

ABI-5366, a Potent HSV Helicase-Primase Inhibitor, with Potential for Weekly or Monthly Oral Dosing for Recurrent Genital Herpes

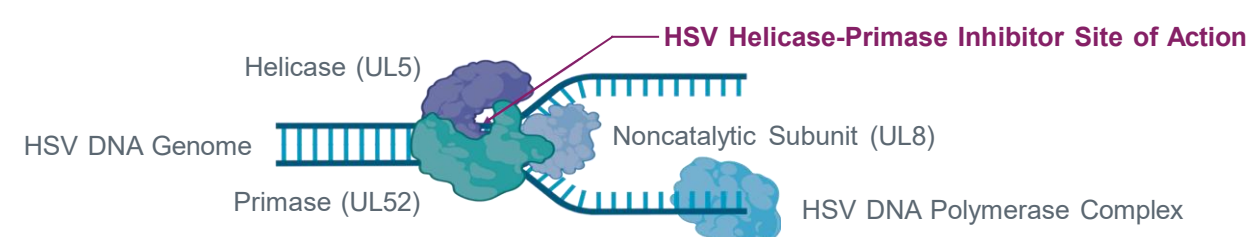
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Background

- Worldwide, approximately 491.5 million people aged 15 to 49 years are infected with herpes simplex virus type 2 (HSV-2), the primary cause of genital herpes^{1,2}
- Recurrent genital herpes (RGH) results in painful lesions that often last a week or more, psychological stress, and increased risk of HIV-1 infection^{1,2}
 - In the US and EU, >4 million people with initial symptomatic genital herpes infection go on to have 3+ recurrences per year²⁻⁸
- Standard-of-care nucleoside analogue (NA) suppressive therapy is limited by suboptimal efficacy in the majority of patients⁹
- Helicase-primase inhibitors (HPIs) are a novel class of antivirals with improved efficacy compared with NAs, as measured by reductions in viral shedding and symptoms^{10,11}
 - The HP enzyme complex is essential for viral replication, with no human homologue¹² (Figure 1)
- ABI-5366 is a novel, oral, long-acting HSV HPI in development for suppression of RGH

Figure 1. The HSV Helicase-Primase Enzyme Complex



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HSV, herpes simplex virus.

Objective

- To describe the preclinical potency and pharmacokinetic (PK) profile of ABI-5366, a novel HPI in development for the treatment of RGH

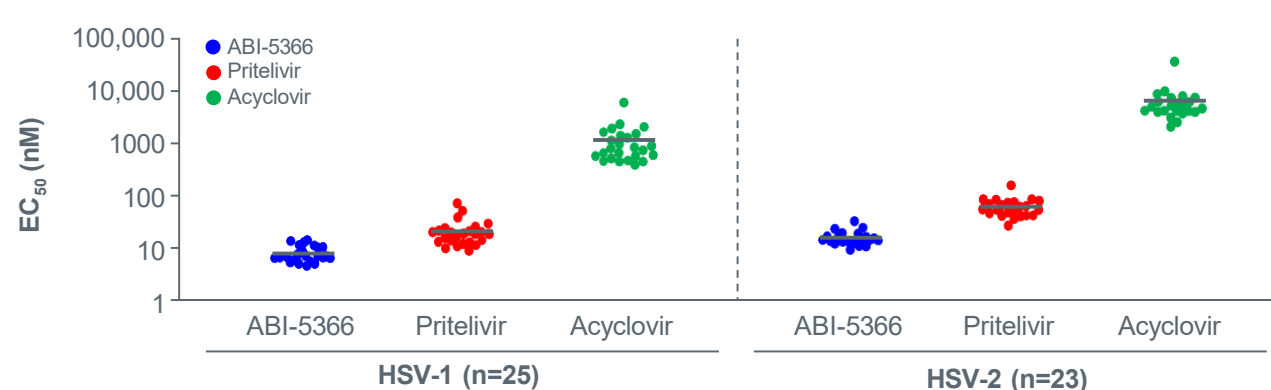
Methods

- Antiviral activity assays:** Vero cells were infected with HSV (laboratory strains or clinical isolates) and treated with compounds for 5 days. Virally reduced cytopathic effects and half-maximal effective concentrations (EC_{50}) were measured by CellTiter-Glo®
- Metabolic stability:** Liver microsomes from rats, dogs, monkeys, and humans were incubated with 10 μ M ABI-5366 for 45 minutes, and then levels of ABI-5366 were measured to determine intrinsic clearance
- Preclinical PK studies:** Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys were dosed intravenously (IV) with 0.1 to 1 mg/kg ABI-5366, and ABI-5366 plasma levels were monitored for up to 120 hours. Beagle dogs were dosed with a single oral (PO) dose of 100 mg ABI-5366, and ABI-5366 plasma levels were monitored for 14 days
- Bile duct cannulated study:** Bile duct cannulated Sprague-Dawley rats were dosed IV with 0.5 mg/kg ABI-5366. Bile, urine, and feces were collected up to 120 hours postdose and ABI-5366 levels were measured
- Reabsorption study:** Beagle dogs were dosed IV with 0.1 mg/kg ABI-5366 \pm 25 g/dog activated charcoal dosed PO every 2 to 8 hours from 2 hours pre-ABI-5366 dosing to 120 hours post-ABI-5366 dosing
- Tissue distribution studies:** Rats received a single PO dose of ABI-5366 or pritelivir at 15 mg/kg via gavage needle. The concentration of ABI-5366 or pritelivir in plasma and tissues was determined using liquid chromatography with mass spectrometry

