Pre-clinical characterization of ABI-5366: a highly potent long-acting helicase-primase inhibitor for the treatment of high recurrence genital herpes

Heidi Contreras, Michael Shen, Gene Schulze, Kirsten Stray, Dinara Azimova, Ran Yan, Hassan Pajouhesh, Zhixin Zong, Min Zhong, Michael Walker, Nicole White, Kathryn Kitrinos, Michel Perron, William Delaney

Assembly Biosciences, Inc., South San Francisco, CA, USA

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Presenter Disclosures

- Heidi Contreras is an employee and stockholder of Assembly Biosciences, Inc.

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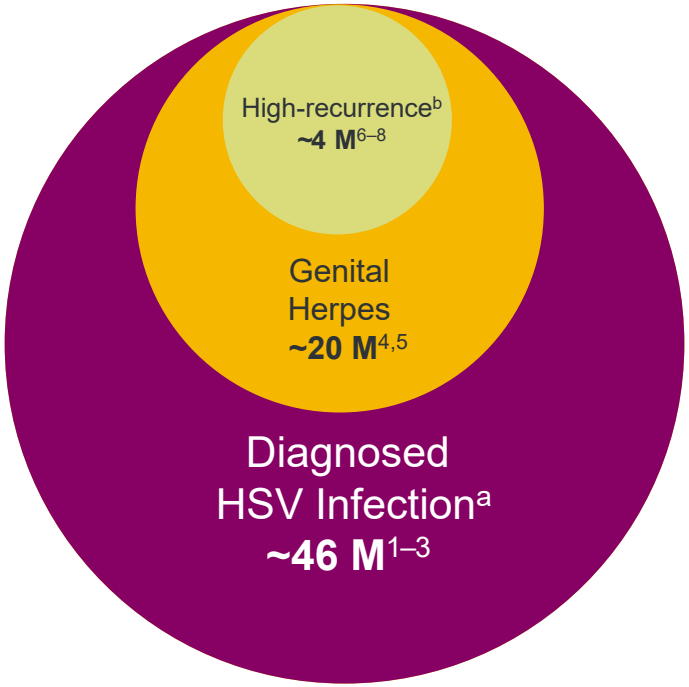
High-Recurrence Genital Herpes: The Need for Better Antivirals



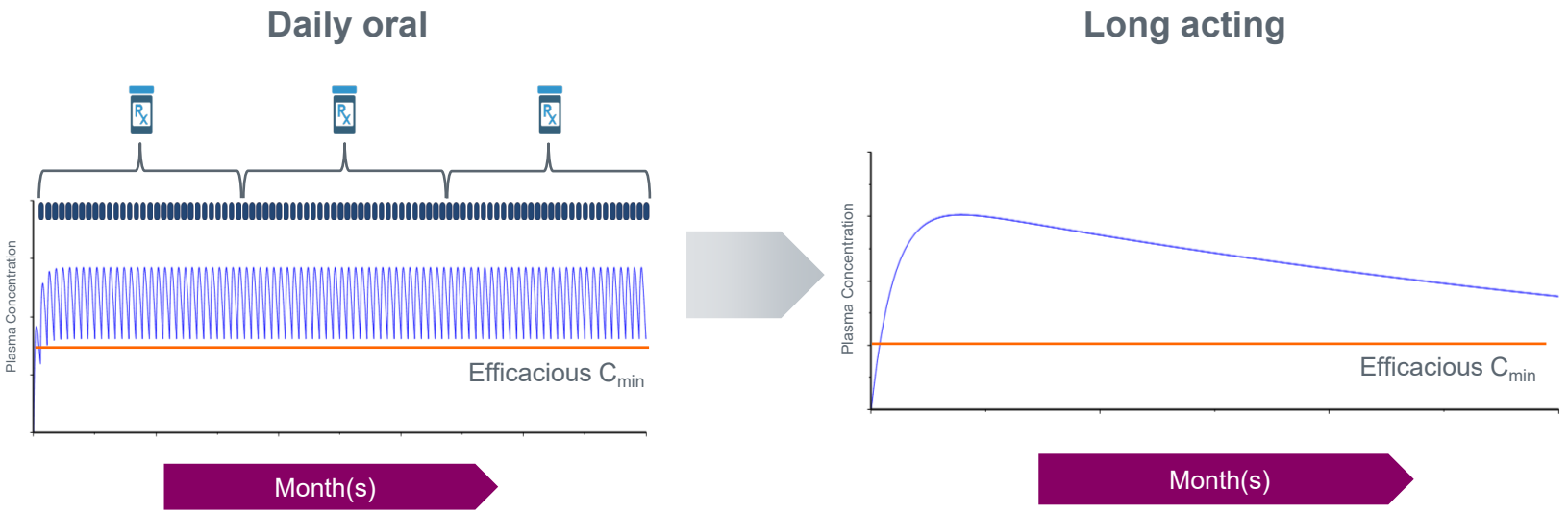
The existing treatment paradigm for high-recurrence genital herpes is inadequate

