ABI-1179, a Novel, Orally Administered, Long-Acting HSV Helicase-Primase Inhibitor: Interim Analysis of Safety and Pharmacokinetic Data From a Phase 1a Study in Healthy Participants

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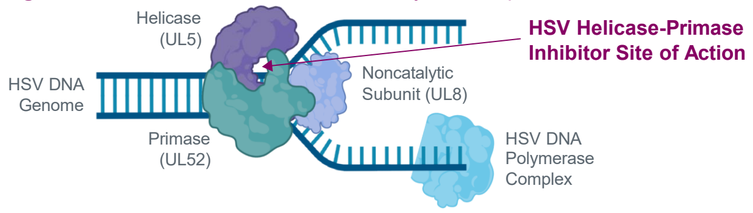
Background

- Herpes simplex virus type 2 (HSV-2), the primary cause of genital herpes (GH), is estimated to infect 491.5 million people aged 15 to 49 years worldwide[1,2]
- Recurrences associated with pain and psychological stress are frequent after an initial symptomatic outbreak, and suppressive therapy with nucleoside analogues is suboptimal[2-6]
- ABI-1179 is a potent, orally administered, investigational agent that interferes with the HSV helicase-primase enzyme complex (**Figure 1**) and is under development for suppression of recurrent GH[7]
- *In vitro*, ABI-1179 inhibits herpes simplex virus type 1 (HSV-1) and HSV-2 laboratory strains and clinical isolates with low nanomolar potency[7]
- Here, we report single-dose safety and pharmacokinetic (PK) data in healthy participants

Figure 1. The HSV Helicase-Primase Enzyme Complex



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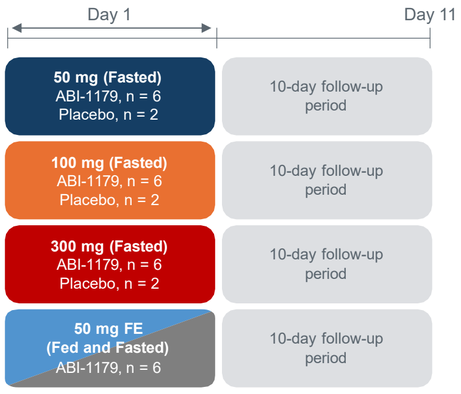
HSV, herpes simplex virus; UL5, helicase; UL8, noncatalytic subunit; UL52, primase.

Objective

- To report the safety and PK data in healthy participants following single-dose administration from a randomized, blinded, Phase 1a study assessing ABI-1179 (NCT06698575)

Figure 2. Study Design: Phase 1a Single-Ascending Dose



Key inclusion criteria
- Male or nonpregnant female, aged ≥18 to ≤60 years
- BMI ≥18.0 kg/m² to <32.0 kg/m²
- In good health, as determined by the investigator

Key exclusion criteria
- Current infection with HIV, HBV, HCV, or acute HAV
- Clinically significant medical, behavioral, or mental condition, or pharmacologic or surgical treatment that, in the opinion of the investigator or the sponsor, may interfere with safety assessments, or the absorption, distribution, and/or elimination of the study drug, or make the participant unsuitable for study participation

For the purposes of this analysis, results from placebo recipients have been pooled across cohorts.
BMI, body mass index; FE, food effect; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Methods

- The Phase 1a part of this study planned to enroll up to 5 cohorts (A1–A5) evaluating ascending single doses of ABI-1179 or placebo in the fasted state, in addition to 1 cohort (A7) evaluating the potential for a food effect on ABI-1179 safety and PK
  - Cohorts A1 through A5 were to each enroll 8 participants: 6 assigned to ABI-1179 and 2 assigned to placebo
  - The "Food Effect" cohort (A7) was to enroll 6 participants in a 2-period crossover design. Each participant received a single dose of ABI-1179 both with and without consumption of a high-fat meal in a randomized manner with a 28-day washout between the 2 periods
- After administration of the assigned single dose of the study drug, participants were to be followed for up to 10 days
- Safety assessments included physical examinations, vital sign monitoring, adverse event (AEs) monitoring, lab parameter measurements, and electrocardiogram testing
- ABI-1179 PK was characterized throughout
- The presented data summarize the 4 completed cohorts assessing 50-mg (fed and fasted), 100-mg, and 300-mg single doses of ABI-1179 (**Figure 2**)