Results

Figure 2. ABI-5366 Exhibits Broad Activity Against HSV-1 and HSV-2 Clinical Isolates

A. Clinical Isolate Sensitivity



B. Mean Antiviral Activity

Virus	Strain	EC_{50} (nM)		
		ABI-5366	Pritelivir	Acyclovir
HSV-1	Laboratory strain (HF)	18 \pm 5	66 \pm 23	3380 \pm 1070
	Clinical isolates (n=25)	7 \pm 3	21 \pm 13	1174 \pm 1211
HSV-2	Laboratory strain (G)	10 \pm 3	38 \pm 12	1080 ^a
	Clinical isolates (n=23)	17 \pm 6	62 \pm 26	6606 \pm 7173

In panel A, the horizontal lines indicates the mean. In panel B, EC_{50} values are mean \pm SD; each EC_{50} represents \geq 3 replicates.

^an=1
 EC_{50} , half-maximal effective concentration; HSV, herpes simplex virus; SD, standard deviations

- ABI-5366 exhibits potent activity against both HSV-1 and HSV-2 laboratory strains and clinical isolates (Figure 2A)
- ABI-5366 is approximately 4-fold more potent than pritelivir and approximately 400-fold more potent than acyclovir against HSV-2 clinical isolates (Figure 2B)

Table 1. ABI-5366 Is Metabolically Stable

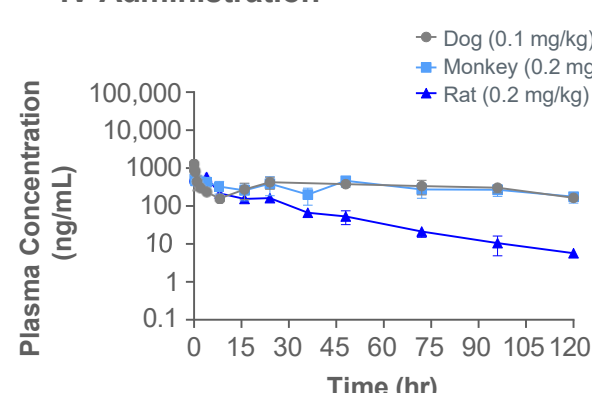
	Rat	Dog	Monkey	Human
CL_{int} (mL/min/kg)	8.99	7.35	6.89	0.803

CL_{int} , intrinsic clearance.

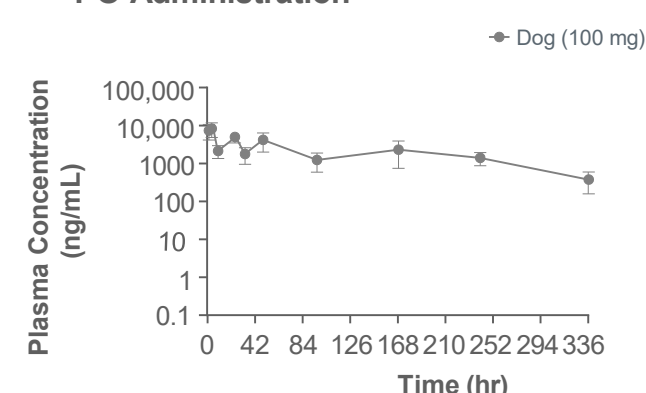
- ABI-5366 was metabolically stable in liver microsomes from rats, dogs, monkeys, and humans, with intrinsic clearance (CL_{int}) values <9 mL/min/kg. ABI-5366 was most stable in human liver microsomes, with a CL_{int} value of \sim 0.8 mL/min/kg (Table 1)

Figure 3. ABI-5366 PK Profile in Preclinical Species

A. PK Profile of ABI-5366 After IV Administration



B. PK Profile of ABI-5366 After PO Administration



C. Summary of IV PK Parameters

Parameter	Rat	Dog	Monkey
CL (L/hr/kg)	0.02	0.0023	0.004
Half-life (hr)	20	55	71

In panels A and B, concentrations are mean \pm SD.
CL, clearance; hr, hour; IV, intravenous; PK, pharmacokinetic; PO, by mouth; SD, standard deviation.

