Disease Modifying Strategies in Neurodegenerative Disorders

α-Synuclein (ASN), a 14-kDa protein is implicated in several neurodegenerative disorders such as Parkinson's disease, lewy body dementia, Alzheimer's disease, multiple system atrophy, Gaucher's disease, Tay–Sachs and Sandhoff diseases (HEXA/HEXB), Hunter's syndrome (I2S), and Niemann–Pick type C.

ASN toxicity implicates multiple conformational forms (such as amyloidogenic oligomers) and the aggregates start affecting the various cell organelles. Evidence suggests that these aggregates can be transmitted from neuron to neuron, resulting in a propagation of pathology that causes neuronal dysfunction and loss. The critical need in neurodegenerative disorders is to reverse or modify the disease pathophysiology.

Various therapeutic strategies are being evaluated to mitigate the impact of synuclein toxicity pathways in neurodegenerative disorders. These include:

Therapeutic Strategies

01 **Reducing the ASN production (by targeting with anti-sense oligo nucleotides)**

02 **Increasing ASN lysosomal and/or autophagic degradation (utilizing antibody-based approach and enzyme replacement therapies)**

03 **Reducing the ASN aggregation (targeting with selective antibodies)**

04 **Blocking the propagation of ASN (antibodies against C-terminal truncated α-synuclein)**

One such ASN targeting therapy in clinical development is prasinezumab (Hoffmann-La Roche, Prothena) for patients with early Parkinson's disease, which is the second most common neurodegenerative disorder, impacting 7 to 10 million people worldwide. Prasinezumab is designed to block the cell-to-cell transmission of the aggregated, pathogenic forms of alpha-synuclein in Parkinson's disease, thereby slowing clinical decline. Such a development is a first of its kind disease modifying strategy to move beyond the symptomatic management provided with the existing dopamine supplementing therapies in the management of patients with Parkinson's disease.

The company has recently progressed the development of prasinezumab into Phase IIb despite failure to meet the primary end point in the earlier Phase IIa trial.

The central nervous system involves complex and integrated functioning of various physiological and pathological pathways in which a disease modifying agent may not be able to completely address/ modify the pathophysiology. The development of prasinezumab has invoked the need to relook at trial designs, endpoints, and patient selection to specifically address which pathways of the disease are reversed by these agents, to improve success rates in clinical development.

SmartAnalyst can support drug development decision making in this area by addressing these key questions:

- What disease-modifying strategies in neuroscience will shape the future treatment landscape?
- What is the competitive landscape and what will be required for differentiation?
- What are the appropriate patient segments and clinical endpoints for development programs?
- What is the commercial opportunity for disease-modifying approaches?
- What is the value proposition and evidence required to support market access?

Please contact:
John.L'Ecuyer@smartanalyst.com

GLOBAL HEADQUARTERS
(New York, USA)
285 Madison Ave
22nd Floor, New York
NY 10017
Mobile: +1 (646) 852-5097

EUROPE
(London, UK)
1.04 Power Road Studios
114 Power Road, Chiswick
London W3 5PY
Mobile.: +44-(0)-752-163-8242
Mobile.: +44-(0)-772-574-4296

ASIA PACIFIC
(Gurgaon, INDIA)
First Floor, DLF Plaza Tower
DLF Qutub Enclave, DLF City
Phase-I, Gurgaon 122002
Haryana, India
Tel.: 91-124-4313800