Results

Table 1. Baseline Demographics

Characteristics	ABI-1179 50 mg (n = 6)	ABI-1179 100 mg (n = 6)	ABI-1179 300 mg (n = 6)	ABI-1179 50 mg FE, Fed and Fasted (n = 6)	Placebo (n = 6)
Age, years, mean (SD)	35.2 (6.0)	37.2 (11.8)	32.0 (7.8)	48.0 (12.7)	33.3 (13.5)
Sex, n (%)					
Male	4 (66.7)	5 (83.3)	6 (100)	6 (100)	5 (83.3)
Female	2 (33.3)	1 (16.7)	0	0	1 (16.7)
Race, n (%)					
White	4 (66.7)	5 (83.3)[a]	4 (66.7)[b]	4 (66.7)	4 (66.7)
Black or African American	0	0	0	0	0
American Indian or Alaska Native	0	0	1 (16.7)	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	2 (33.3)
Asian	0	0	3 (50.0)[b]	2 (33.3)	0
Other[c]	2 (33.3)	2 (33.3)[a]	0	0	0
BMI, kg/m², mean (SD)	26.0 (1.8)	26.5 (3.1)	25.9 (2.8)	24.8 (2.2)	22.6 (2.8)

[a]One participant reported race as White and Other. [b]Two participants reported race as White and Asian. [c]Other includes Maori, Chilean-Latin American, Fijian Indian, and Latino.
BMI, body mass index; FE, food effect; SD, standard deviation.

- Overall, demographics were comparable between ABI-1179 dose levels and placebo (**Table 1**)
- Most healthy participants were male (20/24, 83.3%) and White (17/24, 70.8%), with age and BMI ranging from 32 to 37 years and 22.6 to 26.5 kg/m², respectively

Table 2. TEAEs Reported in >1 Participant Overall (Safety Population)

Adverse events, n (%)	ABI-1179 50 mg (n = 6)	ABI-1179 100 mg (n = 6)	ABI-1179 300 mg (n = 6)	ABI-1179 50 mg FE, Fed (n = 6)	ABI-1179 50 mg FE, Fasted (n = 6)	Placebo (n = 6)
Any TEAE	4 (66.7)	4 (66.7)	3 (50.0)	1 (16.7)	3 (50.0)	2 (33.3)
TEAE by maximum toxicity grade						
Grade 1	3 (50.0)	4 (66.7)	3 (50.0)	1 (16.7)	3 (50.0)	2 (33.3)
Grade 2[a]	1 (16.7)	0	0	0	0	0
TEAE by preferred term						
Contact dermatitis	1 (16.7)	0	2 (33.3)	0	0	1 (16.7)
Fatigue	1 (16.7)	0	0	0	0	1 (16.7)
Headache	0	2 (33.3)	0	1 (16.7)	1 (16.7)	0
Rash	0	1 (16.7)	1 (16.7)	0	1 (16.7)[b]	
Nasopharyngitis	0	0	0	0	1 (16.7)	0
Arthropod sting	1 (16.7)	0	0	0	0	0
TEAE related to ABI-1179/placebo	0	0	0	0	0	0
TEAE leading to study termination	0	0	0	0	0	0
Serious TEAEs	0	0	0	0	0	0
Death	0	0	0	0	0	0

[a]Arthropod sting occurred in a single participant and was the only Grade 2 adverse event reported. [b]Rash from adhesive bandage, right antecubital fossa.
FE, food effect; TEAE, treatment-emergent adverse event.

- After 10 days of follow-up, ABI-1179 was well tolerated, with no Grade >2 treatment-emergent AEs (TEAEs), serious TEAEs, TEAEs leading to study discontinuation, or deaths reported in any cohort (**Table 2**)
- The most frequently reported TEAEs occurring in more than one participant were contact dermatitis, fatigue, headache, and rash
- An unrelated Grade 2 TEAE of an arthropod sting was reported in a single participant receiving 50 mg ABI-1179
- No TEAEs considered related to ABI-1179 or placebo were observed in any participant (**Table 2**)

Table 3. Laboratory Abnormalities Reported in >1 Participant Overall (Safety Population)

