ABI-5366, a Novel, Oral, Long-Acting Herpes Simplex Virus Helicase-Primase Inhibitor: Interim Safety and Pharmacokinetic Results From a Phase 1a Study in Healthy Participants

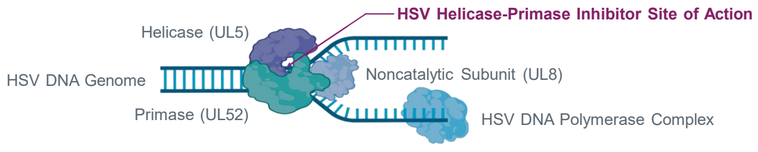
Edward J Gane[1], Christian Schwabe[2], Grace Wang[3], Jieming Liu[3], Steven J Knox[3], Kathryn M Kitrinos[3], Anuj Gaggar[3], Katie Zomorodi[3]

[1]University of Auckland, Auckland, New Zealand; [2]New Zealand Clinical Research, Auckland, New Zealand; [3]Assembly Biosciences, Inc., South San Francisco, CA, USA

Background

- Worldwide, an estimated 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]
- Nucleoside analogue therapy, the current standard of care, is suboptimal with frequent disease recurrence[3,4] resulting in pain, psychological stress, and increased risk of HIV-1 infection.[5,6] There is an unmet medical need for novel therapeutic agents that are safe and provide improved efficacy
- The HSV helicase-primase enzyme complex plays an essential role in HSV replication (**Figure 1**)
- ABI-5366 is a novel, orally administered, long-acting inhibitor of the HSV helicase-primase enzyme complex
- In vitro, ABI-5366 inhibits HSV-1 and HSV-2 laboratory strains and clinical isolates with low nanomolar potency[7]
- ABI-5366 is currently in development for suppression of recurrent genital herpes
- 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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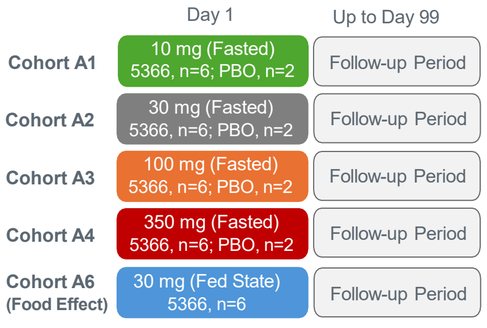
Objective

- To report the safety and PK data following single-dose administration of ABI-5366 in healthy participants from a randomized, blinded, Phase 1a study (NCT06385327)

Methods

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



Key inclusion criteria
- Male or nonpregnant female, aged 18–60 years
- BMI ≥18.0 kg/m^2 and <32.0 kg/m^2
- In good health, as determined by the investigator

Key exclusion criteria
- Current infection with HIV, HBV, HCV, acute HAV, or acute HEV
- 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

Note: For the purposes of this analysis, results from participants receiving placebo have been pooled across cohorts.
BMI, body mass index; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; PBO, placebo.

- Phase 1a planned to enroll up to 5 cohorts (A1–A5) evaluating single doses of ABI-5366 or placebo in a fasted state. Additionally, Cohort A6 was to evaluate the potential for a food effect on ABI-5366 safety and PK (**Figure 2**)
  - Cohorts A1-A5 were to each enroll 8 participants, (6, ABI-5366 and 2 placebo)
  - Cohort, A6, was to enroll 6 participants, all receiving 30 mg ABI-5366 following consumption of a high-fat meal
- After single-dose administration participants were to be followed up to Day 99, as determined by the observed half-life of ABI-5366
- Safety assessments included physical exams, vital signs, adverse events (AEs), laboratory parameters, and 12-lead electrocardiograms
- ABI-5366 PK was characterized throughout the study
- The presented data summarize completed cohorts assessing 10 mg, 30 mg (fasted and with a high-fat meal), 100 mg, and 350 mg doses of ABI-5366 with pooled placebo data

Results

Table 1. Baseline Demographic Information

Characteristics	ABI-5366 10 mg (n=6)	ABI-5366 30 mg (n=6)	ABI-5366 100 mg (n=6)	ABI-5366 350 mg (n=6)	ABI-5366 30 mg FE (n=6)	Placebo (n=8)
Age, years	35 (12.4)	34 (12.5)	37 (11.5)	26 (4.9)	36 (10.4)	40 (12.7)
Sex, n (%)						
Male	5 (83.3)	5 (83.3)	3 (50.0)	4 (66.7)	6 (100)	7 (87.5)
Female	1 (16.7)	1 (16.7)	3 (50.0)	2 (33.3)	0	1 (12.5)
Race, n (%)						
White	3 (50.0)[a]	3 (50.0)	2 (33.3)	4 (66.7)	4 (66.7)	4 (50.0)
Black or African American	1 (16.7)[b]	0	0	0	0	1 (12.5)
Native Hawaiian or Other Pacific Islander	1 (16.7)[a]	0	1 (16.7)	0	0	1 (12.5)
Asian	1 (16.7)	1 (16.7)	3 (50.0)	1 (16.7)	2 (33.3)	2 (25.0)
Other	2 (33.3)[b]	2 (33.3)	0	1 (16.7)	0	0
BMI, kg/m^2	23.9 (4.34)	25.0 (2.61)	26.1 (3.65)	23.5 (3.61)	25.2 (4.22)	25.8 (2.31)

