A Phase 1 Randomized, Single-Bled, Placebo-Controlled, Single Ascending Dose and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Subcutaneously Administered ALN-PCSsc in Subjects with Elevated Low Density Lipoprotein Cholesterol

**Abstract**

ALN-PCSsc is an investigational RNAi therapeutic targeting PCSK9 protein synthesis. We report here a positive interim analysis of the initial Phase I of ALN-PCSsc. In this trial, 22 healthy volunteers with at least two documented elevated LDL-C values were randomized to ALN-PCSsc or placebo. In addition, subjects with LDL-C ≥150mg/dL on stable statin therapy were treated with the two subcutaneous injections of ALN-PCSsc given 28 days apart (SAD #2). Our results not only demonstrate a robust knockdown of both PCSK9 protein and LDL-C, but also a single dose of ALN-PCSsc achieved a highly durable response, supporting a quarterly or potentially biannual dosing regimen. ALN-PCSsc was generally well tolerated, with no clinically significant changes in laboratory parameters or muscle mass. No serious adverse events or discontinuations due to adverse events occurred.

**Results**

**Safety and tolerability**

ALN-PCSsc was generally well tolerated.

- One subject with clinically significant change in LFTs.
- One subject in 300 mg statin group was incarcerated on Day 14.
- One placebo subject elected to discontinue; 22/33 ALN-PCSsc.

**Pharmacodynamic Activity**

- Mean knockdown per day for Days 1-84 compared via mixed effects ANCOVA.
- Pairwise comparisons vs. Placebo examined via Tukey’s tests under ANOVA/ANCOVA models.

**Conclusions**

- Initial ALN-PCSsc Phase I Study Results

**Summary and Next Steps**

ALN-PCSsc is progressing first in class PCSK9 synthesis inhibitor.

- Generally well tolerated.
- No SAEs and no discontinuations due to AEs.
- No clinically significant changes in laboratory parameters or muscle mass.
- Single subcutaneous injection of ALN-PCSsc resulted in up to 86% maximal PCSK9 knockdown and up to 72% maximal reduction in LDL-C lowering, with up to mean maximal LDL-C reduction of 58%.
- Two monthly doses of ALN-PCSsc resulted in up to 54% maximal knockdowns of PCSK9 and up to 83% maximal reduction of LDL-C, with up to mean maximal LDL-C reduction of 44%.
- Initial ALN-PCSsc Phase I Study Results

**Declaration of Interest:** Employees of Alnylam Pharmaceuticals.