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

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Presenter Disclosures

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

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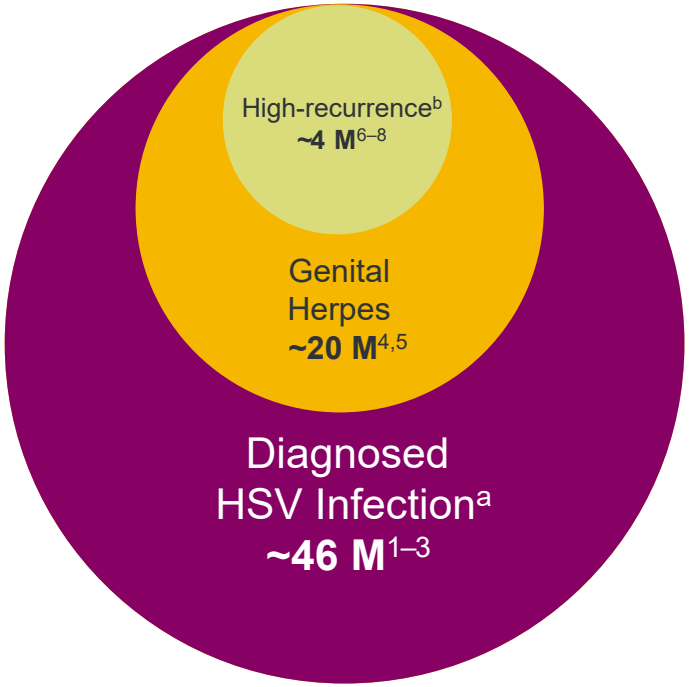
High-Recurrence Genital Herpes: The Need for Better Antivirals



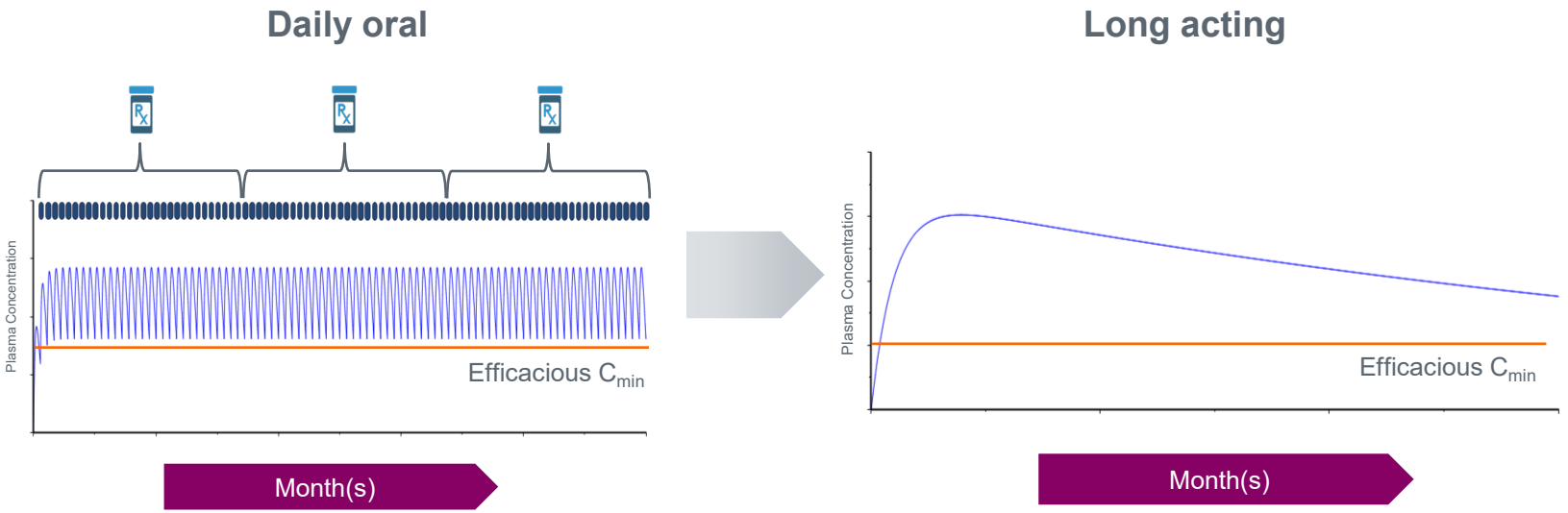
The existing treatment paradigm for high-recurrence genital herpes is inadequate

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 [c]Does not adjust for lost to follow-up, discontinuations due to adverse events, and consent withdrawn.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.

