Preclinical Profile of ABI-5366, a Novel Potent HSV Helicase-Primase Inhibitor, With Potential for Weekly or Monthly Oral Dosing for the Treatment of Recurrent Genital Herpes

P0212

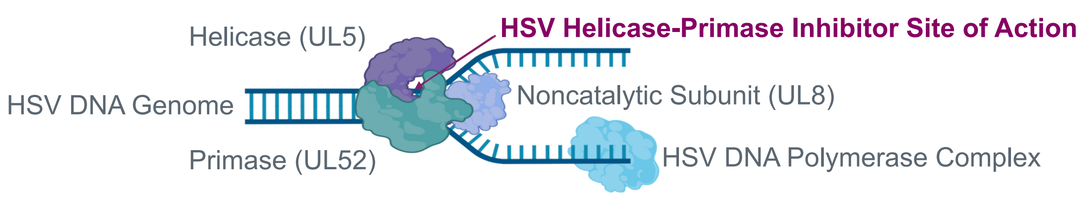
Michael Shen, Carl Li, Zhixin Zong, Heidi Contreras, Ran Yan, Michel Perron, William E Delaney, Kathryn M Kitrinos

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

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 year[2-8]
- Standard-of-care nucleoside analogue (NA) suppressive therapy is limited by suboptimal efficacy in the majority of patients[9]
- 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 homologue[12] (**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

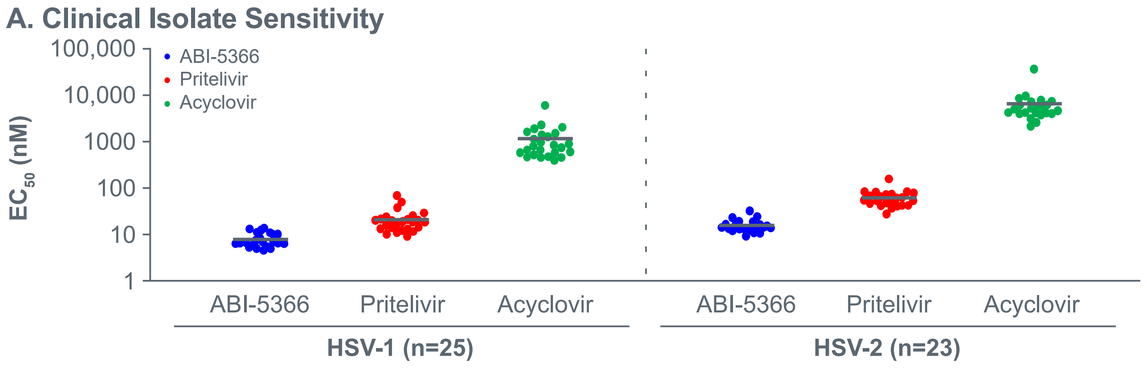
Methods

- **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 µM 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 ± 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±5	66±23	3380±1070
	Clinical isolates (n=25)	7±3	21±13	1174±1211
HSV-2	Laboratory strain (G)	10±3	38±12	1080[a]
	Clinical isolates (n=23)	17±6	62±26	6606±7173

In panel A, the line indicates the mean. In panel B, EC_{50} values are mean ± SD; each EC_{50} represents ≥3 replicates.
[a]n=1.
EC_{50}, half-maximal effective concentration; HSV, herpes simplex virus; SD, standard deviation.

- 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

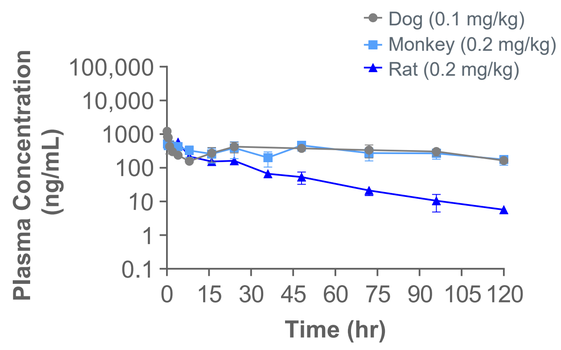
	Rat	Dog	Monkey	Human
CL_{int} (mL/min/kg)	8.99	7.35	6.89	0.803

CL_{int}, intrinsic clearance.

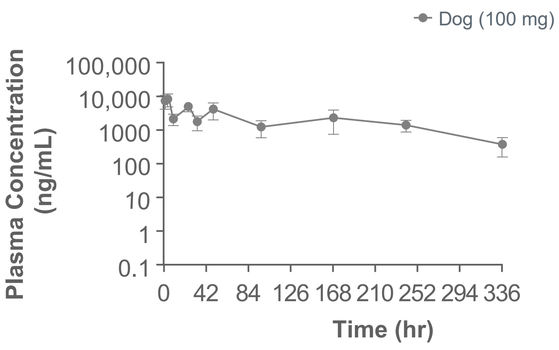
- ABI-5366 was metabolically stable in liver microsomes from rats, dogs, monkeys, and humans, with intrinsic clearance (CL_{int}) values <9 mL/min/kg. ABI-5366 was most stable in human liver microsomes, with a CL_{int} value of ~0.8 mL/min/kg (**Table 1**)

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 ± SD.
CL, clearance; hr, hour; IV, intravenous; PK, pharmacokinetic; PO, by mouth; SD, standard deviation.

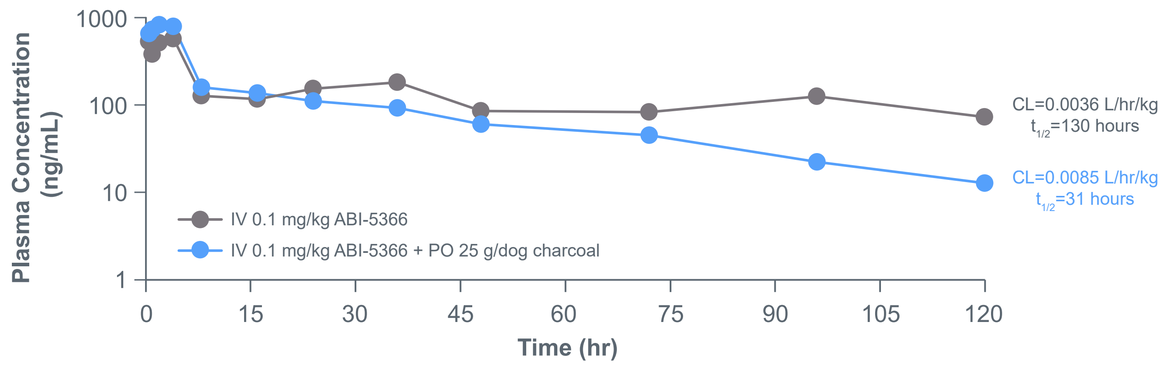
- Preclinical IV PK studies in dogs, rats, and monkeys demonstrated that ABI-5366 has a very low clearance (CL=0.002–0.02 L/hr/kg) and an extended half-life (20–71 hours; **Figure 3**)

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

	Ratio $AUC_{tissue}/AUC_{plasma}$	
Tissue	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 (see Abstract 02465, Session EF039)
  - In Phase 1b, once-weekly and once-monthly oral regimens are planned to be evaluated

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DISCLOSURES

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