Inadequate suppression	**2 of 3**[c] patients not adequately treated[9]
Continued transmission	**<50%** transmission reduction on suppressive treatment[10]
High pill burden	Nucleoside analogues must be taken **once to twice daily** for life

[a]Estimated for US & EU4/UK. [b]High-recurrence is defined as >3 recurrences/year. [c]Does not adjust for lost to follow-up, discontinuations due to adverse events, and consent withdrawn.

1) McQuillan G, et al. *NCHS Data Brief*. 2018;304:1-8. **2)** Yousuf W, et al. *BMJ Global Health*. 2020;5:e002388. **3)** Fanfair R, et al. *Sex Transm Dis*. 2013;40:860-64. **4)** Alareeki A et al. *Lancet Reg Health Eur*. 2022;25:100558. **5)** James C, et al. *Bull World Health Organ*. 2020;95:315-29. **6)** HSV Fact Sheet-WHO. **7)** Engelberg R, et al. *Sex Transm Dis*. 2003;30:174-77. **8)** Benedetti J, et al. *Ann Intern Med*. 1999;131:14-20. **9)** Valtrex (valacyclovir) product insert. **10)** Corey L, et al. *N Engl J Med*. 2004;350:11-20.

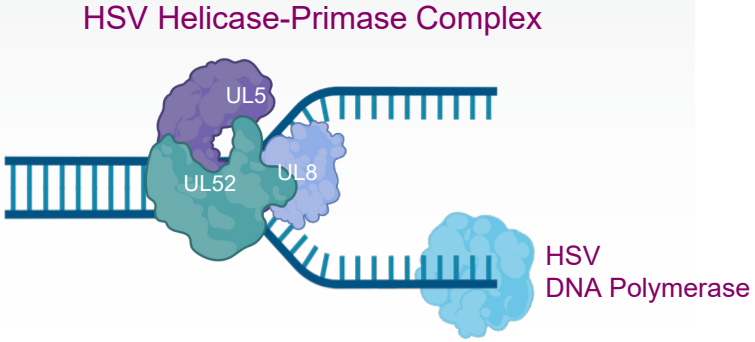
Long-Acting Therapy for Recurrent Genital Herpes



- Long-acting therapy → consistent drug levels, better compliance[1,2] → improved efficacy
- Reduced dosing frequency → greater discretion → lower barrier to continued use

1) Sabate E, et al. *Adherence to long-term therapies: evidence for action.* World Health Organization, 2003. **2)** Romanowski B, et al. *Sex Transm Dis*. 2003;30:226-31.

ABI-5366 Targets HSV Helicase/Primase



- Clinically-validated mechanism (pritelivir)[1]
  - Greater reductions in HSV shedding vs valacyclovir
  - Fewer days with lesions and pain
- Acts immediately, unlike current standard of care
- Active against nucleoside analog-resistant HSV