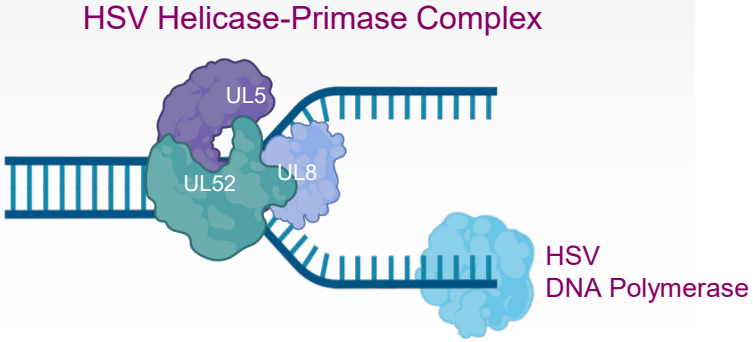
Long-Acting Therapy for Recurrent Genital Herpes



- 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

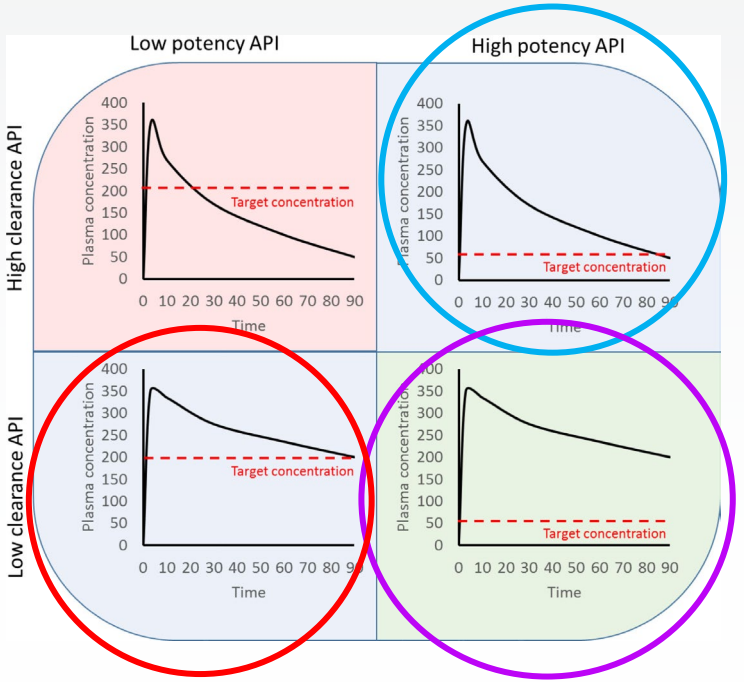
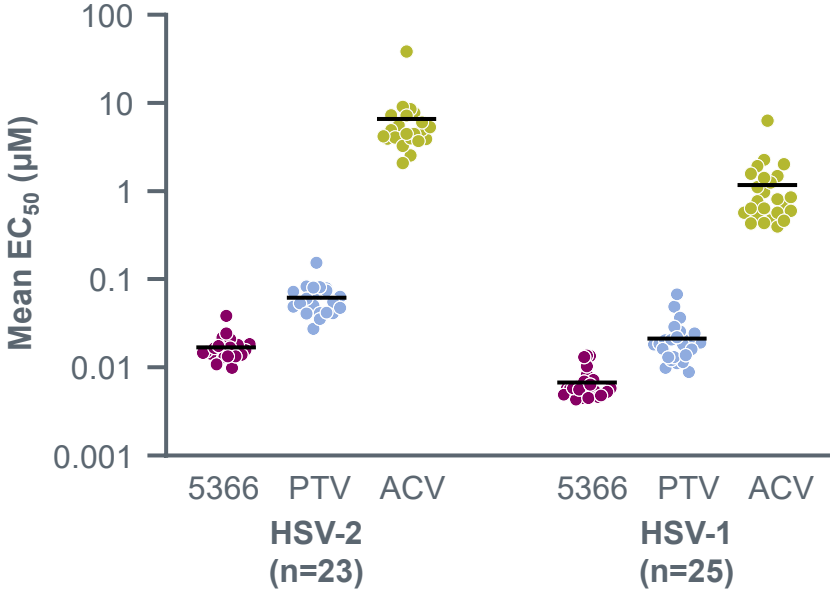


Figure from Owen, A, et al. *Adv Drug Deliv Rev*. 2016;103:144-56.

API, active pharmaceutical ingredient.

