

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

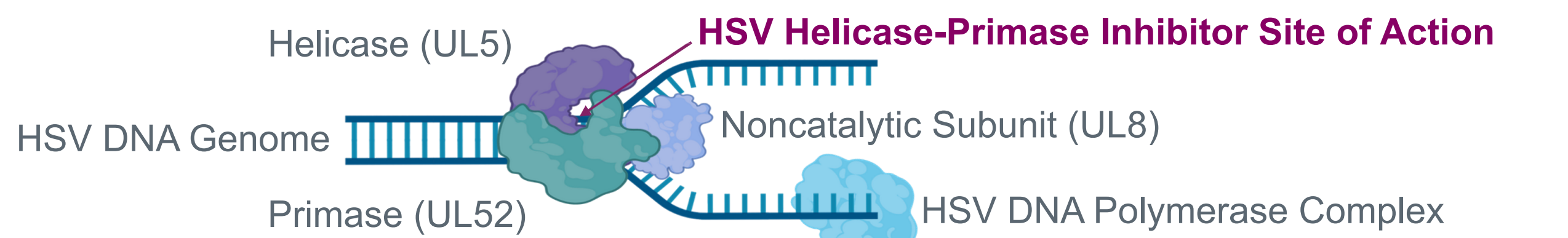
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Background

- 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

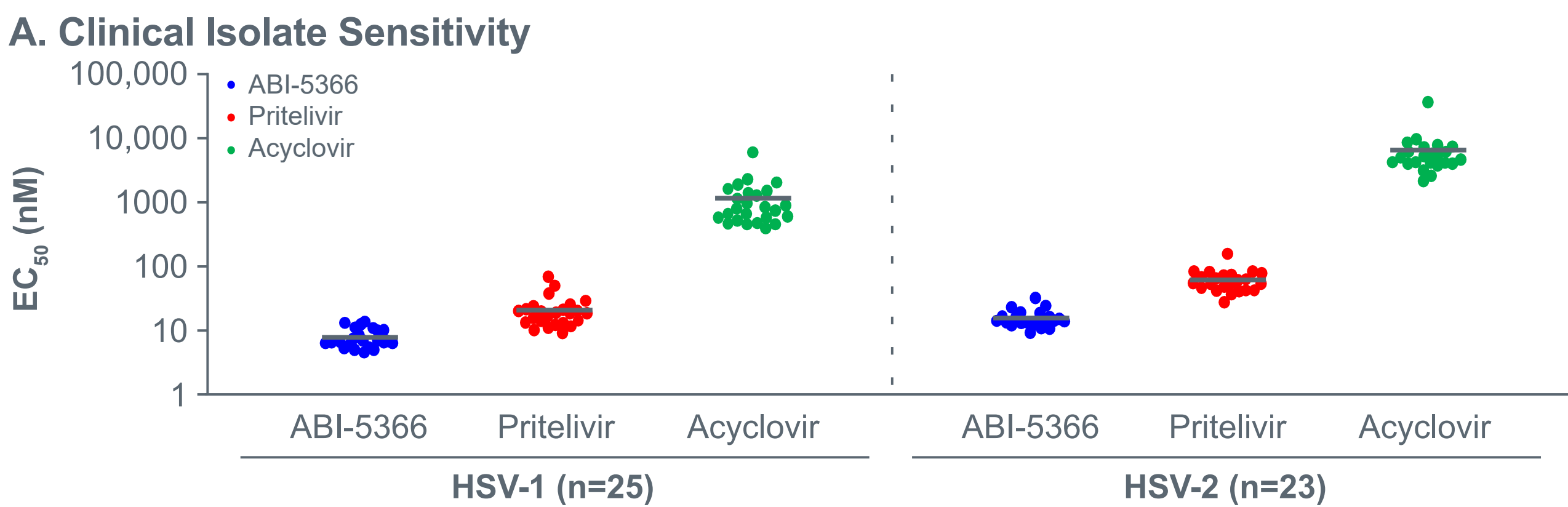
- To describe the preclinical potency and pharmacokinetic (PK) profile of ABI-5366, a novel HPI in development for the treatment of RGH

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 (EC₅₀) 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



Virus		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, EC₅₀ values are mean ± SD; each EC₅₀ represents ≥3 replicates.
^an=1.
EC₅₀, 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**)

