Characterization of Orally Bioavailable Small Molecule Inhibitors of Complement C5

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Complement C5: A Central Target for the Therapeutic Intervention of Complement Mediated Disorders

**Alternative Pathway**
- Activated by non-self cells

**Classical Pathway**
- Activated by antibody-antigen complexes
  - C1q – C1r – C1s

**Lectin Pathway**
- Activated by pathogen surfaces

**Multiple Indications**
- PNH: rupture of RBC
- gMG: destruction of neuromuscular junction
- aHUS: hemolytic anemia, thrombocytopenia, and renal failure
- LN: inflammation of kidney glomerulus

- **C5 Small Molecule Inhibitor (SMi)**
- eculizumab
- Binds C5
- C5a
  - Proinflammatory cytokine
- C5b6
  - Membrane attack complex (MAC)
- C7, C8, C9
Properties of Small Molecule Inhibitors (SMi) of Complement C5

- SMi bind to cryptic site on C5 and prevent cleavage into C5a and C5b
- SMi block C5 activation by classical/lectin pathway and alternative pathway convertases; also prevents fluid phase C5 activation by Cobra Venom Factor
- SMi exhibit desirable drug-like properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Compound A</th>
<th>Compound B</th>
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<tbody>
<tr>
<td>Binding Affinity (K_D)</td>
<td>24 nM</td>
<td>2.5 nM</td>
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<tr>
<td>Solubility (pH 7.4)</td>
<td>~0.4 mM</td>
<td>~0.5 mM</td>
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<tr>
<td>EPSA</td>
<td>79</td>
<td>77</td>
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<tr>
<td>MW</td>
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<td>HBD+HBA</td>
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<td>CLogP</td>
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<td>3.4</td>
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<tr>
<td>tPSA</td>
<td>80</td>
<td>72</td>
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</table>
MAC-Driven Endpoint: ABO Mismatch Hemolysis Assay (90% Human Sera)

- Modeling incompatible transfusion reaction that causes intravascular hemolysis of donor erythrocytes
- Antibodies present in serum of donor cause strong and acute activation of classical cascade resulting in C3 deposition on RBC and MAC formation

![Diagram showing A+ RBC, A+ Serum (Compatible), A+ RBC, B+ Serum (Incompatible), and C5 Cleavage with serum samples showing A+, B+, and AB+ results.]
MAC-Driven Endpoint: ABO Mismatch Hemolysis Assay (90% sera)

Potent SMi achieve full inhibition of MAC driven hemolysis

Compound A
IC$_{50}$: 1250 nM

Compound B
IC$_{50}$: 420 nM

Eculizumab (bivalent binder)
IC$_{50}$: 115 nM

Compound B – Dose dependent response
C5a-Driven Endpoint: Whole Blood Neutrophil Oxidative Burst

SMi compare favorably to C5aR1 antagonists in a bacterial complement-dependent neutrophil activation assay.

- **Compound B**
  - IC$_{50}$: 313 nM

- **Avacopan**
  - IC$_{50}$: 112 nM

* 100% defined as response to Eculizumab at 2.85µM
Dose-Proportional Pharmacokinetics Observed in Lead Compound Series

In vivo DMPK (Mouse and Dog)
- Pharmacokinetics characterization in different species demonstrates dose-proportional exposure
- Excellent bioavailability after oral dosing across species
Humanized Liver Mouse Model: Inhibition of Complement C5 Following Oral Dosing

- SMi do not bind to mouse complement C5
- Immunodeficient mice transplanted with human hepatocytes provide circulating human complement

Oral dosing of SMi results in full blockade of ex-vivo zymosan-mediated C5 activation (incubation in whole blood)
Summary: First-in-class Complement C5 SMi

- Exhibit favorable drug like properties and are orally bioavailable
- Demonstrated efficacy in rigorous, whole blood ex vivo models of complement activation
  - MAC mediated hemolysis: Potential use in PNH, aHUS, and MG
  - C5a mediated neutrophil oxidative burst: Potential use in ANCA vasculitis, neutrophilic dermatoses, inflammatory diseases
- Exhibit dose proportional exposure upon oral dosing and are highly bioavailable via this route in multiple preclinical species
- Oral dosing results in complete inhibition of complement C5 in humanized mouse model (evaluated using whole blood)
- GLP toxicology studies supporting initial evaluation in man to be completed by 1H19