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

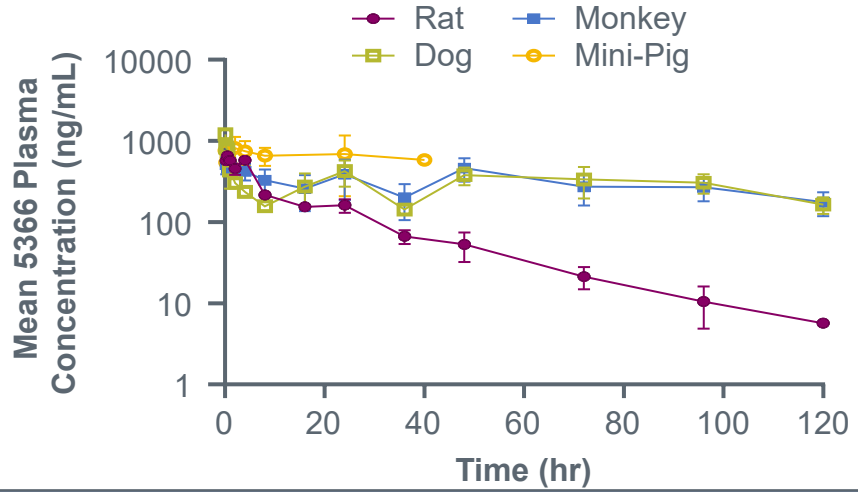
ABI-5366 Demonstrates Broad Antiviral Activity Against HSV-2 and HSV-1 Clinical Isolates



- 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

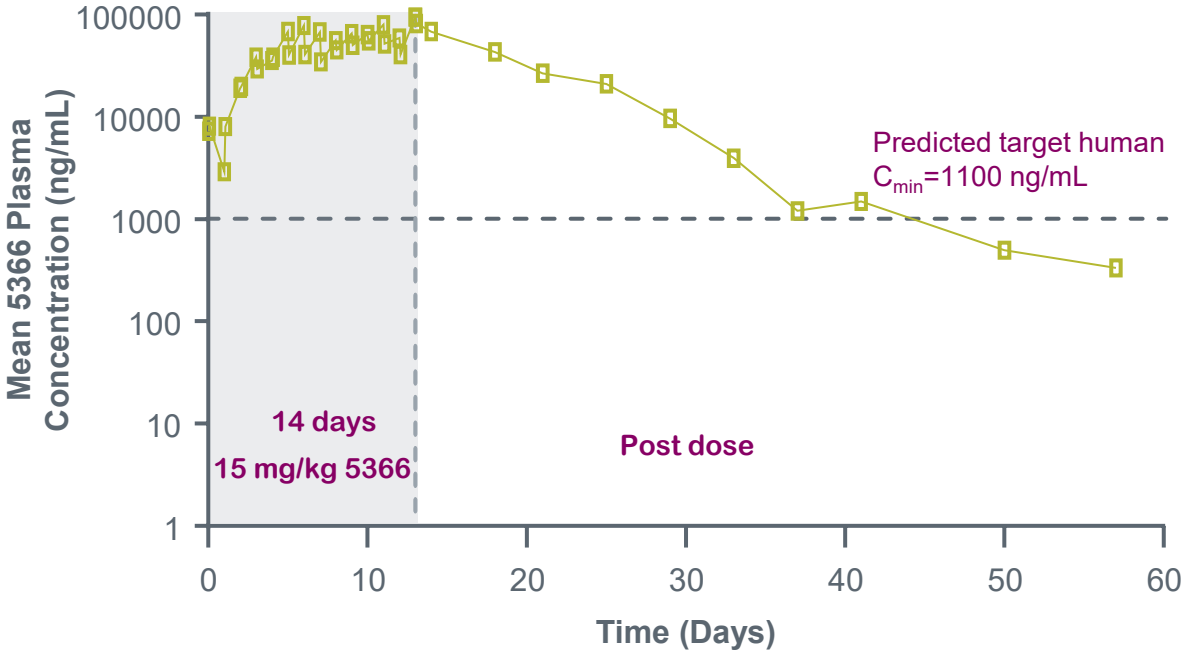


Parameter	ABI-5366				
Species	Rat	Dog	Monkey	Mini-Pig	Human
CL (IV, L/hr/kg)	0.02	0.0023	0.004	0.0018	0.00086[a,b]
Half-life (hr)	20	55	71	134	182[a]

