BIIB014: Adenosine A2a antagonist Program for Parkinson’s Disease

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Parkinson’s Disease: A Common Debilitating Disease

Sir William Richard Gowers
A Manual of Diseases of the Nervous System, 1886
Parkinson’s Disease is a Multisystem & Disabling Disease

• **Motor Effects**
  – Tremor, slow movement, rigidity, balance problems
  – Average 15 year progression from Stage I (mild) to V (severe)

• **Non-Motor Effects**
  – Psychiatric
  – Cognitive
  – Sleep Disorders
  – Sensory Symptoms
  – Autonomic Symptoms
    • Cardiovascular
    • Gastrointestinal
    • Urogenital
    • Sudomotor
    • Thermoregulatory
Limitations of Existing PD Therapeutics

- Most PD Therapeutics Target Striatal Dopaminergic Pathways
  - L-DOPA (Carbidopa/Benserazide)
  - Dopamine agonists
  - COMT Inhibitors
  - MAO-B Inhibitors
  - Amantadine
  - Anti-cholinergics

- Window and Duration of Therapeutic Effect Diminish as PD Progresses
  - Dyskinesias
  - End-Of-Dose Wearing Off
  - Unpredictable “off” episodes
  - Delayed “on”
  - Failure of dose

\[ \text{Clinical Effect} \]

\[ \text{Levodopa} \]

\[ \text{Time (h)} \]

\[ \text{Dyskinesia Threshold} \]

\[ \text{Response Threshold} \]

\[ \text{Dopaminergic Target} \]

\[ \text{Vernalis} \]
BIIB014: Best in Class Molecule Targeting a New PD Pathway

Molecule
• Selective, non-xanthine adenosine A2A receptor antagonist

Indication
• Early and late PD

Dosing
• Once daily oral

Therapeutic Hypothesis
• Normalizes motor effects of dopamine depletion
• Reduces dyskinesia
• Non-sedating

Partnerships
• Vernalis
BIIB014 Reduces Disability Without Provoking Dyskinesias in Parkinsonian Marmosets

On Time

Activity counts = On time + Dyskinesia

On Time (min)

Activity counts

BIIB014 (mg/kg)

BIIB014 (mg/kg)

LDopa

BIIB014 (mg/kg)

LD

(8)

Vehicle 2.5 5 10 20

LDopa

BIIB014 (mg/kg)

0 2500 5000 7500 10000

activity counts

BIIB014 (mg/kg)

0 2500 5000 7500 10000

activity counts

vehicle 2.5 5 10 20

BIIB014 (mg/kg)

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Dyskinesia

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activity counts

On Time (min)
BIIB014 Maximally Occupies Human Striatal A2a Receptors at Readily Achieved Exposures

C\textsuperscript{11} PET

Pre-Dose
Post-Dose

Bayesian Logistic Regression - Individual Predictions

- Trial data
- 2.5% values
- 97.5% values

Receptor Occupancy (%) vs. AUCss (\mu g*h/mL)
BIIB014 Efficacy

BIIB014 is Efficacious as Adjunct Therapy in Late PD Patients

- BIIB014 has clinically relevant effects:
  - Decrease “Off” Time
  - Increase “On” Time

- Efficacy is dose dependent

- BIIB014 is well tolerated

BIIB014 is Efficacious as Mono-Therapy in Early PD Patients

- BIIB014 has clinically relevant effect:
  - Decrease UPDRS Part III (Motor)

- Efficacy is dose dependent

- BIIB014 is well tolerated
BIIB014
Summary of Opportunity

• BIIB014 is a novel non-dopaminergic therapy that selectively antagonizes the adenosine A2A receptor

• Class Effect
  • Dyskinesia sparing
  • Non-sedating
  • Well tolerated

• Best-in-Class
  • Once daily dosing
  • Efficacy as:
    • Early PD monotherapy
    • Late PD adjunct therapy

• Next Step: Developing data package to support registrational trials