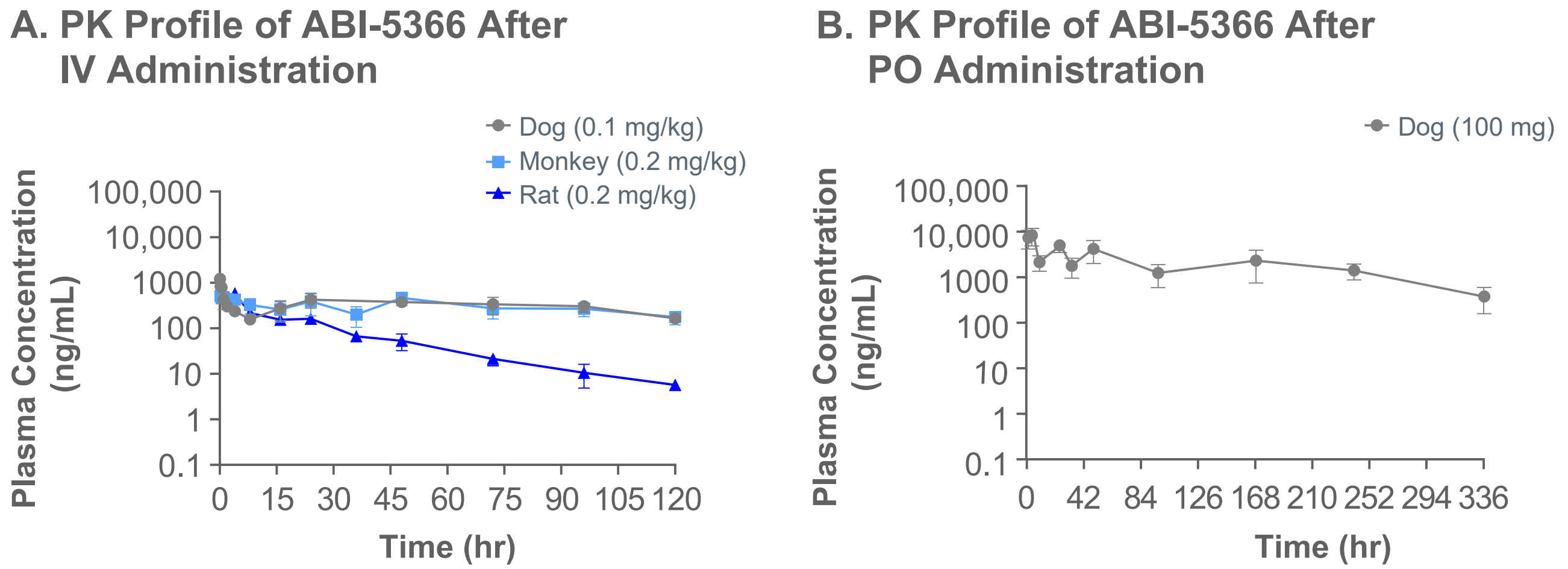
Table 1. ABI-5366 Is Metabolically Stable

	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



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.

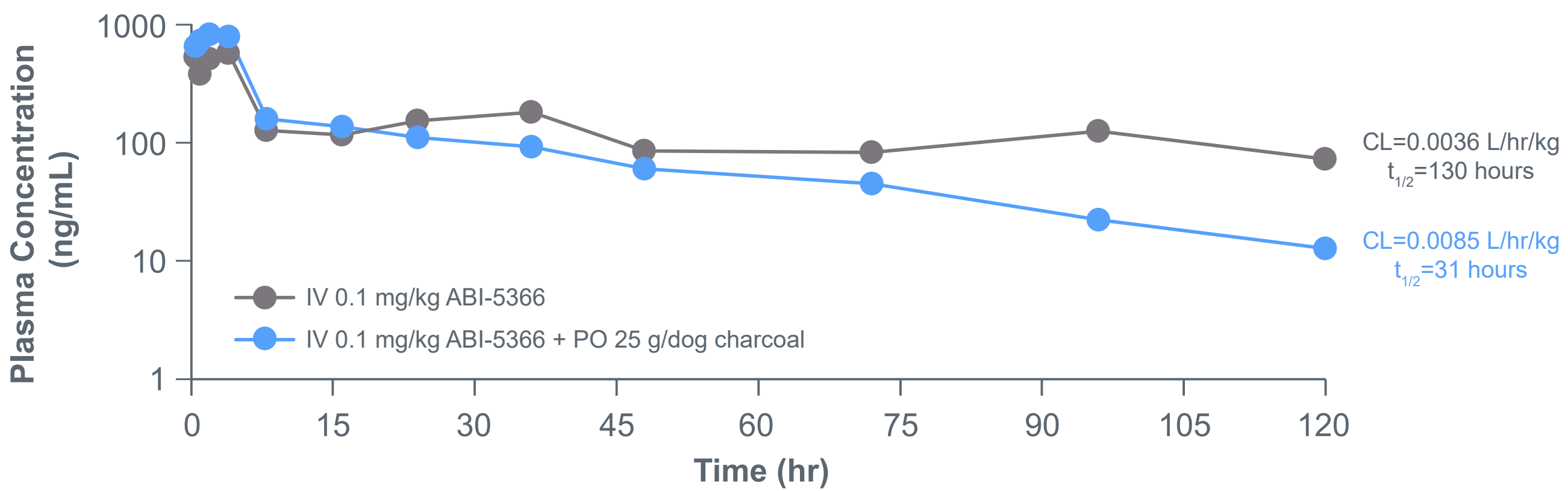
- Preclinical IV PK studies in dogs, rats, and monkeys demonstrated that ABI-5366 has a very low clearance (CL=0.002–0.02 L/hr/kg) and an extended half-life (20–71 hours; **Figure 3**)

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

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 (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.