GLPG1972: a potent, selective, orally bioavailable ADAMTS-5 inhibitor for the treatment of OA

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Therapeutic Area Head

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ADAMTS-5 a promising therapeutic target in OA

- ADAMTS-5 plays a key role in aggrecan degradation
- Target validated in human OA cartilage explants (Song - 2007)
- In the DMM model adamts-5/- mice showed protection from cartilage degradation and mechanical allodynia (Glasson - 2005 and Malfait - 2010)
- Mice treated with an ADAMTS-5 mAb had attenuated joint damage and were protected from mechanical allodynia (Miller – 2016)
- ARGs levels increased in human knee synovial fluid after joint injuries and in OA (Larsson – 2009)
High potency and anti-catabolic activity *in vitro*

<table>
<thead>
<tr>
<th></th>
<th>GLPG1972 IC&lt;sub&gt;50&lt;/sub&gt; range (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>h-ADAMTS-5 potency</td>
<td>&lt;25</td>
</tr>
<tr>
<td>r-ADAMTS-5 potency</td>
<td>&lt;25</td>
</tr>
<tr>
<td>h-ADAMTS-5 (Aggrecan-ELISA)</td>
<td>&lt;70</td>
</tr>
<tr>
<td>GAG release inhibition in <em>mouse</em> cartilage explants</td>
<td>&lt;1,500</td>
</tr>
<tr>
<td>AGN×1 release inhibition in <em>human</em> cartilage explants</td>
<td>&lt;1,000</td>
</tr>
</tbody>
</table>
Mouse cartilage explants: IC$_{50}$ < 1.5 µM

Mouse (C57Bl6) 4 week old

3 days triggering with IL1$\alpha$ +/- GLPG1972

Supernatant Femoral head

Quantification of aggrecan release

GAG % inhibition

Human cartilage explants: IC$_{50} < 1$µM

Human articular cartilage from OA patient

12/19 days triggering with IL1β +/- GLPG1972

Quantification of AGNx1 in the supernatant

[Graph showing AGNx1 levels over time with different treatments and statistical significance marks]
High *in vitro* selectivity vs. other metalloproteinases

<table>
<thead>
<tr>
<th>Target</th>
<th>Selectivity (fold)</th>
</tr>
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<tbody>
<tr>
<td>ADAMTS-5</td>
<td>-</td>
</tr>
<tr>
<td>ADAMTS-4</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>ADAMTS-1</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>ADAMTS-13</td>
<td>&gt; 5,000</td>
</tr>
<tr>
<td>ADAM17 (TACE)</td>
<td>&gt; 1,000</td>
</tr>
<tr>
<td>MMP-1</td>
<td>&gt; 1,500</td>
</tr>
<tr>
<td>MMP-2</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>MMP-7</td>
<td>&gt; 1,500</td>
</tr>
<tr>
<td>MMP-9</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>MMP-13</td>
<td>&gt; 1,000</td>
</tr>
<tr>
<td>MMP-14</td>
<td>&gt; 150</td>
</tr>
</tbody>
</table>
GLPG1972 in mouse DMM model

Experimental design

- Destabilization meniscus surgical procedure
- Start of dosing
- Male C57/bl6 mice n=20/group
- Treatment period (p.o.) from D2 to D56
- DMM paws
- Histology

Mouse model of destabilization of the medial meniscus adapted from: Glasson et al., Osteoarthritis Cartilage, 2007
GLPG1972 in mouse DMM model

Representative images

Vehicle

GLPG1972 30 mg/kg bid

GLPG1972 60 mg/kg bid

GLPG1972 120 mg/kg bid

Scoring system modified from Shu et al., Arthritis Rheum. 2016
GLPG1972 in mouse DMM model
Reduction in proteoglycan loss

Articular Cartilage PG Cumulative Score

Scoring system modified from Shu et al., Arthritis Rheum. 2016
GLPG1972 in mouse DMM model
Reduction in structural cartilage damage

Cartilage Cumulative Structure Score

<table>
<thead>
<tr>
<th>Score</th>
<th>vehicle</th>
<th>GLPG1972 30mg/kg bid</th>
<th>GLPG1972 60mg/kg bid</th>
<th>GLPG1972 120mg/kg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- 23%</td>
<td>- 21%</td>
<td>- 33%</td>
</tr>
</tbody>
</table>

Scoring system modified from Shu et al., Arthritis Rheum. 2016
GLPG1972 in mouse DMM model
Reduction in subchondral tibia sclerosis

Scoring system modified from Shu et al., Arthritis Rheum. 2016
Conclusions

• ‘1972 is a potent and selective chondroprotective ADAMTS-5 inhibitor

• ‘1972 is orally available and showed a significant protective effect in the DMM model

• ‘1972 features a robust preclinical pharmacology package with good drugability characteristics

‘1972 has been progressed to First-in-Human studies
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