

## Stage 1: Hit-to-Lead – Target Compound Profile

**Stage 1: Hit-to-Lead Target Compound Profile (TCP):** This document provides draft Stage 1 TCP criteria, including Essential requirements and Optimal targets defining success at completion of Stage 1: Hit-to-Lead. These criteria are preliminary and subject to change. Additional details on Stage 1 submission evaluation, including scoring guidance and review procedures, will be provided at the launch of Stage 1: Hit-to-Lead (anticipated Summer 2026).

Attribute	Essential success criteria	Optimal success criteria
<b>Early Safety Liabilities (<i>in silico</i> &amp; screening tox)</b>	<i>Genotoxicity:</i> No AMES-positive prediction <i>in silico</i> . If positive result predicted in silico, no AMES-positive result must be confirmed with an <i>in vitro</i> screen.	
	<i>Target-organ liabilities:</i> No flags for target-organ toxicities (e.g., hepatotox, nephrotox, etc) identified <i>in silico</i> (e.g., QSAR, AI modeling, etc.) or in early <i>in vitro</i> screening assays at concentrations <b>≥ 3-fold above the anticipated EC90 concentration</b> .	<i>Target-organ liabilities:</i> No flags for target-organ toxicities (e.g., hepatotox, nephrotox, etc.) identified <i>in silico</i> (e.g., QSAR, AI modeling, etc) or in early <i>in vitro</i> screening assays at concentrations <b>≥ 10-fold above the anticipated EC90 concentration</b> .
	<i>hERG:</i> Free (unbound) hERG IC50 ≥ 10 μM, or ≥10-fold above anticipated free EC90.	<i>hERG:</i> Free (unbound) hERG IC50 ≥ 30 μM, or ≥30-fold above anticipated free EC90, <b>confirmed using a high-throughput screening patch clamp assay</b> (or equivalent method).
	For any toxicity liabilities identified, provide evidence the toxicity <b>is not pharmacophore driven</b> and is related to <b>optimizable criteria</b> (e.g., solubility, rapid metabolic turnover, etc.) <b>and</b> that there is a clear SAR plan to address identified liabilities.	
	<b>Disqualifying:</b> If toxicities appear in <b>≥ 80% of hits in a series (at least 6 or more hits)</b> , indicating limited ability to optimize due to pharmacophore risk.	

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<b>Aqueous Solubility</b>	<p>Aqueous solubility (kinetic) <b>≥50 μM at pH 7.4, and two other pH levels (one acidic pH and one basic pH).</b></p> <p>If ≤ 50 μM, provide an executable plan to address.</p>	
<b>Antiviral Activity and Selectivity</b>	<p><b>EC50 ≤ 2.5 μM</b> for the primary target virus, and <b>EC50 ≤ 5 μM</b> for each of the two additional viruses.</p>	<p><b>EC50 ≤ 0.5 μM</b> for the primary target virus, and <b>EC50 ≤ 1 μM</b> for each of the two additional viruses.</p>
	<p><b>SI (CC50/EC50) ≥ 10×</b> for all three viruses.</p>	<p><b>SI (CC50/EC50) ≥ 30×</b> for all three viruses.</p>
	<p>For <b>Flaviviridae</b> entries, the required 3-virus panel must include <b>dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4) and two elective viruses within the same family.</b></p> <p>For <b>Togaviridae</b> entries, the required 3-virus panel must include <b>Chikungunya virus (CHIKV) and two elective viruses within the same family.</b></p> <p>Antiviral activity must be demonstrated in <b>cell-based, live-virus infection assays</b>, and <b>at least one</b> potency determination must use a <b>plaque-reduction readout</b> (e.g., PRNT or plaque reduction assay).</p> <p>Virus isolates must be <b>clinically relevant</b> (e.g., non-attenuated and non–animal-adapted).</p> <p>For selectivity index (SI) calculations, <b>CC50 must be measured in the same cell line and under the same assay conditions used for the corresponding live-virus potency (EC50) assay.</b></p>	

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<b>In vitro ADMET / DDI risk</b>	CYP inhibition: No significant inhibition in <b>CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4</b> ; <b>IC50 &gt; 10 μM</b> across all major isoforms. If inhibition is observed for one or more isoforms, provide an executable SAR strategy to address, with <i>in silico</i> analysis (e.g., QSAR or AI modeling) used to support the strategy.  <b>Disqualifying:</b> <ul style="list-style-type: none"> <li>• <b>Time-dependent inhibition (TDI/MBI):</b> a decrease in IC50 upon pre-incubation with NADPH indicates MBI and is disqualifying.</li> </ul>	
	Microsomal stability: <b>t<sub>1/2</sub> ≥ 30 minutes</b> in mouse and human; <b>CL (&lt;25 μL/min/mg)</b> in human liver microsomes.	
	Hepatocytes intrinsic clearance (rodent and human): <b>CL<sub>int</sub> &lt; 30 μL/min/mg protein.</b>	Hepatocytes intrinsic clearance (rodent and human): <b>CL<sub>int</sub> &lt; 15 μL/min/10<sup>6</sup> cells.</b>
	Permeability (e.g., PAMPA, MDCK, Caco-2, etc.): <b>P<sub>app</sub> &gt; 5 × 10<sup>-6</sup> cm/s</b>	
	<b>Plasma protein binding (screen):</b> Report <b>fraction unbound (fu, % unbound)</b> in <b>human/rodent plasma</b> (method and conditions stated).  Flag compounds with <b>very high, non-specific binding (fu &lt; 1%)</b> .  Provide evidence that <b>free (unbound) plasma exposures</b> achieved <i>in vivo</i> are consistent with the observed antiviral activity <i>in vitro</i> (e.g., free concentrations support the efficacy target).	
	Lipophilicity:  <b>cLogP ~1-5 for neutral compounds</b>	

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	<p><b>OR</b></p> <p><b>cLogD ~1–3 for ionizable compounds</b></p>	
<p><b>Preliminary PK (<i>in vivo</i>)</b></p>	<p>PK study: Either <b>PO or IV single-dose PK</b> in an appropriate preclinical species.</p>	<p>PK study: <b>Both PO + IV single-dose PK</b> (same species; ideally cross over design at comparable dose levels).</p> <p>Oral exposure: Absolute oral bioavailability (F%) reported and <b>F ≥ 10%</b> (calculated from matched PO and IV exposures).</p>
	<p>Report (minimum): <b>C<sub>max</sub>, AUC, t<sub>1/2</sub>, CL</b> (compatible with no more than <b>TID dosing</b> in humans to achieve therapeutic levels to cover EC<sub>50</sub>/EC<sub>90</sub>).</p>	<p>Report (minimum): <b>C<sub>max</sub> (PO), AUC (PO and IV), t<sub>1/2</sub> (PO and IV), and CL (IV)</b> (compatible with no more than <b>BID dosing</b> in humans to achieve therapeutic levels to cover EC<sub>50</sub>/EC<sub>90</sub>).</p>
	<p>Includes a plan to optimize/improve bioavailability/PK.</p>	
<p><b>Off-target pharmacology (panel)</b></p>	<p><b>~50 target screening panel at 10 μM.</b></p> <p>Threshold for high selectivity: <b>≤ 5% targets with 50% inhibition at 10 μM</b> (low promiscuity index).</p> <p>If off-target effects are identified, include a risk assessment of target and an executable plan for addressing.</p> <p><b>Disqualifying:</b></p> <ul style="list-style-type: none"> <li>• Low selectivity: <b>&gt; 20% targets with 50% inhibition at 10 μM.</b></li> </ul>	