Nonclinical Development of Enzyme Replacement Therapies for Severely Affected Patients of Orphan Diseases: Assessment of Animal Model and Normal Animal Toxicology Data

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Own Stock and/or Options in the following companies:

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Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders (LSDs)- Molecular Pharmacology

Rare genetic, defect results in missing lysosomal enzyme needed to degrade product that accumulates. Most disorders are extremely debilitating/life threatening

Lysosomal enzymes work in series to degrade substrates that accumulate in the lysosome. pH 5 is optimum; small probability of off target toxicity

ERTs bind to the mannose-6-phosphate receptor (M6PR) and are trafficked to the lysosome to catabolize the substrate that has accumulated as a result of the missing/reduce activity enzyme

In Press, Vuillemenot et al, Molecular Genetics and Metabolism

Short t½ predicates ERTs be infused with matrix (eg plasma, CSF) levels remaining above the Kuptake of the M6PR to insure trafficking to the pharmacological site of action.

Primary Pharmacodynamics assessed by substrate reduction in matrix (eg urine, plasma, CSF)
Current Nonclinical Practices

Clinical Trials often initiate Chronic dosing in the Patient Population at subtherapeutic levels with intrapatient dose escalation to expected pharmacological dose levels

Starting/Pharmacological dose levels derived from Pharmacology and Toxicity Studies

Nonclinical Toxicity of rhERTs in normal animals is, for the most part, restricted to anti-drug antibody (ADA) emergence and possible associated immune related findings:

- Blocking uptake ERT by M6PR – assessed by PD response and correlated with exposure
- Enhancing or diminishing ERT exposure – assessed by PK and correlated with PD
- Immune complex toxicity – assessed by Clin Chem/Urinanalysis and Ophthalmic Exam
- Trigger Infusion Associated Reactions (IARs) or IgE Mediated Hypersensitivity - managed by slowing infusion rate and/or antihistamine/steroid pretreatment

Nonclinical Approaches

Conservative - ICH M3 – FIH involves chronic ERT; support with chronic toxicity studies

Alternative Approach - ICH S6 – Use data from compelling Animal Model studies to support FIH. Study design should allow for toxicity of test article in normal and affected animals (assess toxicity in the pathology of the disease; clinically relevant)

Predicated on similarity of the animal disease model to clinical disease manifestations

Alternative Approach in the case of no suitable animal models – ICH S9 - Equates LSD Patient Population with Oncology Population thereby supporting Phase 1 and 2 ERT clinical trials with 1 month toxicity studies
EXAMPLE: Recombinat Human Tripeptidyl Peptidase (rhTPP1) for Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL)

LINCL Molecular Pathology

- TPP1 Cleaves tripeptides from the N-termini of polypeptides in lysosomes
- Progressive substrate accumulation
- Primary Neurological and Ophthalmological Involvement

Clinical Presentation and Prognosis

Age 2 to 4: Seizures, Ataxia, Motor and Cognitive Decline
Age 6: Wheelchair-bound and Blind; Neuron Loss Visible with MRI
Age 8 to 12: Death

Estimated prevalence 350-1000 patients worldwide; no treatment exists
LINCL Age-dependent Changes: Weill Cornell Disease Score/Index- Phenotypic Homogeneity

MRI from Normal and Late Stage LINCL patient; Worgall, Crystal, et al., *Neurology*, 2007
TPP1-null dachshunds recapitulates human cLINCL

• Animal model of cLINCL developed at the University of Missouri
• Dachshunds lack expression of TPP1 due to a frameshift mutation
• Affected animals display visual and cognitive deficits, ataxia, tremors, and myoclonic seizures similar to humans (Awano et al., 2006, Mol Genet Metab)
• Autofluorescent storage bodies, similar to those observed in the human disease, accumulate throughout the CNS; life expectancy is 10 to 12 months
• Pilot study demonstrated activity of cisternally administered TPP1 in reducing storage accumulation with no toxicity (Vuilleumenot et al., 2011, Mol Genet Metab)
Quantification of ventricle area on MRI indicates that TPP1 treatment slows enlargement, possibly due to prevention of neuron death.

N=1-3 per time point, error bars = SD
Every Other Week Long Term rhTPP1 ICV Infusion improves Cognitive Function in T-maze Test of Reversal Learning

- Measures spatial learning and memory

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Sanders et al. *Genes, Brain and Behavior*, 2011
Every Other Week Long Term rhTPP1 ICV Infusion Improves Cognitive Function and Survival
### rhTPP1 Nonclinical Program Highlights