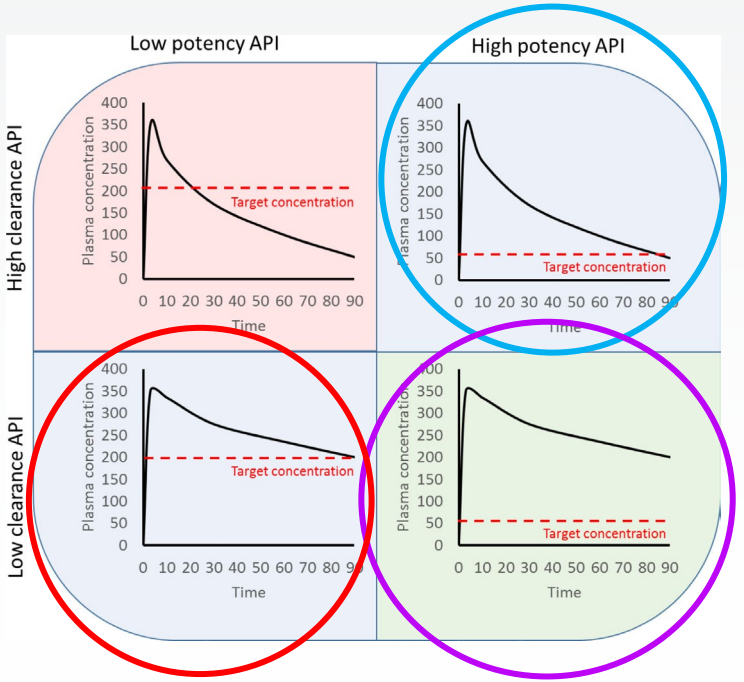
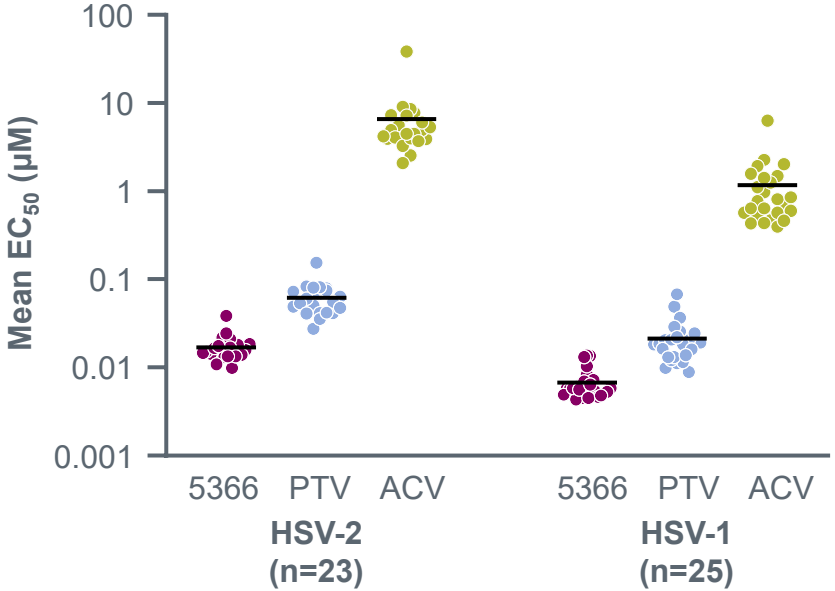


Figure from Owen, A, et al. *Adv Drug Deliv Rev*. 2016;103:144-56.

API, active pharmaceutical ingredient.

1) Wald, A et al. *JAMA*. 2016;316:2495-2503.

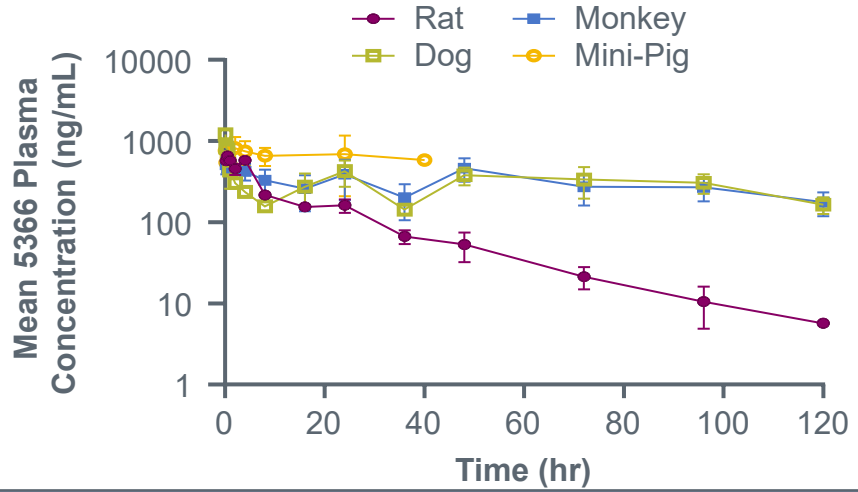
ABI-5366 Demonstrates Broad Antiviral Activity Against HSV-2 and HSV-1 Clinical Isolates



- No clinical isolates tested exhibited reduced susceptibility against ABI-5366 (5366)[a]
- No significant differences in ABI-5366 antiviral potency were observed between lab strains and clinical isolates
- ABI-5366 is ~4x more potent than pritelivir and ~400x more potent than acyclovir against HSV-2 clinical isolates

The number of clinical isolates tested is noted underneath the respective virus. [a]Data generated by Assembly Biosciences, Inc.

