A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-AT3) Targeting Antithrombin for Treatment of Hemophilia: Interim Phase 1 Study Results in Volunteers and Patients with Hemophilia A and B
Antithrombin (AT) is genetically defined target

- AT is key natural anticoagulant
  - Inactivates factors Xa and thrombin
  - Attenuates thrombin generation
- Human AT deficiency associated with increased thrombin generation
- Expressed in liver; circulates in plasma

Co-inheritance of thrombophilic traits in hemophilia

- Associated with milder bleeding, reduced factor requirements, fewer complications
- Includes heterozygous
  - Antithrombin deficiency
  - Factor V\textsubscript{Leiden}
  - Protein C deficiency
  - Protein S deficiency

ALN-AT3 in clinical development

- ESC-GalNAc-siRNA for SC dosing
- Positive top-line SAD Phase 1 results
- Orphan drug status in U.S. and EU (HA/HB)
- Phase 1 MAD study in patients ongoing

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RNA Interference (RNAi)
A New Class of Innovative Medicines

RNAi Therapeutics
• Harness natural pathway
  » Catalytic mechanism
  » Mediated by small interfering RNA or “siRNA”
• Therapeutic gene silencing
  » Any gene in genome
  » Distinct mechanism of action vs. other drug classes
  » Unique opportunities for innovative medicines
• Clinically validated platform
“Enhanced stabilization chemistry” (ESC) utilized for potency and durability of effect

Weekly SC dosing results in potent and sustained suppression of AT levels
ALN-AT3 Preclinical Proof-of-Concept

Improved thrombin generation in NHP inhibitor hemophilia model

Proof-of-concept in multiple preclinical settings

- Increased thrombin generation in human hemophilia A and B plasma
- Correction of APTT in hemophilia mice
- Survival benefit in hemophilia mice treated w ALN-AT3
- Enhanced thrombus formation in microvessel laser injury model in hemophilia mice
- Improved hemostasis in saphenous vein bleeding model in hemophilia mice
- Increased thrombin generation in hemophilia A inhibitor model in NHPs

*similar results obtained by ETP (p<0.01 at 0.50 mg/kg)
ALN-AT3 Phase 1 Study
Dose-Escalation Study in Two Parts

Primary objectives
• Safety, tolerability

Secondary objectives
• AT knockdown, thrombin generation

Part A
Single-Ascending Dose (SAD)
- 30 mcg/kg x 1 SC

Part B
Multiple-Ascending Dose (MAD)
- 15 mcg/kg qW x 3 SC
- 45 mcg/kg qW x 3 SC

Randomized 3:1, N=4
Single-blind
Placebo-controlled
Healthy volunteers

Open-label
Hemophilia A or B
N=3/cohort

Ongoing
Up to 4 additional cohorts
### ALN-AT3 Phase 1 Study Part A (SAD)*
Cohort 1 Demographics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age</th>
<th>Ethnicity</th>
<th>Follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>38</td>
<td>Black</td>
<td>56 days</td>
</tr>
<tr>
<td>30 mcg/kg x 1</td>
<td>21</td>
<td>Asian</td>
<td>83 days</td>
</tr>
<tr>
<td>30 mcg/kg x 1</td>
<td>29</td>
<td>Asian</td>
<td>70 days</td>
</tr>
<tr>
<td>30 mcg/kg x 1</td>
<td>38</td>
<td>White</td>
<td>70 days</td>
</tr>
</tbody>
</table>

*Data as of Nov. 24, 2014*
ALN-AT3 Phase 1 Study Part A (SAD)*
Safety/Tolerability; All TEAEs

- No serious adverse events
- All adverse events mild
- No discontinuations
- No injection site reactions
- No thromboembolic events or clinically significant D-dimer increases
- Normal physical exams, vital signs, and ECG
- No laboratory AEs (LFTs, CBC, coagulation parameters)

*Data as of Nov. 24, 2014
AT knockdown after single dose in human volunteers

- Maximum AT knockdown relative to baseline up to 28%
- Mean maximum AT knockdown of 19% ± 4.4% (mean ± SEM)
  » Placebo vs. treated, ANOVA p<0.01
- AT knockdown durable for over 60 days

*Data as of Nov. 24, 2014
Increase in thrombin generation with AT knockdown

- Significant association between AT knockdown and peak thrombin generation
- Up to 152% increase in peak thrombin generation
- Mean maximum increase of peak thrombin 138% ± 8.9% (mean ± SEM)
  - Consistent with increased sensitivity for thrombin generation increase with AT knockdown in background of normal levels of Factor VIII or IX

