Hereditary ATTR (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, life-threatening disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and GI tract1

- Affecting approximately 50,000 people worldwide2 with mortality within 2 to 15 years of clinical presentation3

- Multi-systemic disease with heterogeneous clinical presentation; includes sensory, motor, autonomic, cardiac symptoms4,5

- Disease continuum includes patients who present with predominantly polyneuropathies (formerly FAP) or cardiomyopathies (formerly FAC) yet many experience a variety of symptoms

- Disease penetrance and rate of progression may be influenced by TTR genotype which can vary by geographical region6

- Limited treatment options with continued high unmet medical need for novel therapeutic options

- Liver transplant: high-risk option for a limited subset of patients

- Tetramer stabilizers
  - Tafamidis approved in EU for Stage 1 hATTR amyloidosis and certain other countries outside the United States

- Disease-related organ involvement: predominant in heart and peripheral nerves, less common in gastrointestinal, hepatic, renal

- Median survival of patients with hATTR amyloidosis with polyneuropathy1,8

- Phase 2 OLE: positive multi-center results (N=27) in Phase 2 OLE3 with patisiran 0.3mg/kg IV

- Phase 3, APOLLO: study met primary efficacy endpoint (mNIS+7) and all secondary endpoints with favorable safety profile9

- TTR genotype
  - Val122Ile (V50M) = 1
  - Ser77Tyr (S77Y) = 2
  - Ser77Pro (S77P) = 2

- Mean serum TTR (µg/mL)
  - Stage 1: 24
  - Stage 2: 3
  - Stage 3: 2

- TTR knockdown: 93%

- Similar TTR knockdown in patients on tafamidis, diflunisal, or none

- Related AEs in ≥4 patients were
  - IRRs (2 patients, 8.0%) and certain other countries outside the United States

- Long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy

- Phase 2 OLE Study Design

- Patients with HATTR amyloidosis on patisiran on the Phase 2 patisiran study were eligible to roll over onto a Phase 2 OLE study and continue receiving patisiran 0.3mg/kg IV q4w for a total of 24 months (NTG191921) (Figure 2)

- Primary endpoint was safety; secondary objectives included: effects on neurologic improvement (mNIS+7; NIS; Figure 3), QOL, mBMI, mobility, gas strength, autonomic symptoms, and serum TTR levels

- Following completion of the study, patients were eligible to continue treatment on a global OLE study (NCT02510281)

- Tolerability out to 25 Months (Table 2)

- Mean maximal serum TTR knockdown: 97%

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