Laboratory abnormalities, n (%)	ABI-1179 50 mg (n = 6)	ABI-1179 100 mg (n = 6)	ABI-1179 300 mg (n = 6)	ABI-1179 50 mg FE, Fed (n = 6)	ABI-1179 50 mg FE, Fasted (n = 6)	Placebo (n = 6)
Participants with postbaseline abnormalities						
Grade 1	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	1 (16.7)
Grade 2	0	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)
Grade 3	0	0	0	1 (16.7)	0	0
Laboratory abnormality						
Cholesterol (increased)						
Grade 1	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0
Grade 2	0	1 (16.7)	1 (16.7)	1 (16.7)	0	0
Amylase (increased)						
Grade 1	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)
Grade 2	0	0	0	1 (16.7)	0	
Lipase (increased)						
Grade 1	0	0	1 (16.7)	0	0	0
Grade 2	0	0	0	0	1 (16.7)	1 (16.7)
Grade 3	0	0	0	1 (16.7)	0	0
Triglycerides (increased)						
Grade 1	0	1 (16.7)	1 (16.7)	1 (16.7)	0	0

FE, food effect.

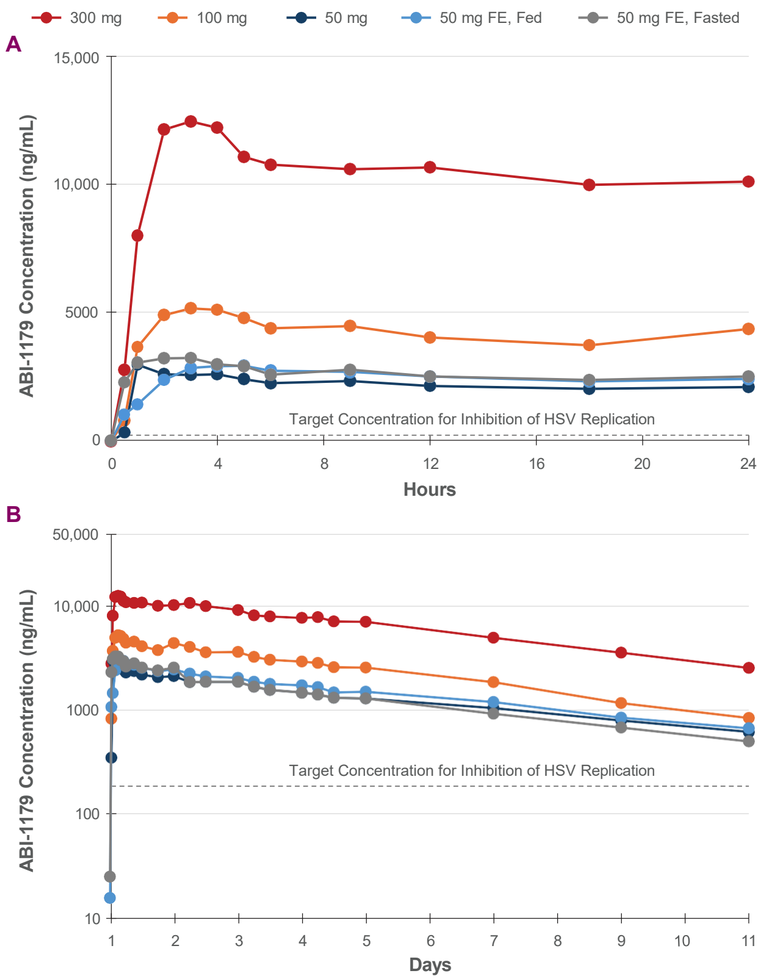
- All treatment-emergent laboratory abnormalities were either Grade 1 or Grade 2 (**Table 3**)
- The most commonly reported laboratory abnormality in participants receiving ABI-1179 was increased serum cholesterol. There did not appear to be a dose relationship in either the frequency or severity of cholesterol increases, which occurred to similar extents across ABI-1179 recipients
- Grade 1 or 2 elevations in serum amylase and lipase were observed at similar severities and frequencies between ABI-1179 and placebo recipients. A single, self-limiting Grade 3 elevation in serum lipase was observed in a participant receiving ABI-1179 in a fed state
- A single participant receiving 300 mg ABI-1179 reported a Grade 2 elevation in alanine aminotransferase (maximum 136 U/L at Day 5) and a Grade 1 elevation in aspartate aminotransferase (maximum 75 U/L at Day 5) without changes in bilirubin or albumin. Both parameters returned to baseline levels during follow-up. No other ABI-1179 recipients at any dose level experienced graded increases in liver enzymes

