PHASE 3 CLINICAL STUDY FINDINGS

*Difference in least squares mean change from baseline between treatment groups. Values in parentheses are the 95% confidence interval.

The mean life expectancy is 3-15 years.

Safety and Efficacy of Inotersen in Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy (NEURO-TTR)

Inotersen-treated patients achieved statistically significant benefit compared to placebo for both primary endpoints in the composite modified Neuropathy Impairment Score +7 (mNIS+7) and patient-reported Norfolk Quality of Life—Diabetic Neuropathy (QoL-DN) scale. This benefit was evident in both primary (ambulant or Stage I) and secondary (ambulant with assistance or Stage II) disease. Key safety findings were thrombocytopenia and renal dysfunction. More than 80% of patients who completed treatment had no events associated with the open-label extension study.

INTRODUCTION

Translating TTR (transthyretin) into amyloidopeptide causes a range of debilitating diseases. In patients with hereditary TTR amyloid polyneuropathy (hATTR-PN), a mutant variant in the TTR gene results in TTR protein deposits, leading to amyloid deposition of amyloidogenic proteins also present in peripheral and autonomic tissues. Amyloid deposition eventually leads to multiple organs, with life expectancy of 15-20 years depending on the extent of organ involvement.

TTR mutation

Inotersen (IONIS-TTRRx) is an RNA-targeting approach for the treatment of hereditary TTR-related amyloid diseases. Inotersen binds wild-type and mutant TTR mRNAs to inhibit expression of the mutant transthyretin protein.

Major clinical manifestations of hATTR are peripheral axonal neuropathy and autonomic neuropathy.

Sensory and motor neuropathy are predominantly affective, with high prevalence of peripheral and autonomic symptoms.

Sensory symptoms include painful dysesthesia, paresthesia, and burning.

Autonomic dysfunction results in impaired autonomic function.

Thrombocytopenia is a significant side effect, often associated with intracranial hemorrhage and low platelet levels.

The mean life expectancy is 3-15 years.

Pre-motor phenomena are associated with early neuropathy involvement.

The most common causes of death are malnutrition and cachexia, renal failure, or cardiac disease.

TTR Amyloidosis is a Severe, Progressive and Fatal Disease Affecting Multiple Organs

Inotersen (IONS-TTRRx) is an RNA-Targeting Approach for Treat TTR-Related Amyloid Disorders

Inotersen is a generation 2 antisense oligonucleotide (ASO) that targets the transthyretin (TTR) gene.

Inotersen is orally administered and can be used in patients without liver involvement.

Inotersen is well tolerated with no events associated with intracranial hemorrhage or low platelet levels.

Inotersen-treated patients achieved a statistically significant benefit compared to placebo for both primary endpoints in the composite modified Neuropathy Impairment Score +7 (mNIS+7) and patient-reported Norfolk Quality of Life—Diabetic Neuropathy (QoL-DN) scale. This benefit was evident in both primary (ambulant or Stage I) and secondary (ambulant with assistance or Stage II) disease.

Key safety findings were thrombocytopenia and renal dysfunction. More than 80% of patients who completed treatment had no events associated with the open-label extension study.

CONCLUSIONS

- Both primary endpoints were met by inotersen in the randomized placebo-controlled phase 3 study, NEURO-TTR.
- Inotersen demonstrated an acceptable safety and tolerability profile for hATTR, a severe and fatal disease with few treatment options.
- The results from this pivotal phase 3 study support a highly favorable benefit-risk profile for patients with hATTR.
- Marketing authorization submissions are planned for Q4, 2017.