Preclinical Characterization of ABI-1179, a Potent Helicase-Primase Inhibitor for the Treatment of Recurrent Genital Herpes

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Presenter Disclosures

- Heidi Contreras is an employee and stockholder of Assembly Biosciences, Inc.
- This study was sponsored by Gilead Sciences, Inc.

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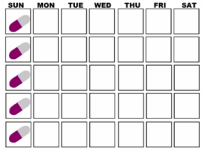
Significant Medical Need: Currently Limited Treatments Options

4M+ in US & EU with initial symptomatic genital herpes infection have 3+ recurrences per year[1-6]

Suppressive SOC is 1-gram daily valacyclovir, a viral polymerase inhibitor approved in 1995[7]

Only 1 in 3 with frequent outbreaks[a] remain recurrence free for a year on SOC[7]



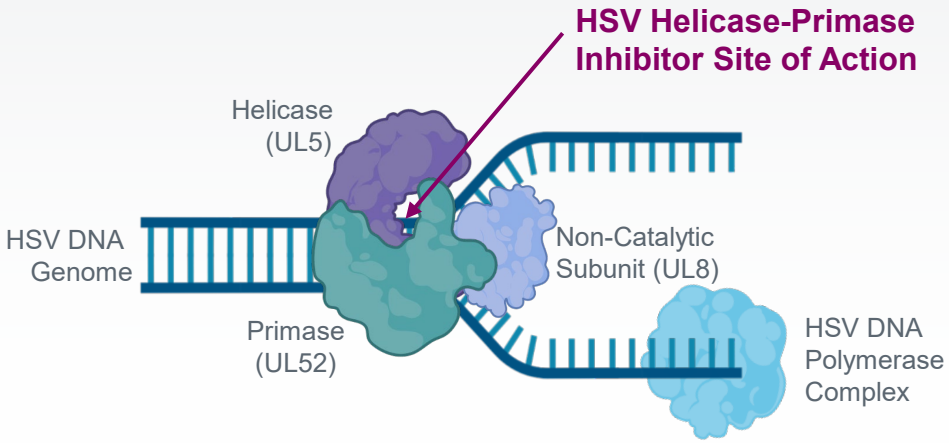
Targeting a suppressive therapy for recurrent genital herpes with **superior efficacy** to SOC in reducing outbreaks and **once-weekly oral dosing**

HSV helicase-primase inhibitors can address this need

[a]In a study of patients with 6 or more annual recurrences; did not include discontinuations, withdrawals, or loss to follow-up.
SOC, standard of care.

1. James C, et al. *Bull World Health Organ*. 2020:98(5):315-29. 2. McQuillan G, et al. *NCHS Data Brief*. 2018:(304):1-8. 3. Alareeki A, et al. *Lancet Reg Health Eur*. 2022:25:100558. 4. Fanfair RN, et al. *Sex Transm Dis*. 2013;40(11):860-4. 5. Benedetti J, et al. *Ann Intern Med*. 1994;121(11):847-54. 6. Benedetti JK, et al. *Ann Intern Med*. 1999;131(1):14-20. 7. Valtrex (valacyclovir). US package insert. GlaxoSmithKline; revised 2021.

ABI-1179 Targets the HSV Helicase-Primase Complex



- Clinically-validated mechanism (pritelivir)[1]
  - Further reduction in HSV shedding and fewer days with lesions and pain vs SOC
- Unlike current SOC, does not require activation by viral and host kinases[1]
- Active against SOC-resistant HSV[2]

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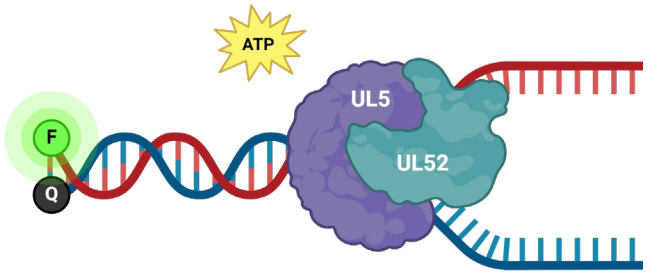
SOC, standard of care; UL5, helicase; UL52, primase.
1. Wald A, et al. *JAMA*. 2016;316(23):2495-503; 2. Field HJ and Biswas S. *Drug Resist Updat*. 2011;14(1):45-51.