Table 4. Pharmacokinetics of ABI-1179

Pharmacokinetic parameter	ABI-1179 50 mg (n = 6)	ABI-1179 100 mg (n = 6)	ABI-1179 300 mg (n = 6)	ABI-1179 50 mg FE, Fed (n = 6)	ABI-1179 50 mg FE, Fasted (n = 6)
T_{max}, hours, median (range)	1.0 (1.0–4.0)	3.5 (3.0–5.0)	3.5 (3.0–36.0)	5.0 (0.5–5.0)	1.5 (0.5–3.0)
$T_{1/2}$, hours, mean (CV%)	127.0 (48.3)[a]	88.1 (26.6)	102.4 (14.5)	110 (13.9)	98.5 (22.8)
C_{max}, ng/mL, mean (CV%)	3037 (19.5)	5377 (16.0)	13,450 (27.3)	3193 (25.0)	3797 (16.5)
AUC_{0-24}, hour·ng/mL, mean (CV%)	52,800 (13.4)	99,630 (12.5)	247,600 (24.9)	59,330 (16.7)	63,010 (12.9)
AUC_{last}, hour·ng/mL, mean (CV%)	302,200 (23.7)	555,000 (9.5)	1,491,000 (16.6)	268,500 (43.6)	254,400 (22.8)
C_{Day7}, ng/mL, mean (CV%)	1038 (35.5)	1840 (24.7)	4920 (17.0)	1189 (37.6)[b]	915.0 (17.5)[b]

[a]n = 5. [b]n = 3.
AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours postdose; AUC_{last}, area under the concentration-time curve from the time of dosing to the time of last measurable concentration; C_{Day7}, ABI-1179 concentration on Day 7; C_{max}, maximum plasma concentration; CV, coefficient of variation; FE, food effect; $T_{1/2}$, apparent terminal elimination half-life; T_{max}, time when C_{max} is observed.

Figure 3. Mean Plasma Concentrations vs Time Profile by Dose Level Following Single-Dose Administration



In panel A, the y-axis is on a linear scale. In panel B, the y-axis is on a semilogarithmic scale.
FE, food effect; HSV, herpes simplex virus.

- ABI-1179 was rapidly absorbed, with median time to maximum concentration of approximately 1 to 3.5 hours in the fasted state (**Figure 3**)
- Increases in ABI-1179 exposure appeared to be dose proportional in the 50-mg to 100-mg dose range and slightly less than dose proportional between 100-mg and 300-mg doses (**Table 4**; **Figure 3**)
- Consumption of a high-fat meal did not appear to change ABI-1179 exposures at the 50-mg dose level (**Table 4**; **Figure 3**)
- Mean elimination half-life ranged from 88.1 to 127 hours and is supportive of once-weekly dosing regimens (**Table 4**)
- Based on these data, trough levels following weekly dosing are projected to be in multiple-fold excess of protein-adjusted half-maximal effective concentration (EC_{50}) values for HSV replication at all dose levels

Conclusions

- ABI-1179, a novel, oral, long-acting HSV helicase-primase inhibitor, was well tolerated when administered orally as a single dose up to 300 mg
- Consumption of a high-fat meal does not appear to change the PK exposure of ABI-1179 at a 50 mg dose
- Plasma trough concentrations following weekly dosing are projected to be in multiple-fold excess of the *in vitro* plasma-adjusted EC_{50} values for the inhibition of HSV replication
- The data indicate that ABI-1179 has the potential to provide potent suppression of HSV replication with once-weekly dosing
- Part B of the study will assess the safety, PK, and preliminary antiviral activity of ABI-1179 following multiple-dose administration in patients seropositive for HSV-2 with recurrent GH

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DISCLOSURES

EJG is a member of scientific advisory boards for Aligos Therapeutics, Assembly Biosciences, Inc., AusperBio, Gilead Sciences, GSK, Janssen, Precision BioSciences, Roche, Surrozen, Tune Therapeutics, Vir Biotechnology, and Virion Therapeutics and and has given sponsored lectures for AbbVie and Roche Diagnostics. **CS** is an employee and a stockholder of New Zealand Clinical Research. **GW**, **JL**, **SJK**, **KMK**, **AG**, and **KZ** are employees and stockholders of Assembly Biosciences, Inc.

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