

Development of LCN2 inhibitor for multiple sclerosis

Disease Area	Autoimmune																					
Product Type	Small molecule																					
Indication	Multiple sclerosis																					
Target	Lipocalin-2 (LCN2)																					
Mechanism of Action	Inhibition of immune cell infiltration by LCN2 inhibition																					
Competitiveness	1. Differentiated MOA : LCN2-LCN2R interaction inhibition 2. Potential to by-pass BTK-related adverse effects																					
Development Stage	H2L																					
Route of Administration	Oral																					
Key Data	<div>1. Proposed mechanism : Inhibition of LCN2-induced neuroinflammation</div> <div><p>Glial cell activation &amp; Neuroinflammation amplification</p><p>MOG</p><p>Dendritic cell</p><p>Macrophage</p><p>LCN2</p><p>Th0 cell</p><p>CD4+/IL-17+ T-cell</p><p>CD4+/IFN-γ T-cell</p><p>T-cell differentiation &amp; activation</p><p>BBB</p><p>LCN2</p><p>CXCL10</p><p>T-cell infiltration</p><p>Demyelination</p><p>Demyelination &amp; Neurotoxicity</p></div> <div>2. Hit profile compared to Tecfidera</div> <table><tr><th>Items</th><th>Tecfidera</th><th>LCN2 inhibitor (DN301950)</th></tr><tr><td>in vitro chemokine inhibition (ELISA, IC<sub>50</sub>, μM)</td><td>8.8 μM (CCL2)* , 30.0 μM (CXCL9)**</td><td>up to 6.2 (CXCL10, astrocyte)</td></tr><tr><td>in vitro cytokine inhibition (ELISA, IC<sub>50</sub>, μM)</td><td>12.2 μM (IL6)*</td><td>n/a</td></tr><tr><td>LPS-induced neuroinflammation mouse</td><td>clinical score ~50% decrease (30 mpk, i.p.)***</td><td>Reduced inflamm. (20 mpk, i.c.v.), Tnf mRNA ~50%, Il1b mRNA ~75% decrease</td></tr><tr><td>EAE mouse</td><td>clinical score ~62% decrease (100 mpk, i.p.)****</td><td>clinical score ~20% decrease (5 mpk, i.p.)</td></tr><tr><td>MOA</td><td>- Oxidative stress induced Nrf2 activation - Nrf2 independent immune system control - Multi-target mechanism (NF-κB, GSH, etc.) *****</td><td>- Inhibition of neuroinflammation by LCN2-LCN2R interaction</td></tr><tr><td>Toxicity, side effect</td><td>Kidney, liver, stomach tox. / brain infection</td><td>No target related toxicities reported</td></tr></table> <p><small>*Arthritis. Res. Ther. <b>2016</b>, 18, 139; **WO2020169054; ***Front. Immunol. <b>2021</b>, 12, 737065; ****Brain, <b>2021</b>, 144, 3126-3141; *****Autoimmunity Rev. <b>2021</b>, 144, 3126.</small></p>	Items	Tecfidera	LCN2 inhibitor (DN301950)	in vitro chemokine inhibition (ELISA, IC <sub>50</sub> , μM)	8.8 μM (CCL2)* , 30.0 μM (CXCL9)**	up to 6.2 (CXCL10, astrocyte)	in vitro cytokine inhibition (ELISA, IC <sub>50</sub> , μM)	12.2 μM (IL6)*	n/a	LPS-induced neuroinflammation mouse	clinical score ~50% decrease (30 mpk, i.p.)***	Reduced inflamm. (20 mpk, i.c.v.), Tnf mRNA ~50%, Il1b mRNA ~75% decrease	EAE mouse	clinical score ~62% decrease (100 mpk, i.p.)****	clinical score ~20% decrease (5 mpk, i.p.)	MOA	- Oxidative stress induced Nrf2 activation - Nrf2 independent immune system control - Multi-target mechanism (NF-κB, GSH, etc.) *****	- Inhibition of neuroinflammation by LCN2-LCN2R interaction	Toxicity, side effect	Kidney, liver, stomach tox. / brain infection	No target related toxicities reported
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ID	To be filed (Patentability confirmed)																					