Long-Acting HIV Capsid Inhibitor Effective as PrEP in a SHIV Rhesus Macaque Model

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Lenacapavir (LEN) and GS-CA1 Are Novel Long-acting HIV/SIV Capsid Inhibitors

- Daily PrEP is highly effective at preventing HIV infection when taken as directed
- It is estimated that only 20% of those who meet PrEP eligibility criteria are taking oral PrEP
- Long-acting agents can address unmet need among people not benefiting from oral PrEP options

![Chemical structures and data]

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<tr>
<th>Structure</th>
<th>Status</th>
<th>PBMC EC_{50} (nM)</th>
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| LEN¹ (GS-6207) | • Favorable safety & tolerability profile in clinical trials*  
• 2.3-log_{10} HIV-1 RNA decline after 9 days of monotherapy*  
• Q6M formulation in Phase 2/3 trials in PLWH | HIV⁺ 0.050  
SHIV⁺ 0.569 |
| GS-CA1² (LEN analog) | • Preclinical efficacy in hu-mice  
• Tool compound for preclinical research studies | HIV⁺ 0.130  
SHIV⁺ 0.748 |

Study Design: Repeat Mucosal Challenge Macaque Model

**Study objective:** To determine the efficacy of GS-CA1 long-acting formulation at preventing infection after repeat SHIV exposure in rhesus macaques

- **Single SC drug dose**
- **Drug washout**
- **Indian rhesus macaques** (weight ~7 kg)
- **Infection monitoring:** weekly plasma viral load (qRT-PCR) & serology
- Weekly SHIV.SF162P3 intrarectal challenges (10-100 TCID₅₀)

<table>
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<tr>
<th>n=8</th>
<th>Placebo</th>
<th>GS-CA1 150 mg/kg</th>
<th>GS-CA1 300 mg/kg</th>
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**Analysis:** per-exposure risk reduction (Cox proportional hazard model)

qRT-PCR, quantitative reverse transcription polymerase chain reaction; SC, subcutaneous; TCID₅₀, median tissue culture infectious dose

GS-CA1 Protects from Repeat Intrarectal SHIV Challenges

- 100% infection of placebo controls within 15 challenges
- Significant infection risk reduction with GS-CA1 vs placebo (86% and 96% for low- and high-dose groups, respectively)
- Infections in GS-CA1-dosed groups occurred only after marked compound washout (9+ weeks post dose*)

CI, confidence interval. *Assumes 2-week infection-detection window.
Protection Correlates with GS-CA1 Exposure

Main conclusions:
- Single GS-CA1 dose achieved long-acting exposure (>IQ1 for 2-4 months) in macaques
- Mean IQ at time of infection was 1* (0.41-1.5 range)
- Complete protection from infection observed with GS-CA1 exposures above IQ1.5 (1.5x paEC95)
- GS-CA1 preclinical data support clinical evaluation of capsid inhibitors for HIV prevention

IQ, inhibitory quotient (protein-adjusted 95% effective concentration). LOD, limit of detection. *Assumes 2-week infection-detection window.
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