- 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

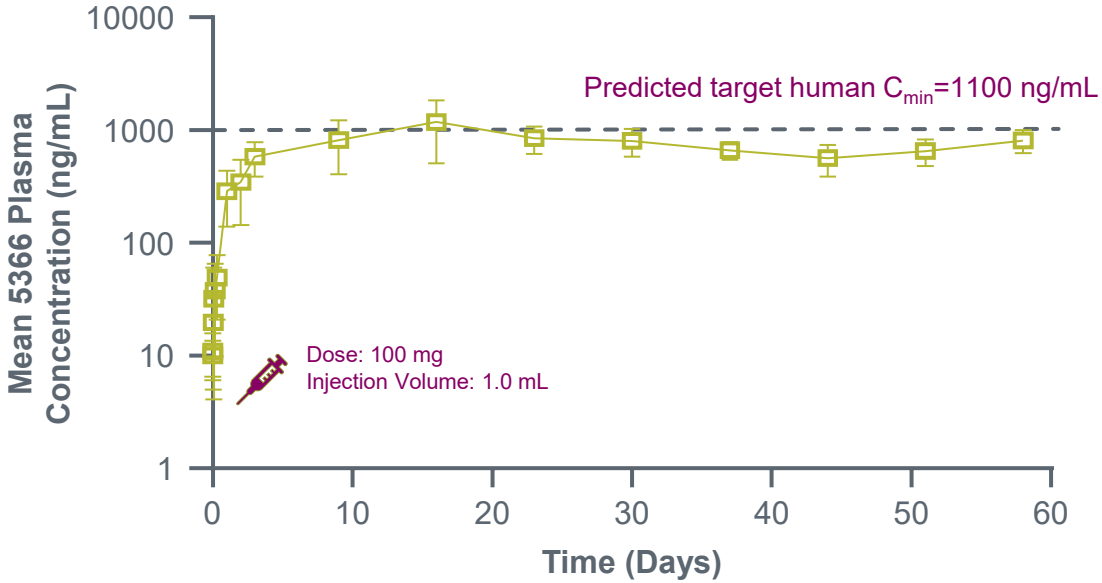
[a]Denotes predicted values using four species. [b]Calculated using an estimated human weight of 70 kg.

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



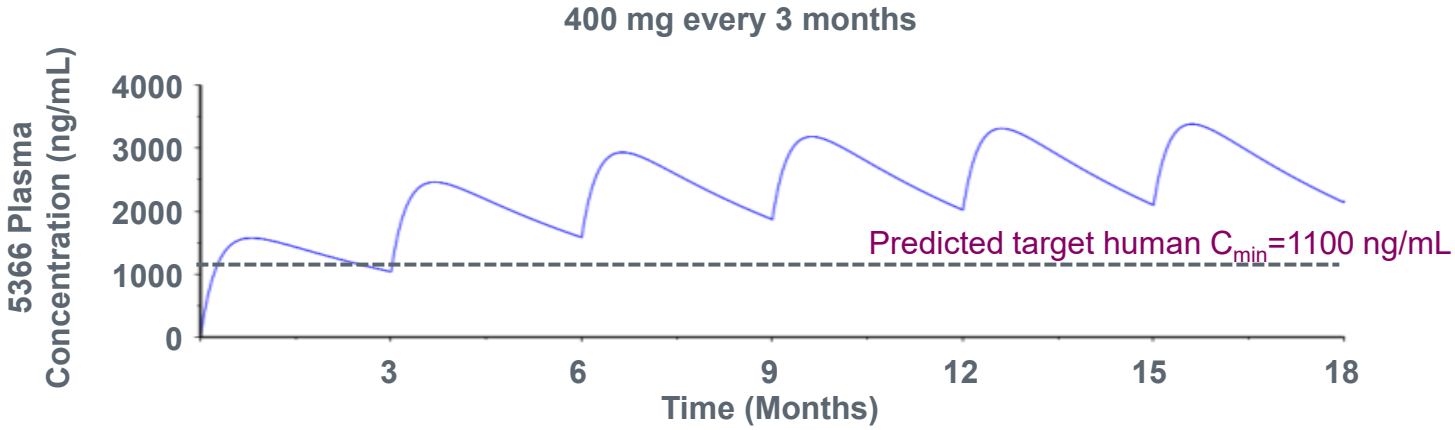
- The dog PK study achieved high sustained exposure to 40+ days
- ABI-5366 was well tolerated for the duration of the study

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

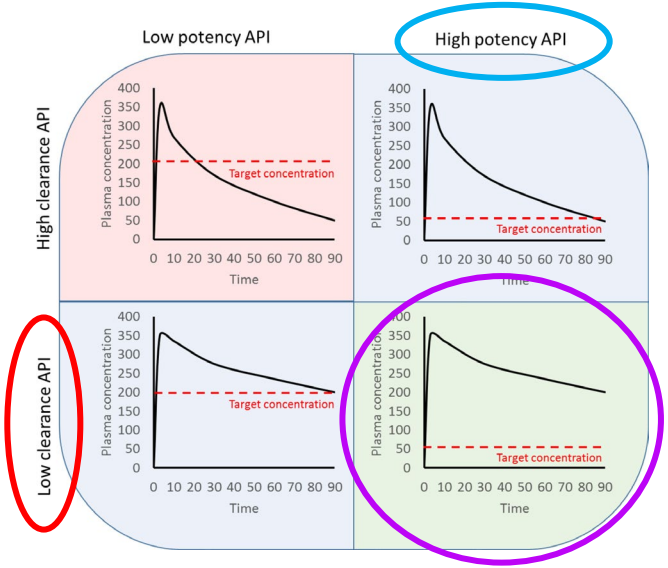


Figure from Owen, A, et al. *Adv Drug Deliv Rev*. 2016;103:144-56.

API, active pharmaceutical ingredient.

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