ABI-5366 Shows Low Clearance After IV Administration in Rat, Dog, Monkey, and Mini-Pig

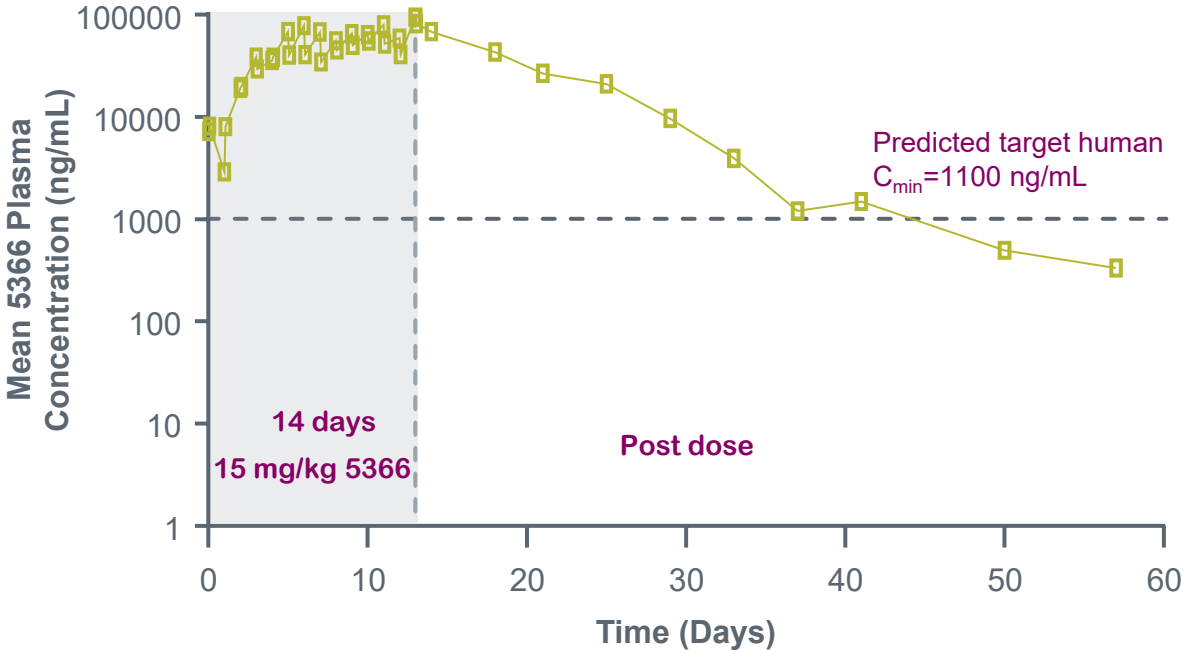


Parameter	ABI-5366				
Species	Rat	Dog	Monkey	Mini-Pig	Human
CL (IV, L/hr/kg)	0.02	0.0023	0.004	0.0018	0.00086[a,b]
Half-life (hr)	20	55	71	134	182[a]

- ABI-5366 has an extremely low clearance in all preclinical species
- Human PK modeling predicts ABI-5366 will have an extremely low human plasma clearance

