RNAi therapeutic targeting antithrombin for treatment of hemophilia and rare bleeding disorders

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Alnylam Pharmaceuticals, Inc. announced today the publication in *Nature Medicine* of pre-clinical results with ALN-AT3, an investigational RNAi therapeutic targeting antithrombin (AT) for the treatment of hemophilia and rare bleeding disorders (RBD). The paper, titled "An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia",documents a broad set of pre-clinical data supporting the clinical advancement of ALN-AT3. Among the many findings reported, subcutaneous administration of ALN-AT3 led to potent, dose-dependent, and durable knockdown of AT in wild-type mice, hemophilia A mice, and non-human primates (NHPs). In addition, ALN-AT3 treatment improved hemostasis in hemophilia mice and normalized thrombin generation in a non-human primate "inhibitor" model of hemophilia A (HA). Furthermore, long-term ALN-AT3 administration – even at highly exaggerated doses – was shown to be well tolerated in hemophilia mice, supporting a wide therapeutic index in the disease setting.

"ALN-AT3 is a key program in our RNAi therapeutics pipeline, and is aimed at re-balancing the coagulation cascade as a potential disease modifying therapy for people with hemophilia and rare bleeding disorders. Indeed, we believe that once-monthly subcutaneous administration of ALN-AT3 could provide a functional correction of the bleeding phenotype in hemophilia, representing a significant advance in the field. Our pre-clinical research findings demonstrate robust efficacy,

safety, and durability for ALN-AT3 in mouse and NHP models of hemophilia, and we are pleased to be publishing these peer-reviewed data in *Nature Medicine*. Amongst other study results, safety data in hemophilia mice suggest that ALN-AT3 administration – even at highly exaggerated doses – should be well tolerated in the disease condition," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D and Chief Medical Officer of Alnylam. "Meanwhile, we are continuing to advance ALN-AT3 in an ongoing Phase 1 clinical trial in subjects with hemophilia. Recent results from this trial presented earlier this year provided clinical evidence for the first time suggesting that AT knockdown with ALN-AT3 has the potential to correct the hemophilia phenotype. While early and based on a limited number of subjects, we believe that these data support further development of ALN-AT3, a potentially promising and innovative strategy for the treatment of hemophilia and rare bleeding disorders as a once-monthly subcutaneous injection. We look forward to the continued data from our Phase 1 study and expect to present additional results in mid-2015 and then again later in the year."

As documented in the new publication, single and multiple subcutaneous doses of ALN-AT3 led to dose-dependent and durable knockdown of serum AT in wild-type and HA mice and in NHPs. In microvessel laser injury and saphenous vein bleeding models in HA mice, subcutaneous administration of ALN-AT3 provided hemostatic protection that was comparable to or better than that achieved with intravenously administered factor VIII replacement therapy. Furthermore, in wild type NHPs, repeat dosing with ALN-AT3 resulted in potent, titratable, and reversible knockdown of plasma AT. Studies were also performed in an NHP hemophilia "inhibitor" model, in which a hemophilia phenotype was induced via administration of a polyclonal anti-factor VIII antibody. ALN-AT3 treated animals showed robust AT knockdown as well as dose-dependent increases in thrombin generation, restoring this hemostatic parameter back to normal levels. These results demonstrate that ALN-

AT3 can normalize thrombin generation in the absence of functional levels of factor VIII and/or in the presence of anti-factor VIII antibodies in a large animal model, providing key pre-clinical proof of concept for the program.

In addition, the new paper documents the results of tolerability studies that suggest a wide therapeutic index for ALN-AT3 in the hemophilia setting. Specifically, highly exaggerated doses of ALN-AT3 resulting in essentially complete ablation of AT were evaluated in wild-type and hemophilia mice. Weekly administration of ALN-AT3 in HA mice for 7 weeks at 10, 30, or 100 mg/kg was well tolerated across all dose levels, with no toxicologically significant findings in clinical or anatomic pathology exams, including the absence of any evidence for thrombosis. Finally, a 26-week toxicity study was performed in HA mice to evaluate long-term safety. As in the 7-week study, ALN-AT3 was well tolerated across all dose levels, with no adverse clinical signs. Further, compared to placebo treatment, ALN-AT3 administration was shown to confer a statistically significant survival benefit (p