Patisiran, an Investigational RNAi Therapeutic for Patients with Hereditary Transthyretin-Mediated Amyloidosis: Regional and Genotypic Subgroup Analyses from the APOLLO Study

**Background and Rationale**

**Hereditary Transthyretin-Mediated (hATTR) Amyloidosis**
- Rare, inherited, rapidly progressive, life-threatening disease caused by a mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract
- Affecting approximately 50,000 people worldwide; median survival of 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy
- Multi-systemic amyloid accumulation often leads to dysfunction in multiple organs, including the peripheral nervous system, heart, gastrointestinal tract, and kidneys
- Accumulation of fibrils in nerves can lead to manifestations of neuropathy, including peripheral neuropathy, autonomic dysfunction, and motor weakness causing fine and gross motor impairments whereas accumulation in heart can lead to cardiomyopathy
- Disease penetrance and rate of progression may be influenced by TTR genotype which can vary by geographical region
- Limited treatment options are available
- Continued high unmet medical need for novel therapeutic options

**Patisiran**
- Lipid nanoparticle formulation of siRNA targeting hepatic production of WT and mutant TTR (Figure 1)
- Treatment history shown for patients with hATTR amyloidosis
- Patisiran generally well-tolerated, with no baseline deaths
- No death-related severe adverse events
- Significant improvement was observed following patisiran treatment within each subgroup compared to placebo (Figure 5) and consistent with the overall population which showed a LS mean change from baseline (patisiran- placebo) (95% CI) of -21.11 (-27.24, -15.01)

**Methods**

**Phase 3 Study Design**
- Multi-center, international, randomized, double blind, placebo-controlled study designed to evaluate the efficacy and safety of patisiran in patients with hATTR amyloidosis with polyneuropathy (Figure 2)
- Primary endpoint was the change in the modified Neuropathy Impairment Score (mNIS+7) from baseline at 18 months; secondary endpoints are shown in Figure 2
- mNIS+7 is a quantitative and referenced assessment to quantify motor, sensory and autonomic components of the polyneuropathy in patients with hATTR amyloidosis; higher score is indicative of worsening of neuropathy
- Norfolk QOL-DN is a 35-point patient reported outcome scale used to evaluate subjective perceptions of neuropathy symptoms sensitive to small fiber, large fiber, and autonomic nerve function; higher score is indicative of worsening quality of life

**Results**

**APOLLO Baseline Demographics**
- 225 patients with hATTR amyloidosis from 44 sites in 19 countries enrolled between December 2013 and January 2016 (Figure 3)
- Mean age: 60.5 years (24-83), males 74%
- Cardiac involvement defined as patients with baseline left ventricular (LV) wall thickness >13mm and no medical history of aortic valve disease or hypertension 65%

**APOLLO Regions and Genotypes**
- Patients enrolled had 39 different mutations and were divided into the following groups: North America, Western Europe and Rest of World (Figure 3, Table 1)

**Improvement in mNIS+7 Following Patisiran Treatment**
- **APOLLO** had an average mean mNIS+7 (SD) at baseline of 74.6 (37.0) and 80.9 (41.5) for placebo and patisiran groups, respectively
- Overall, patisiran demonstrated significant improvement in mNIS+7 compared to placebo with an LS mean change from baseline (patisiran-placebo) (95% CI) of -33.9 (-39.86, -28.13) at 18 months, which was consistent within each subgroup (Figure 4)

**Summary**
- **APOLLO**, the largest controlled study observed following patisiran treatment within each subgroup compared to placebo, is representative of the global patient population
- Patisiran demonstrated a consistent benefit over placebo for both mNIS+7 and Norfolk QOL-DN in all subgroups regardless of region or genotype
- Patisiran was generally well tolerated, with safety events similar in both groups