Matrix Metalloproteinase Inhibitor for the Treatment of Amyotrophic Lateral Sclerosis (ALS).

Non-Confidential Presentation
Amyotrophic Lateral Sclerosis (ALS)

➢ A progressive neurodegenerative disease.

➢ 5600 new US cases per year, 40-70 y/o.

➢ Sporadic - 90 to 95% of all cases.

➢ Familial - accounts for 5 to 10% of all cases.

➢ The average life expectancy after diagnosis is two to five years.

➢ The disease affects fast-twitch fatigable (FF) motor neurons “the cells that control voluntary muscle activity such as speaking, skeletal muscle movement, breathing & swallowing” but leave slow-twitch (S) motor neurons alone “the cells that control eye movement.”
The MMP family consists of 24 members of zinc dependent proteinases that are responsible for digesting the various structural components of the extracellular matrix.

MMP-2 and MMP-9 are a subset of MMPs that can breakdown myelin basic protein (MBP) which is a key component of the myelin sheath of motor neurons.

MMP-2 and MMP-9 can activate various cytokines & chemokines during the inflammatory process.
Elevated levels of MMP-2 & MMP-9 have been reported in the skin, CSF and blood of people with ALS (PALS).\(^1,2\)

Microarray profiling studies in SOD1 mice have shown that MMP-9 is one of a few genes that are selectively expressed >10 fold in FF motor neurons as compared to S motor neurons\(^3\)

MMP-9 knockout of SOD-1 mice extend animal survivability by 25% as compared to wild-type and significantly alter gene expression of many physiological processes.\(^3\)


3) Kaplan, A; et al., Neuronal matrix metalloproteinase-9 is a determinant of selective neurodegeneration, Neuron, 81, 333-348, (2014).
Aquilus tested the blood of a group of people with ALS (PALS) (n=30) and found a 7.5-fold higher (650%) mean MMP-9 protein level as compared to healthy, aged matched controls.

Aquilus tested the blood of a group of aged matched, diabetics clinically diagnosed with peripheral diabetic neuropathy (n=124) and found the PALS group exhibited a 5-fold higher mean MMP-9 protein level over that of the aged matched diabetics.
Oral Dosing With a MMP Inhibitor to Reduce Inflammatory Processes Leading to Motor Neuron Cell Death

- Aquilus believes that ALS is a result of systemic inflammatory processes initiated through various known (SOD1 or TDP-43, et al.) gene mutations that trigger overproduction of MMP-9 in FF motor neurons. MMP-9 then degrades the BBB, MBP and neurofilament, activates various cytokines and upregulates caspase levels, all leading to neuronal cell death.
AQU-118 is a potent, small molecule inhibitor of MMP-2 and MMP-9 which when given orally has been found to significantly reduce nerve damage in several different rodent animal models of neuropathic pain & nerve injury.


**AQU-118 Project Status for IND Submission for the Treatment of ALS**

<table>
<thead>
<tr>
<th>TASK</th>
<th>Completed</th>
<th>12-months</th>
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<tbody>
<tr>
<td>In-vitro tox including hERG</td>
<td>✔</td>
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<tr>
<td>Non-GLP pharmacokinetics</td>
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<td>Preclinical efficacy observed in animal pain models</td>
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<tr>
<td>Off-target screening</td>
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<tr>
<td>GMP synthesis &amp; API stability studies*</td>
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<tr>
<td>GLP rat tox (MTD &amp; 28 day) &amp; Irwin (CNS)</td>
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<td>GLP dog tox (MTD), respiratory &amp; cardiovascular</td>
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<td>Pre-IND meeting</td>
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<tr>
<td>Formulation stability testing of drug product</td>
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<tr>
<td>GLP 28-day dog tox and rat micronucleous Study</td>
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<tr>
<td>IND submission</td>
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*Sufficient GMP AQU-118 has been produced for both IND studies and early clinical development.
AQU-118 Is Fully Protected By Global Patents

- Fully issued patents for **composition of matter** and method of use in the following countries:

  - United States
  - Mexico
  - England
  - Ireland
  - France
  - Germany
  - Spain
  - Italy
  - Russia
  - Japan
  - Israel
  - Australia
  - China
  - Korea
Cash Flow Diagram & AQU-118 Trial Time-Line

<table>
<thead>
<tr>
<th>Timeline</th>
<th>2022</th>
<th>2023</th>
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<tr>
<td>Cost</td>
<td>Fully Funded*</td>
<td>Needing to Raise</td>
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<tr>
<td>Milestones</td>
<td>Complete remaining IND enabling safety studies &amp; preclinical formulation stability study.</td>
<td>Phase 1/2 ALS Biomarker Clinical Trial of orally dosed AQU-118 in people with ALS (PALS) (includes biomarker analysis, PK &amp; physical exam).*</td>
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</tbody>
</table>

*Aquilus has received funds through a Lawrence and Isabel Barnett Drug Development grant award sponsored by the ALS Association and a grant award from the Department of Defense (DOD) that will allow Aquilus to fully complete all of the remaining IND enabling studies."
Management

Irving Sucholeiki, Ph.D., President & CEO
- 24 years industrial experience as a medicinal chemist (Eli Lilly, MDS Proteomics, Alantos Pharmaceuticals).

Darrell J. Nix, Ph.D., Vice President of R & D
- 18 years industrial experience as a pharmacologist.
- Development team for VELCADE™ CTD, Nutropin Depot® and the recently approved, ISTODAX®

Dr. Roy Sucholeiki, M.D. Vice President of Clinical Development & CMO
- Neurologist / Neurophysiologist, Division of Neurosciences - Northwestern Medicine - Central Dupage Hospital.

Consultants/Scientific Collaborators

Professor Robert Bowser, Chairman, Department of Neurobiology, Barrow Neurological Institute
Professor Rita Sattler, Associate Professor, Barrow Neurological Institute.
Professor Daniela Zarnescu, Professor of Molecular & Cellular Biology, University of Arizona
Professor Peter Noakes, Professor, School of Biomedical Sciences, The University of Queensland
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