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Route/Age</th>
<th>Duration</th>
<th>Objective(s)/Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beagle Dog</td>
<td>Single Dose Safety and distribution</td>
<td>IT-C Bolus</td>
<td>2-4 day recovery</td>
<td>Safety, CNS Distribution</td>
</tr>
<tr>
<td>Cynomolgus Monkey</td>
<td>Single Dose Safety and Distribution</td>
<td>ICV 4 hr infusion/ Juvenile</td>
<td>3-14 day recovery</td>
<td>Safety, CSF/Plasma PK, CNS Distribution, Dosing Frequency</td>
</tr>
<tr>
<td>Cynomolgus Monkey</td>
<td>Single Dose Safety and Distribution</td>
<td>IT-L; 4 hr infusion/ Juvenile</td>
<td>3 day recovery</td>
<td>CSF/Plasma PK, CNS Distribution</td>
</tr>
<tr>
<td>TPP1 knockout Mouse (condit.)</td>
<td>Repeat Dose Safety and Pharmacology</td>
<td>IT-L bolus/ 5 Weeks</td>
<td>6 months</td>
<td>Safety, Survival, Substrate Levels</td>
</tr>
<tr>
<td>TPP1-null Dachshund Dog</td>
<td>Repeat Dose Safety Pharmacology and distribution</td>
<td>Monthly IT-C bolus</td>
<td>3 months</td>
<td>Safety, Primary PD, CNS Distribution</td>
</tr>
<tr>
<td>TPP1-null Dachshund Dog</td>
<td>Repeat dose pharmacology, PK, distribution, and safety</td>
<td>Every other Week ICV, IT-L; 4 hr infusion</td>
<td>9-12 months</td>
<td>Long Term Safety, PD/Visual/Cognitive, CSF/plasma PK, CNS distribution</td>
</tr>
</tbody>
</table>

ICV= intracerebroventricular, IT-C= intrathecal-cisternal, IT-L= intrathecal-lumbar
Measures To Increase the Quality/Compliance of a NonGLP Nonclinical Study

Power and Design the Study to characterize:

- **Disease Pathology in Animal Model** (Vehicle Treated Affected Animals)
- **Test Article Toxicity in Normal Animal** (Vehicle/Test Article Treated Normals)
- **Test Article Toxicity In Animal Model** (Test Article Treated Affected Animals)

Intensely Prepare Institutional Study Team and Extensively Monitor Study Activities

Protocol Development Similar to GLP study

**Dose Solution** (all dose levels including vehicle) Prepare at GLP Facility; ship to Institution with enough volumes for retains to be shipped back for Dose Solution and Volume Analysis at GLP Dose Formulation Facility

**Clinical Chemistry/Clinical Pathology/Urinanalysis** to be performed at a certified Veterinary Pathology Laboratory

**PK and Immunogenicity** analysis performed at GLP Compliant Laboratory

**Necropsy** with Board Certified Veterinary Pathologist- macroscopic findings

**Pathology Samples** sent to GLP CRO for processing and evaluation

Peer–review Pathology Report

Study Report Preparation and Finalization as GLP–like as possible
rhTPP1 Program Highlights

Nonclinically

- Nonclinical Safety and Pharmacology Assessments used both Normal and LINCL Dogs
- 31 Dogs treated including TPP1 Null and Normal Littermates Across Controlled Studies
- Extensive Organ Collection/Histopathology Assessed during the Studies evaluated at a GLP CRO
- Disease Model allowed assessment of possible toxicity of BMN 190 associated with the rapid catabolism of TPP1 substrate

 Clinically

- IND/CTAs submitted and approved in US, Germany and UK
- Intrapatient Dose Escalation- 30 mg to 100 mg to 300 mg every other week (n=3/group) using historical control/natural history data as comparator
- Cohorts 1 and 2 complete; Currently, all Patients being dosed at 300 mg
- Endpoints include a subset of Weill Cornell Scale(Gait and Language) and MRI
- No signs of severe toxicity to date
Concluding Remarks

ADA findings are expected toxicity of ERTs; easily monitored and managed clinically/nonclinically

Toxicity Assessment in an Appropriate Animal Model of Disease, that recapitulates clinical disease manifestations, offers significant value:

- Appropriate Dose Levels, Appropriate Dose Frequencies, and Elucidation of nonresponsive tissues/organs can be addressed and can influence clinical trial design in Rare and Severely Debilitating Diseases
  - Imperative with small, orphan disease patient populations
- Characterization of ERT toxicity of Rapid Substrate Catabolism in Affected Animals
- Use of Normal Concurrent Control Animals Characterizes rhERT Toxicity

ICH S6 allows for the consideration of Animal Models of the Disease

ICH S9 defines Nonclinical Testing for Oncology Patient Populations and LSD Patients share a similar clinical morbidity and mortality characteristics

- Rare LSD Patient Populations are rapidly declining with no treatment options
- LSD Risk Benefit Profiles represents opportunities for aggressive development strategies to rapidly affect irreversible disease progression

Variations of Nonclinical Assessment of ERTs Must Account for the Unmet Medical Need of the Patient Population and Data from Appropriate Normal and Animal Model Studies