ABI-1179 Potently Inhibits the DNA Unwinding Activity of the HSV Helicase-Primase Complex



Compound	IC_{50} (nM)		$K_{i, app}$ (nM)	
	HSV-1	HSV-2	HSV-1	HSV-2
ABI-1179	0.17 ± 0.05	0.16 ± 0.07	0.03 ± 0.02	0.03 ± 0.01
Pritelivir	11 ± 3	30 ± 6	5 ± 1	8 ± 0

- ABI-1179 is a potent inhibitor of HSV helicase-primase DNA unwinding activity with a >60-fold improvement in potency compared with pritelivir

The schematic depicts the helicase unwinding assay. IC_{50} and $K_{i, app}$ values are mean ± SD.
F, fluorophore; IC_{50}, half-maximal inhibitory concentration; $K_{i, app}$, inhibitor constant, apparent; Q, quencher; UL5, helicase; UL52, primase.

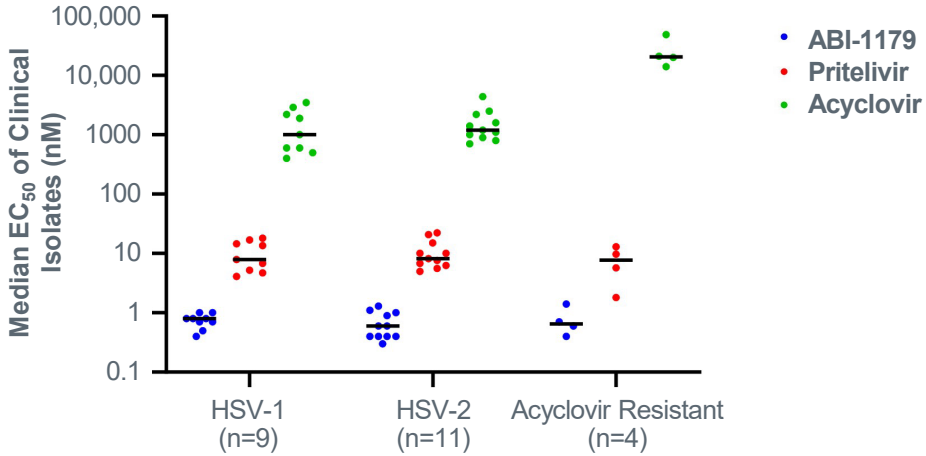
ABI-1179 Demonstrates Low Potential for Off-Target CA Inhibition

CA Hydratase	ABI-1179		Pritelivir	
	IC_{50} (nM)	Selectivity Index	IC_{50} (nM)	Selectivity Index
CAI	>100,000	≥600,000	451 ± 170	22
CAII	6600 ± 750	≥40,000	1800 ± 194	88

- Pritelivir has previously been shown to inhibit various CAs, and CA inhibitors are associated with anemia and other hematological changes[1–3]
- Unlike pritelivir, ABI-1179 does not inhibit CAI. ABI-1179 is also a weaker inhibitor of CAII than pritelivir
- Inhibition of CA(s) is not anticipated for ABI-1179 at the projected human efficacious dose
- The *in vitro* safety profile further shows that ABI-1179 is not cytotoxic

IC_{50} values are mean ± SD. Fold selectivity was calculated using an average IC_{50} against HSV-1 and HSV-2 helicase-primase in DNA unwinding (ABI-1179, IC_{50} = 0.165 nM; pritelivir, IC_{50} = 20.5 nM).
CA, carbonic anhydrase; IC_{50}, half-maximal inhibitory concentration.
1. Carta F, et al. *J Med Chem*. 2017;60(7):3154-64. 2. Hoffmanova I, et al. *Br J Clin Pharmacol*. 2018;84(4):796-9. 3. Leaf DE, et al. *J Appl Physiol (1985)*. 2007;102(4):1313-22.