*Data as of Nov. 24, 2014*
## ALN-AT3 Phase 1 Study Part B (MAD)*
### Cohort 1 and 2 Demographics

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Hemophilia</th>
<th>ALN-AT3 Treatment</th>
<th>Age</th>
<th>Ethnicity</th>
<th>Follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, Severe</td>
<td>15 mcg/kg qw x 3</td>
<td>27</td>
<td>Black</td>
<td>49 days</td>
<td></td>
</tr>
<tr>
<td>B, Severe</td>
<td>15 mcg/kg qw x 3</td>
<td>37</td>
<td>White</td>
<td>35 days</td>
<td></td>
</tr>
<tr>
<td>A, Severe</td>
<td>15 mcg/kg qw x 3</td>
<td>19</td>
<td>White</td>
<td>35 days</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort 2</th>
<th>Hemophilia</th>
<th>ALN-AT3 Treatment</th>
<th>Age</th>
<th>Ethnicity</th>
<th>Follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, Severe</td>
<td>45 mcg/kg qw x 3</td>
<td>61</td>
<td>White</td>
<td>15 days</td>
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*Cohort 1 data as of Nov. 24, 2014; cohort 2 data as of Dec. 5, 2014*
ALN-AT3 Phase 1 Study Part B (MAD)*
Cohort 1 and 2 Interim Safety/Tolerability; All TEAEs

- No serious adverse events
- All adverse events mild/moderate
- No discontinuations
- No injection site reactions
- No thromboembolic events or clinically significant D-dimer increases
- Normal physical exams, vital signs, and ECG
- No laboratory AEs (LFTs, CBC, coagulation parameters)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Cohort 1 N=3</th>
<th>Cohort 2 N=1</th>
<th>Relationship to Study Drug</th>
</tr>
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<tbody>
<tr>
<td>Muscle Bleed</td>
<td>2</td>
<td>0</td>
<td>Not related</td>
</tr>
<tr>
<td>Venipuncture bleed</td>
<td>2</td>
<td>0</td>
<td>Not related</td>
</tr>
<tr>
<td>Idiopathic abdominal pain</td>
<td>1</td>
<td>0</td>
<td>Not related</td>
</tr>
<tr>
<td>Joint Bleed</td>
<td>1</td>
<td>0</td>
<td>Not related</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>0</td>
<td>Possibly related</td>
</tr>
<tr>
<td>Nose Bleed</td>
<td>1</td>
<td>0</td>
<td>Not related</td>
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<tr>
<td>Oral mucosal bleed</td>
<td>0</td>
<td>1</td>
<td>Not related</td>
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*Cohort 1 data as of Nov. 24, 2014; cohort 2 data as of Dec. 5, 2014
Initial data on AT knockdown after multi-dose in hemophilia subjects

- Cohort 1 (n=3) results
  - Mean maximum AT knockdown of 27% ± 13% (mean ± SEM)
  - Maximum AT knockdown up to 52% in most advanced subject; nadir at day 35
  - Conclusions from thrombin generation measurements are pending further analysis

- Cohort 2 (n=1) results
  - AT knockdown in first subject up to 57%; data from local lab reporting
  - Thrombin generation results pending cohort completion

*Cohort 1 data as of Nov. 24, 2014; cohort 2 data as of Dec. 5, 2014*
ALN-AT3 Phase 1 Study
Summary and Next Steps

- ALN-AT3 represents novel approach for treatment of hemophilia and rare bleeding disorders
  - Rebalance coagulation to achieve clinically meaningful improvement of thrombin generation for improved hemostasis
- In ongoing Phase 1 in healthy volunteers (n=3) and subjects with hemophilia (n=4), single- and multi-dose administration of ALN-AT3 was well tolerated
  - No SAEs; all AEs mild or moderate, and transient; no discontinuations
- In Part A performed in healthy volunteers, single 30 mcg/kg dose of ALN-AT3 resulted in an up to 28% knockdown in AT and an up to 152% increase in thrombin generation
  - p<0.01 by ANOVA, relative to placebo
  - AT knockdown was durable, lasting ~60 days
- In Part B performed in hemophilia subjects, ALN-AT3 resulted in up to 57% knockdown in AT
  - Dose escalation continues in Part B, with ongoing cohort of hemophilia subjects at 45 mcg/kg and up to 4 dose cohorts thereafter
- Complete Phase 1 Part A and B results expected to be presented in mid-2015
# Acknowledgements

## Trial Participants

## Investigators

<table>
<thead>
<tr>
<th>Country</th>
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<tbody>
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Thank You