Discovery and Early Clinical Development of MK-8719, a Novel Inhibitor of OGA for the Treatment of Progressive Supranuclear Palsy (PSP)

Sean M. Smith, Ph.D.
Executive Director of Neuroscience
O-GlcNAcylation Influences Activity, Stability and Localization of Proteins

- O-GlcNAcylation is a common post translational modification of proteins that is nutrient responsive
- In healthy adult brain, tau is O-GlcNAcylated at several sites
- Abnormal O-GlcNAcylation is associated with Tauopathies
  - Protein O-GlcNAcylation is reduced in Alzheimer's Disease
- OGA inhibitors increase tau O-GlcNAcylation and show efficacy in multiple tau transgenic models

O-GlcNAc transferase (OGT)
  - Mediates addition of O-GlcNAc

O-GlcNAcase (OGA)
  - Mediates removal of O-GlcNAc
In Vitro and Pharmacokentic Profile of MK-8719

In Vitro Profile

<table>
<thead>
<tr>
<th>Assay</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hOGA (enz Ki / cell IC$_{50}$)</td>
<td>&lt; 0.010 / &lt; 0.100</td>
</tr>
<tr>
<td>Hex A/B; NAGLU</td>
<td>&gt; 1,000</td>
</tr>
<tr>
<td>Cav1.2, Nav1.5, hERG</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Off target binding</td>
<td>No hits at 10 µM</td>
</tr>
<tr>
<td>CNS penetrant, devoid of Pgp transport</td>
<td>✓</td>
</tr>
</tbody>
</table>

Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mice</th>
<th>Rats</th>
<th>Dogs</th>
<th>Monkeys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg/kg IV</td>
<td>2 mg/kg IV</td>
<td>1 mg/kg IV</td>
<td>1 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg PO</td>
<td>10 mg/kg PO</td>
<td>3 mg/kg PO</td>
<td>3 mg/kg PO</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µM*hr)</td>
<td>2.9 ± 0.15</td>
<td>3.5 ± 0.7</td>
<td>5.3 (5.6, 5.1)</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>CLp (mL/min/kg)</td>
<td>43.4 ± 2.2</td>
<td>36.7 ± 7.2</td>
<td>11.5 (11, 12)</td>
<td>28.3 ± 4.7</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>2.0 ± 0.1</td>
<td>4.7 ± 2.0</td>
<td>2.3 (2.0, 2.6)</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>t$_{1/2}$ terminal (hr)</td>
<td>1.7 ± 0.4</td>
<td>2.9 ± 1.7</td>
<td>5.4 (4.7, 6.0)</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>C$_{max}$ (µM)</td>
<td>10.7 ± 2.2</td>
<td>10.6 ± 5.7</td>
<td>8.3 ± 0.6</td>
<td>0.40 ± 0.13</td>
</tr>
<tr>
<td>T$_{max}$ (hr)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µM*hr)</td>
<td>7.8 ± 1.2</td>
<td>14.0 ± 1.8</td>
<td>14.2 ± 1.2</td>
<td>0.61 ± 0.17</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>54 ± 8</td>
<td>80 ± 11</td>
<td>90 ± 3</td>
<td>9.0 ± 1.2</td>
</tr>
</tbody>
</table>
MK-8719 produced a dose-dependent elevation of O-GlcNAcylated protein in rat brain and peripheral blood mononuclear cells (PBMCs).

O-protein was measured by ELISA using the RL2 antibody following WGA capture.

Changes in PBMC O-protein mirror changes in brain O-protein levels.
MK-8719 Reduces Neurofibrillary Tangles (NFTs) in the Entorhinal Cortex of Tg4510 Mice

Tg4510 mice express a repressible form of human tau containing the P301L mutation that has been linked with familial FTD

- NFTs were detected using the AT-8 mAb against phosphorylated Tau
- Tg4510 mice were administered MK-8719 (1 – 100 mg/kg) or vehicle from 8 to 16 weeks of age
- Efficacy of MK-8719 was evaluated in 16-week old Tg4510 mice

* p<0.05
MK-8719 Increases Total O-protein and Reduces Pathological Tau in Tg4510 Mice

**Brain O-protein (WGA/RL2)**

- Baseline
- V
- 10
- 30
- 100

**Aggregated Tau (HT7:HT7)**

- Baseline
- V
- 10
- 30
- 100

**PHF6 Tau**

- Baseline
- V
- 10
- 30
- 100

**AT8Tau**

- Baseline
- V
- 10
- 30
- 100

\*p<0.05  
\**p<0.01

n=55
Longitudinal vMRI Demonstrates MK-8719 Attenuates Brain Volume Loss in Tg4510 Mice