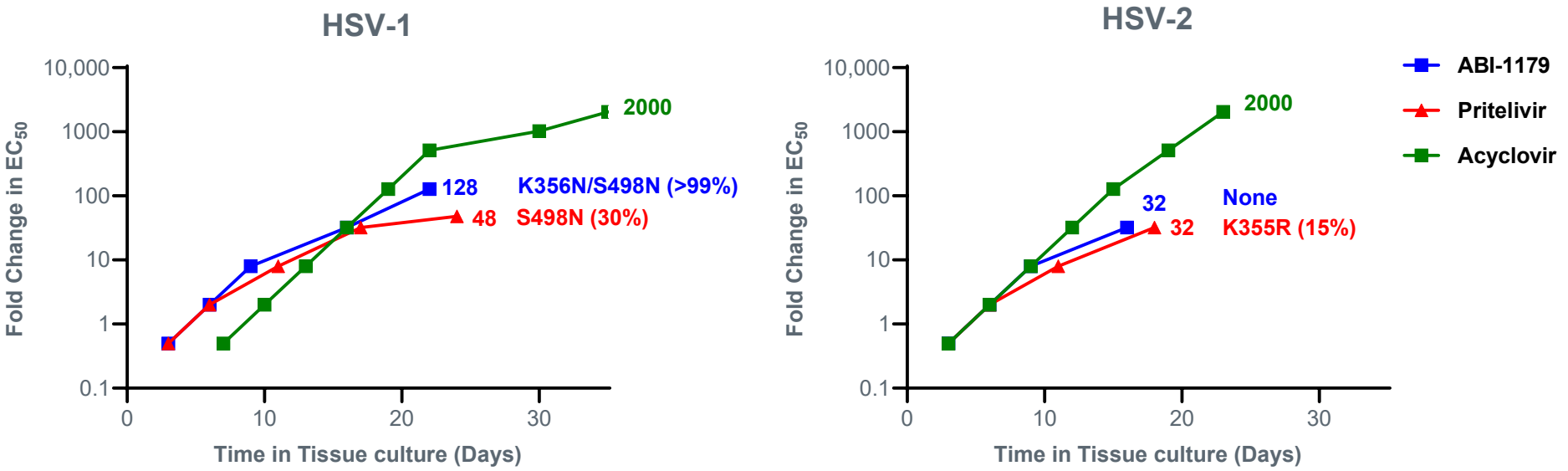
ABI-1179 Is a Potent Inhibitor of HSV-1 and HSV-2 Clinical Isolates and Laboratory Strains



- ABI-1179 is active against HSV-1 and HSV-2 clinical isolates, including those with reduced susceptibility to acyclovir
- ABI-1179 is >12-fold more potent against HSV-1 and HSV-2 clinical isolates than pritelivir and >1500-fold more potent than acyclovir. All 4 acyclovir-resistant HSV isolates remain susceptible to ABI-1179
- ABI-1179 also has potent antiviral activity against HSV-1 (KOS) and HSV-2 (MS) replication in ARPE-19 cells and HSV-2 (MS) in HaCat and NHDF cells

n denotes the number of clinical isolates tested. Each point represents an individual isolate, and the horizontal line depicts the median EC_{50} across all clinical isolates tested.
ARPE-19, retinal epithelial cells; EC_{50}, half-maximal effective inhibitory concentration; HaCat, human keratinocytes; NHDF, neonatal human dermal fibroblasts.

ABI-1179 Has a High Barrier to Resistance *In Vitro*



- Compound concentrations increased (4-fold) upon detection of full CPE from HSV-infected cells at a constant MOI
- Concentrations of ABI-1179 at which CPE was no longer detected occurred on day 22 (HSV-1) and day 16 (HSV-2)

Frequencies of variants detected in ABI-1179– and pritelivir-treated cultures (≥15%) are indicated in parentheses.
CPE, cytopathic effect; EC_{50}, half-maximal effective inhibitory concentration; MOI, multiplicity of infection.

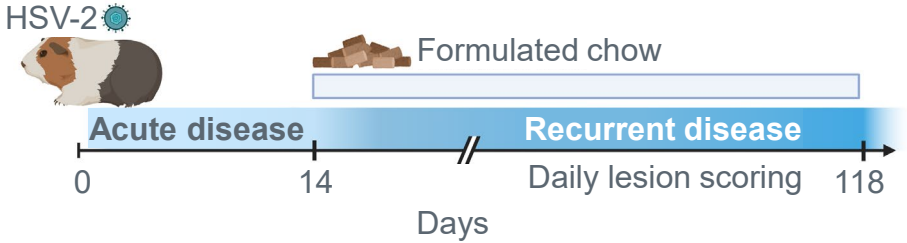
ABI-1179 Is More Resilient to Binding Site Variations Than Pritelivir

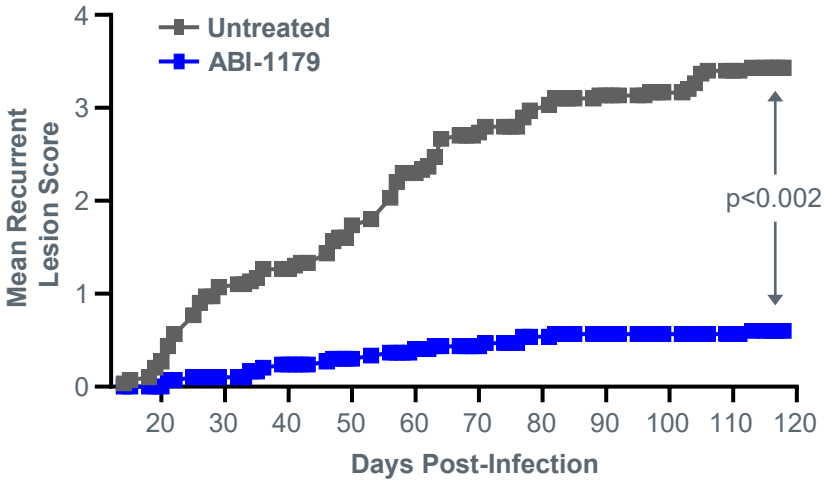
Constructs	EC_{50} (nM) [Fold Change From Wild Type]	
	ABI-1179	Pritelivir
Wild type	0.9	8.2
UL52 A906V	2.3 [3]	377 [46]
UL5 K355N	268 [306]	>2000 [>243]
UL5 K355T	10.7 [12]	562 [68]
UL5 K355R	2.2 [3]	319 [39]
UL5 L805I	1.4 [2]	22.2 [3]
UL5 S497N	2.4 [3]	22.5 [3]
UL5 K355R + UL5 L805I	>1000 [>1111]	>122,000 [>14,878]
UL5 K355R + UL5 L805I + UL52 A906V	>64,000 [>71,111]	>122,000 [>14,878]
UL5 K355N + UL5 S497N	>64,000 [>71,111]	>122,000 [>14,878]

