ALN-PCSsc, an RNAi Investigational Agent That Inhibits PCSK9 With Potential for Effective Quarterly or Possibly Bi-Annual Dosing: Results of Single-Blind, Placebo-Controlled, Phase 1 Single-Ascending Dose (SAD), and Multi-Dose (MD) Trial in Adults With Elevated LDL-C, on and off Statins

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**Background:** ALN-PCSsc is a subcutaneously (sc) delivered RNAi investigational agent that inhibits synthesis of PCSK9 in liver. We previously presented interim data demonstrating up to 94% maximal knockdown of PCSK9 and up to 83% maximal reduction of LDL-C, with mean maximal LDL-C reduction up to 64%.

**Methods:** Individuals were randomized to a single-blind, placebo-controlled, single-ascending dose and multiple dose Phase 1 study to evaluate the safety, pharmacokinetics and pharmacodynamics of sc administered ALN-PCSsc in subjects with elevated LDL-C on and off statins. The primary endpoint was safety and tolerability; secondary endpoints were plasma PK, PCSK9 knockdown, and LDL-C; exploratory endpoints included total cholesterol, HDL-C, VLDL, triglycerides, and Lp(a).

**Results:** A total of 69 subjects were enrolled, with a mean baseline LDL-C =146 mg/dl. 24 subjects were enrolled in 5 SAD cohorts and received placebo (N=6) or drug at fixed doses ranging from 25 mg to 800 mg (N=3-6), per group. 45 subjects were enrolled in 6 MD cohorts, and received: placebo (N=12); 4 doses of 125 mg-qW (N=6); or 2 doses respectively of 250 mg-q2W (N=6); 300 mg-qM (N=6); 300 mg-qM with statin (N=4); 500 mg-qM (N=6); and 500 mg-qM with statin (N=5).

ALN-PCSsc was generally well-tolerated; all treatment-emergent adverse events were mild or moderate in severity. No serious adverse events or discontinuations due to adverse events occurred. Here we report safety and efficacy data (out to 180 days) that support the potential for a robust LDL-C lowering (up to a 83% maximal LDL-C reduction, with 44% mean LDL-C reductions remaining 140 days post a single dose) demonstrating the potential for quarterly or possibly bi-annual dosing. In addition, we report for the first time changes in lipoprotein profiles including total cholesterol, HDL-C, non-HDL-c, ApoB, and Lp(a).

**Conclusion:** Our results suggest that an investigational RNAi therapeutic targeting PCSK9 can provide a differentiated approach for the treatment of hypercholesterolemia. ALN-PCSsc was generally well-tolerated, resulted in LDL-C lowering to levels similar to those published for PCSK9 monoclonal antibodies, with an extensive duration of action supportive of effective quarterly or possibly bi-annual dosing.

**Disclosure:**

**K. Fitzgerald:** Employment; Significant; Alnylam Pharmaceuticals. **A. Simon:** Employment; Significant; Alnylam Pharmaceuticals. **S. White:** Employment; Significant; Alnylam Pharmaceuticals. **A. Borodovsky:** Employment; Significant; Alnylam Pharmaceuticals. **N. Patel:** Employment; Significant; Alnylam Pharmaceuticals. **B. Bettencourt:** Employment; Significant; Alnylam Pharmaceuticals. **V. Clausen:** Employment; Significant; Alnylam Pharmaceuticals. **J.D. Horton:** None. **P. Wijngaard:** Employment;
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