8 Weeks

32 Weeks

Vehicle

MK-8719

Cortical Atrophy

Ventricle Enlargement

n=25 / group

* p<0.05
MK-8719 PN001: A Single Rising Dose Study of MK-8719 in Healthy Subjects

- Single doses of MK-8719 were generally well tolerated in healthy subjects

Safety and Tolerability:
- Most frequent AE was “headache”
  - No increase in AE incidence or severity with increase in doses
- No serious adverse experiences
- No laboratory, ECG or vital sign observations
- No effects on blood glucose levels

MK-8719 PN001 Dosing schedule

<table>
<thead>
<tr>
<th>Panel</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Period 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5 mg</td>
<td>20 mg</td>
<td>80 mg</td>
<td>300 mg</td>
<td>80 mg (fed)</td>
</tr>
<tr>
<td>B</td>
<td>10 mg</td>
<td>40 mg</td>
<td>160 mg</td>
<td>600 mg</td>
<td>1200 mg</td>
</tr>
</tbody>
</table>
Human Pharmacokinetics of MK-8719

- Plasma exposure increased in a dose-proportional manner.
- Peak plasma levels of MK-8719 were observed at a median $T_{\text{max}}$ of 0.75 hours.
- The fractional clearance at the pharmacological dose was 6.9 mL/min/kg and the half-life was $\sim 4.7$ hr.
Pharmacodynamics of MK-8719 in Humans

PBMC O-protein Changes

- MK-8719 dose-dependently increased PBMC O-protein levels after single doses.

- The O-protein response persisted up to 24 hr postdose, even after MK-8719 was eliminated from the plasma.
OGA PET Tracer $[^{18}F]$MK-8553 was Used to Measure MK-8719 Target Engagement in Humans

- $[^{18}F]$MK-8553 regional distribution is consistent with preclinical species and the known distribution of the OGA enzyme
- Blocking studies with MK-8719 demonstrate the ability of $[^{18}F]$MK-8553 to be used as a tool to measure OGA target engagement and guide dose selection
MK-8719 Program Summary

Preclinical Validation

• MK-8719 is a selective and potent small molecule inhibitor of the O-GlcNAcase (OGA) enzyme
• Oral administration of MK-8719 produces a sustained elevation in O-Protein levels in brain and peripheral tissues
• OGA inhibition significantly reduces pathological tau and brain atrophy in Tg4510 transgenic mice

Clinical Results

• MK-8719 was safe and generally well tolerated in a single rising dose study in healthy subjects at doses ranging from 5 to 1200 mg
• Robust increases in PBMC O-protein were detected in response to MK-8719 administration
• The selective OGA PET tracer $[^{18}]$FMK-8553 was used to demonstrate central target engagement of MK-8719 in humans
Acknowledgments

**MSD Team**
- Gladys Arreaza
- Richard Briscoe
- Brent Butts
- Antonella Converso
- Mali Liu Cosden
- Joe Duffy
- Nathaniel Elsen
- Mark Forman
- Renee Gentzel
- Diane Grotz
- Eric Gustafson
- Nick Hastings
- Nathan Hatcher
- Mansuo Hayashi
- Joseph Herring
- Fred Hess
- Eric Hostetler
- Lynn Hyde
- Daniel Jonathan
- Rachel Korn
- Julie Lee
- Jung Hoon Lee
- Diane Levitan
- Wenping Li
- Sherry Lu
- Ellen Locker
- Talakad Lohith, Lei Ma
- Jacob Marcus
- Nadine Margaretten
- Carrie Markgraf
- Maureen Maguire
- Thomas McAvoy
- Maria Michener
- Shahrriar Niroomand
- Xuesong Ouyang
- Eric Parker
- Sophie Parmentier
- Michelle Pearson
- John Renger
- Thomas Rosahl
- Punam Sandhu
- Joel Schachter
- Darryle Schoepp
- Harold Selnick
- Benjamin Sherry
- Brad Smith
- Karen Smith
- Sean Smith
- Mary Savage
- Lixin Song
- Daniel Spellman
- Lindsay Stahl
- Arie Struyk
- Cyrille Sur
- Giuseppe Terracina
- Fiona Thomson
- Dawn Toolan
- Jason Uslaner
- Marija Usenovic
- Stephanie Villarreal
- Xiaohai Wang
- Keith Wessner
- Guoxin Wu
- Lili Zhang

**Alectos Team**
- Ernest McEachern
- Ramesh Kaul
- Tongshuang Li
- David Vocadlo
- Yuanxi Zhou
- Yongbao Zhu