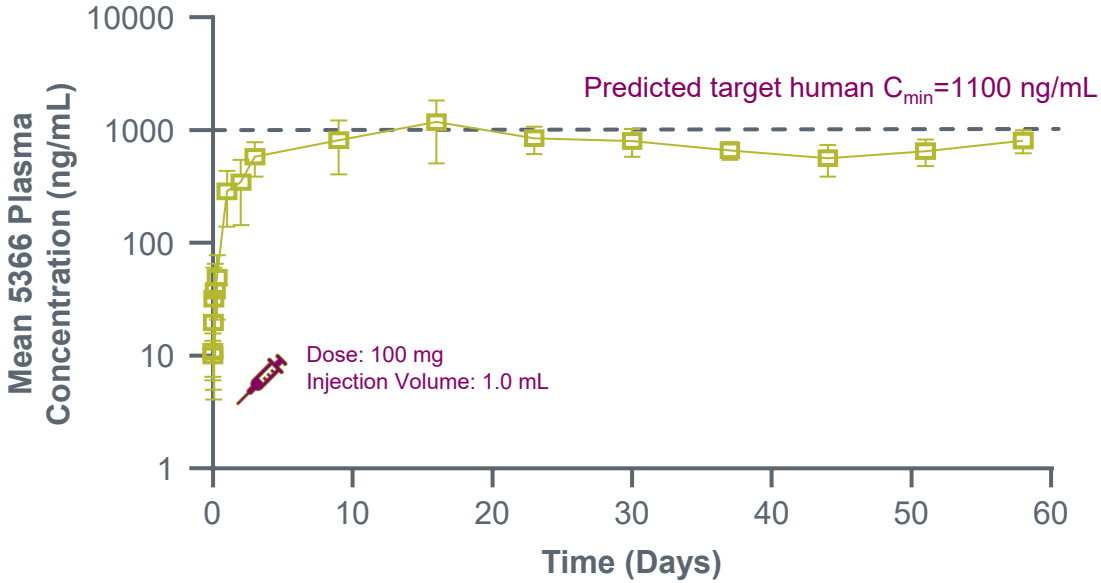
[a]Denotes predicted values using four species. [b]Calculated using an estimated human weight of 70 kg.

ABI-5366 Demonstrates Sustained Exposure 40+ Days After Oral Dosing



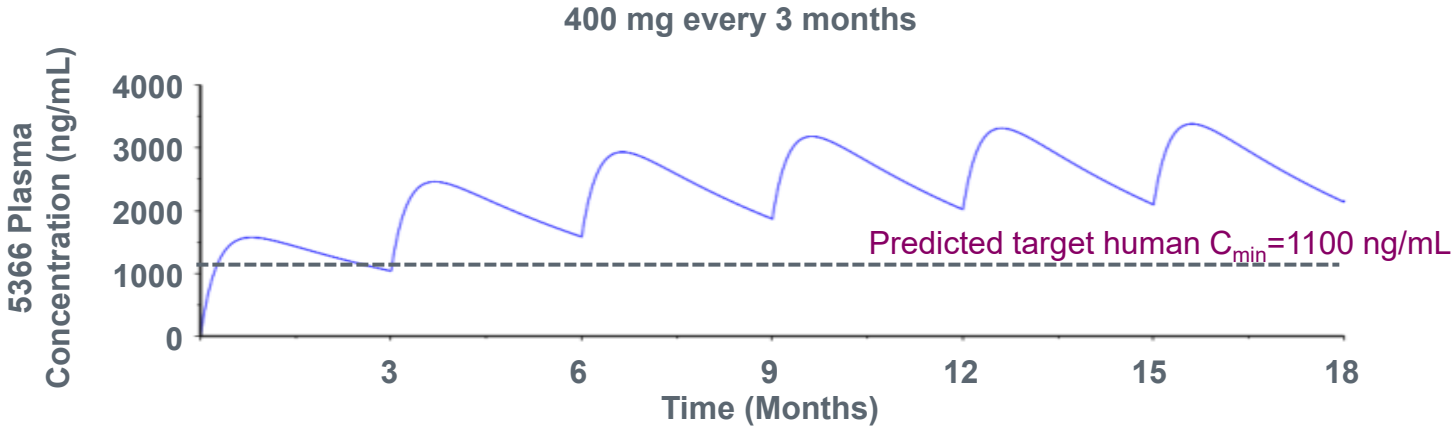
- The dog PK study achieved high sustained exposure to 40+ days
- ABI-5366 was well tolerated for the duration of the study

ABI-5366 Concentration Is Maintained For ~2 Months After a Single SC Injection in Dogs



- Single low-volume SC injection (10 mg/kg) without a loading dose → extended-release profile
- Sustained ABI-5366 plasma concentrations were observed over 9 months after injection
- Ongoing formulation optimization may further increase plasma levels and exposures

Subcutaneous Human PK Prediction: Maintenance of Drug Levels Over Target Concentration



Predicted PK Parameters	Body Weight (kg)	CL (L/hr)	Bioavailability
ABI-5366	70	0.0602	50%–100%