- Phenotypic assessment of HSV helicase single variants previously described in the clinic and identified *in vitro* reveals modest potency shifts for ABI-1179 compared with pritelivir
- Resistance selection and phenotyping data suggest that ABI-1179 binds at the UL5/UL52 interface, consistent with Cryo-EM structure data (not shown)

Cryo-EM, cryogenic electron microscopy; EC_{50}, half-maximal effective inhibitory concentration; UL5, helicase; UL52, primase.

ABI-1179 Reduces the Number of HSV Lesions in the Guinea Pig Model of Recurrent HSV Infection

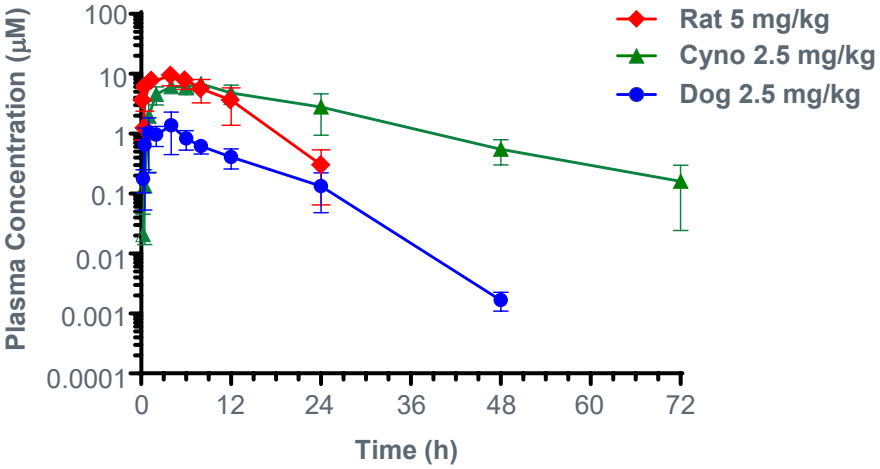




- Following latency establishment, ABI-1179 significantly reduces the development of lesions in a guinea pig model of recurrent HSV infection when treated with formulated chow at therapeutically-relevant concentrations

Pharmacokinetic sampling at 21, 49, 77, and 105 days post-infection. ABI-1179 (0.04% weight/weight) plasma concentrations remain 8-fold greater than the guinea pig protein-adjusted EC_{95} (133 nM).
EC_{95}, 95% effective inhibitory concentration.

ABI-1179 Has a Favorable Oral PK Profile in Preclinical Species



Parameter	Rat	Cyno	Dog	Human[a] (Projected)
Half-life (h)[a]	3.6	11.6	4.8	44
Oral bioavailability (%)	90	149	45	50

- ABI-1179 demonstrates a favorable oral PK profile with a projected human oral dose of 250 mg, once weekly

Plasma concentration is mean ± SD. [a]Half-life after oral administration.
Cyno, cynomolgus monkey; PK, pharmacokinetic.

Highlights of ABI-1179

Target	Status
Confirmed mechanism of action targeting HSV helicase-primase complex (biochemical, Cryo-EM, and resistance studies)	✓
Potent inhibition of HSV replication across clinical isolates and laboratory strains	✓
High barrier to resistance	✓
Efficacy in guinea pig model of recurrent HSV infection	✓
Low potential for off-target activity	✓
Improved dosing regimen (SOC, 1 g QD → ABI-1179, 250 mg QW)	✓

- A Phase 1a/1b first-in-human study with ABI-1179 is planned to start in the second half of 2024

Cryo-EM, cryogenic electron microscopy; SOC, standard of care; QD, once daily; QW, once weekly.