovascular Disease</td>
<td>Partnered with Amgen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARO-JNJ1</td>
<td>Undisclosed</td>
<td>With Janssen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2019 DIA, Inc. All rights reserved.
ARO-AAT Phase 1, NHV SAD/MAD Study

Single dose ARO-AAT

Multiple dose ARO-AAT

Supports quarterly or less frequent dosing
• Rebound initiates at approximately week 12

• All subjects return towards baseline although duration of effect remains durable
AROHBV1001: CHB Patient Data

AROHBV1001: double blind, single dose escalating study in healthy volunteers and open label, multi-dose escalating study in patients with CHB

Mean HBsAg reductions from baseline

- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose
Plasma triglyceride levels are an independent risk factor for cardiovascular disease (Rosenson, ACC, 2014)

- Genetic studies support causal relationship
- Independent of LDL-C or HDL-C
ARO-APOC3 in Healthy Volunteers - Single 100 mg dose through week 12

**APOC3**

![Graph showing the reduction in serum level of APOC3 over weeks.](image)

- **Placebo (APOC3)**
- **100 mg (APOC3)**

**Triglycerides**

![Graph showing the reduction in serum level of triglycerides over weeks.](image)

- **Placebo (TG)**
- **100 mg (TG)**
ARO-ANG3 in Healthy Volunteers – Single 200 mg dose through week 12

**ANGPTL3**

![Graph showing the effect of Placebo (ANGPTL3) and 200 mg (ANGPTL3) on serum level reduction over weeks 0 to 12.]

**Triglycerides**

![Graph showing the effect of Placebo (TG) and 200 mg (TG) on serum level reduction over weeks 0 to 12.]

- **Placebo (ANGPTL3)**
- **200 mg (ANGPTL3)**
- **Placebo (TG)**
- **200 mg (TG)**
• For hepatocyte gene targets, single dose induces deep and prolonged gene target silencing.

• Nadir typically reached within 4 weeks but varies (biology and trigger dependent).

• For single dose administration, dose level to reach maximum hepatocyte gene silencing varies (also biology and trigger dependent).

• Duration implies opportunity for Q3-6 month dosing intervals
Safety: Are There siRNA Class Effects?

Thoughts on oligonucleotide therapeutic safety profile primarily derived from older generation ASOs. siRNA specific profile becoming more clear with late stage data.

Historical Profile Based on ASO, siRNA Literature:

- Renal accumulation/toxicity: Primarily reported in relation to ASOs\(^1\)

- Thrombocytopenia: Only reported for phosphorothioate ASOs\(^2\)
  - MOA not entirely clear\(^3\)
  - To our knowledge, has not been associated with siRNA therapeutics

- Transaminase elevations occasionally seen\(^4\)

- Injection site reactions, also generally mild\(^5\)

2. Witzum et al., NEJM, 2019, Drisapersen briefing document NDA 206031, etc., Chi et al., 2017
3. Volanesorsen advisory committee briefing document, Chi et al., 2017
4. Alnylam RNAi Roundtable 2018
Emerging TRiM™ Platform Safety Data

- Reflecting on fully unblinded placebo controlled studies (AROAAT1001, AROHBV1001 NHV Cohorts, AROANG31001 NHV Cohorts)
- Total enrollment: active (at least 1 dose) = 72, placebo = 43
- Total of 94 doses active drug administered

<table>
<thead>
<tr>
<th></th>
<th>Active (n=72) #/%</th>
<th>Placebo (n=43) #/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>AEs from renal function changes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs of thrombocytopenia or low platelets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs from ALT changes</td>
<td>1(1.4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Local Injection Site Reaction (LISR), all “mild”</td>
<td>4 (5.6% of patients, 4.3% injections)</td>
<td>0</td>
</tr>
</tbody>
</table>

- LISR: All mild, no drop outs due to LISR
## Emerging TRiM™ Safety: Platelets, Renal

<table>
<thead>
<tr>
<th>Shift Table</th>
<th>Active (n=72)</th>
<th>Placebo (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent creatinine increase from Grade 0 to Grade 1</td>
<td>7 (9.7%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Treatment emergent creatinine increase to &gt; Grade 1</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Treatment emergent platelet count decline from Grade 0 to Grade 1</td>
<td>1 (1.4%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Treatment emergent platelet count decline to &gt; Grade 1</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
ALT grade 1 at baseline (Day 1), shift to grade 2 (peak 192 U/L, Day 99) but confounded by temporally associated use of herbal supplement with published liver toxic profile. ALT normal at end of study.
While pharmacologic effect lasts beyond Day 113 (typically End of Study), most excursions in ALT and total bilirubin have returned to baseline by End of Study.
TRiM™ Summary Safety:

• Experience to date with platform suggests findings generally consistent with what has been reported for other liver targeted siRNA conjugates
  • No clear renal or platelet/immune/hematologic signals

• LISRs occur but generally mild

• Adverse ALT changes are infrequent, typically mild and of limited duration
Thank you!