ABI-5366 Nonclinical Safety to Date–Summary

- 7-day rat and dog oral study revealed no findings at the highest doses tested
  - Rat: 300 mg/kg, 15× predicted human efficacious concentration (HEC)
  - Dog: 100 mg/kg, 62× predicted HEC
    - Exposure plateaued between 10 and 100 mg/kg
- 14-day PK study in dogs → ABI-5366 is well tolerated, with no drug-related clinical signs, gross pathology, or clinical pathology at any dose level
- In a rabbit study, single SC doses up to 200 mg/injection were well tolerated, without significant injection-site irritation

Highlights of ABI-5366

Target	Status
Broad potency against HSV clinical isolates	✓
Mechanism of action → helicase (mutation data)	✓
Good predicted human clearance	✓
Sustained exposure after dosing (dogs) > 1 month	✓
Acceptable safety profile in preclinical studies to date with good exposure margins	✓
Low potential for off-target effects	✓

- A Phase 1a first-in-human study with ABI-5366 is planned for 1H-2024

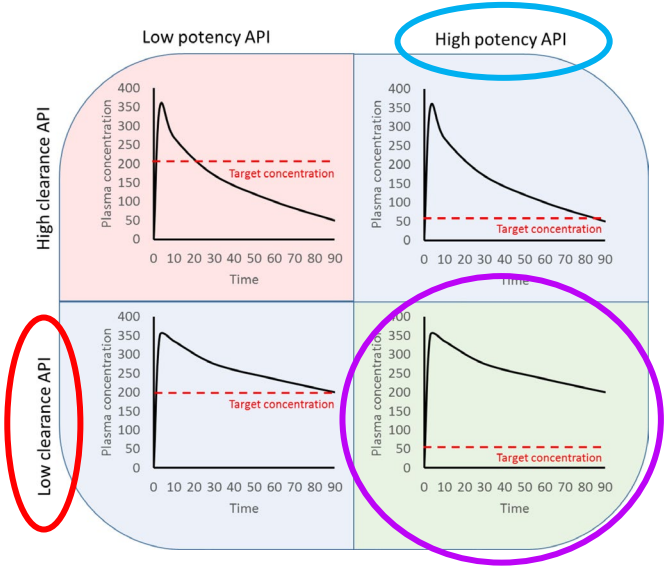


Figure from Owen, A, et al. *Adv Drug Deliv Rev*. 2016;103:144-56.

API, active pharmaceutical ingredient.

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- Writing and editorial support were provided by Gregory Suess, PhD, CMPP, of AlphaBioCom, a Red Nucleus company, and were funded by Assembly Biosciences, Inc.
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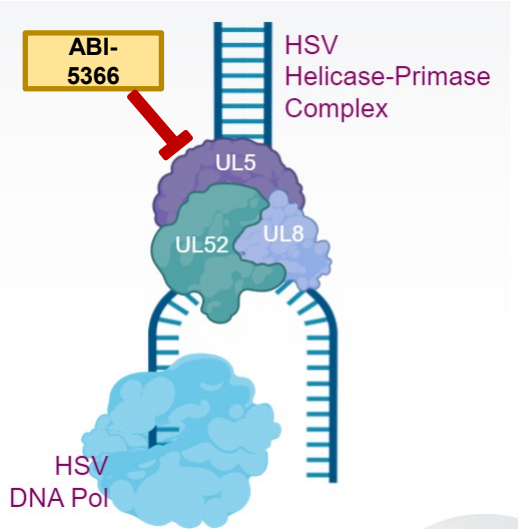
In Vitro Resistance Studies Reveal Mutations in UL5 Helicase → Resistance to ABI-5366 and Pritelivir (BACKUP)

Virus Isolates	Mutation detected	EC_{50} (uM)					
		ABI-5366	Fold change	Pritelivir	Fold change	Acyclovir	Fold change
HSV2-IS18	NA	0.0174	NA	0.0554	NA	6.25	NA
HSV2-IS18R1	UL5 K355R	>50	>2874	2.11	38	4.85	0.78
HSV2-IS18R2	UL5 K355N	>50	>2874	>50	>903	6.23	1.00



- Selection conducted on a representative clinical isolate
- Mutations emerged under selective pressure with ABI-5366
  - Mutations were resistant to pritelivir but sensitive to acyclovir
- ABI-5366 may act upon the helicase-primase complex

NA, not applicable.