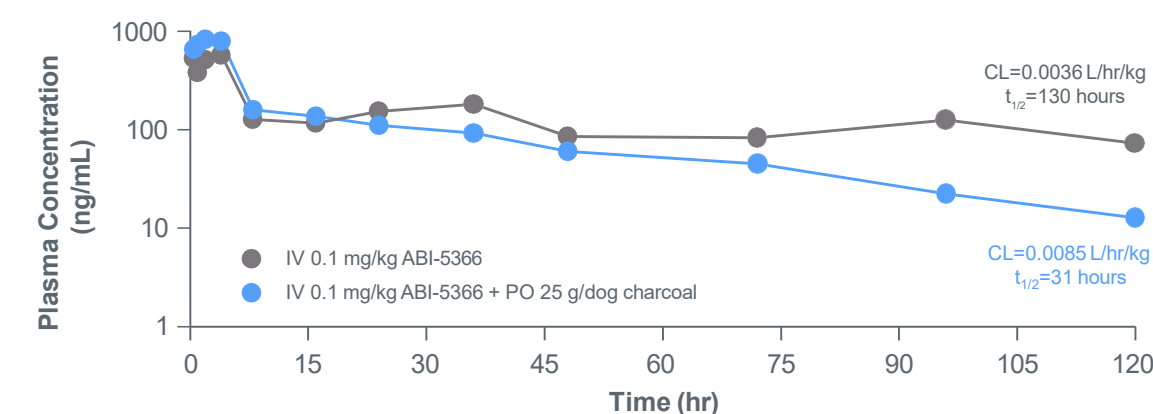
- Preclinical IV PK studies in dogs, rats, and monkeys demonstrated that ABI-5366 has a very low clearance ($CL=0.002-0.02$ L/hr/kg) and an extended half-life (20-71 hours; Figure 3)

Table 2. ABI-5366 Is Predominantly Eliminated Unchanged

Parameter	Urine	Feces	Bile
% of ABI-5366 recovered	0.0572	23.1	2.15

- In an excretion study in bile duct cannulated rats, approximately 25% of ABI-5366 was excreted as the parent molecule within 120 hours, with feces being the predominant route of elimination (Table 2)

Figure 4. ABI-5366 Exhibits Intestinal Resorption



CL, clearance; hr, hour; IV, intravenous; PO, by mouth; $t_{1/2}$, half-life.

- The clearance of ABI-5366 increased approximately 2.4-fold and the half-life decreased by approximately 3-fold in the presence of activated charcoal, suggesting intestinal resorption contributes to the extended half-life of ABI-5366 (Figure 4)

Table 3. Tissue Distribution of ABI-5366

Tissue	Ratio $AUC_{tissue}/AUC_{plasma}$	
	ABI-5366	Pritelivir
Brain	0.041	0.027
Lung	0.704	0.335
Liver	1.70	0.824
Kidney	0.747	0.396
Heart	0.884	0.300
Bone marrow	0.399	0.158
Ganglia	0.125	0.062

AUC, area under the curve.

- ABI-5366 distribution to the rat brain and ganglia as well as other tissues is comparable to or greater than the distribution of pritelivir, another HPI
- Distribution of ABI-5366 is high in the liver, while moderate distribution was observed in the heart, lung, kidney, and bone marrow tissues

Conclusions

- ABI-5366 potently inhibits HSV-1 and HSV-2 replication and exhibits broad potency against HSV clinical isolates
- Preclinical PK studies demonstrate the long-acting potential of ABI-5366
- Intestinal resorption of ABI-5366 contributes to its low clearance and extended half-life
- ABI-5366 readily distributes to tissues relevant to HSV infection
- These results support clinical evaluation of ABI-5366; a Phase 1a/b study is ongoing
- In Phase 1a (NCT06385327), ABI-5366 exhibited a half-life of approximately 20 days
- In Phase 1b, once-weekly and once-monthly oral regimens are planned to be evaluated

REFERENCES

- WHO herpes simplex virus detailed fact sheet. Last revised December 11, 2024. <https://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus>.
- Gupta R, et al. *Lancet*. 2007;370(9605):2127-37.
- James C, et al. *Bull World Health Organ*. 2020;98(5):315-29.
- McQuillan G, et al. NCHS Data Brief. 2018;304:1-8.
- Alareeki A, et al. *Lancet Reg Health Eur*. 2022;25:100558.
- Fanfair RN, et al. *Sex Transm Dis*. 2013;40(11):860-4.
- Benedetti J, et al. *Ann Intern Med*. 1994;121(11):847-54.
- Benedetti JK, et al. *Ann Intern Med*. 1999;131(1):14-20.
- Valtrex (valacyclovir). US package insert. GSK; revised 2022.
- Shiraki K, et al. *Viruses*. 2021;13(8):1547.
- Wald A, et al. *JAMA*. 2016;316(23):2495-503.
- Bernek O, et al. *Open Biol*. 2021;11(6):210011.

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DISCLOSURES

All coauthors are employees and stockholders of Assembly Biosciences, Inc.