[a]One participant reported race as "White" and "Native Hawaiian or Other Pacific Islander"; [b]One participant reported race as "Black or African American" and "Other." Data shown are mean (SD) unless otherwise indicated. BMI, body mass index; FE, food effect; SD, standard deviation.

Results (continued)

- Overall, demographics were comparable between ABI-5366 dose levels and placebo (**Table 1**)
- Most healthy participants were male (30/38, 78.9%) and White (20/38, 52.6%), with age and body mass index ranging from 19 to 59 years and 19.3 to 31.6 kg/m^2, respectively (data not presented)

Table 2. Treatment-Emergent Adverse Events (Safety Population)

Reported in >5% of Participants Overall

Adverse Events	ABI-5366 10 mg (n=6)	ABI-5366 30 mg (n=6)	ABI-5366 100 mg (n=6)	ABI-5366 350 mg (n=6)	ABI-5366 30 mg FE (n=6)	Placebo (n=8)
Any TEAE	5 (83.3)	4 (66.7)	5 (83.3)	4 (66.7)	5 (83.3)	7 (87.5)
TEAE by maximum toxicity grade						
Grade 1	4 (66.7)	2 (33.3)	4 (66.7)	3 (50.0)	5 (83.3)	6 (75.0)
Grade 2	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	0	1 (12.5)
Grade 3	0	0	0	0	0	0
TEAE by preferred term						
Dermatitis contact	3 (50.0)	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	2 (25.0)
Headache	1 (16.7)	1 (16.7)	0	1 (16.7)	0	2 (25.0)
Vessel puncture site bruise	0	0	1 (16.7)	0	1 (16.7)	3 (37.5)
Influenza-like illness	2 (33.3)	0	0	1 (16.7)	0	1 (12.5)
Upper respiratory tract infection	1 (16.7)	1 (16.7)	0	0	1 (16.7)	1 (12.5)
Back pain	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0
Catheter site pain	0	0	1 (16.7)	0	0	2 (25.0)
TEAE related to ABI-5366/placebo	0	0	0	0	0	0
TEAE leading to study termination	0	0	0	0	0	0
TESAE	0	0	0	0	0	0

Data shown are n (%) unless otherwise indicated.
FE, food effect; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

- After a median of 70 days of follow-up, ABI-5366 was well tolerated, with no Grade >2 treatment-emergent AEs (TEAEs), treatment-emergent serious AEs, TEAEs leading to study discontinuation, or deaths reported in any cohort (**Table 2**)
- Grade 2 TEAEs were reported in 5 participants who received ABI-5366: 10 mg, influenza-like illness; 30 mg, abdominal pain, gout; 100 mg, oropharyngeal pain; 350 mg, upper respiratory tract infection. A Grade 2 TEAE of upper respiratory tract infection was also reported in a participant receiving placebo
- There were no apparent dose-response relationships in the frequency or severity of TEAEs. No TEAEs considered related to ABI-5366 or placebo were observed in any participant (**Table 2**)

Table 3. Laboratory Abnormalities (Safety Population)

Reported in >5% of Participants Overall

Laboratory Abnormalities	ABI-5366 10 mg (n=6)	ABI-5366 30 mg (n=6)	ABI-5366 100 mg (n=6)	ABI-5366 350 mg (n=6)	ABI-5366 30 mg FE (n=6)	Placebo (n=8)
Participants with postbaseline abnormalities						
Grade 1	3 (50.0)	2 (33.3)	4 (66.7)	2 (33.3)	1 (16.7)	5 (62.5)
Grade 2	0	2 (33.3)	0	1 (16.7)	2 (33.3)	3 (37.5)
Grade 3	1 (16.7)	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Laboratory abnormality						
Cholesterol (increased)						
Grade 1	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (12.5)
Grade 2	0	0	0	0	0	1 (12.5)
Triglycerides (increased)						
Grade 1	0	0	1 (16.7)	0	1 (16.7)	3 (37.5)
Grade 2	0	1 (16.7)	0	0	0	0
Sodium (decreased)						
Grade 1	1 (16.7)	0	0	1 (16.7)	0	1 (12.5)
ALT (increased)						
Grade 1	1 (16.7)	1 (16.7)	0	0	0	0

Data shown are n (%) unless otherwise indicated.
ALT, alanine aminotransferase; FE, food effect.

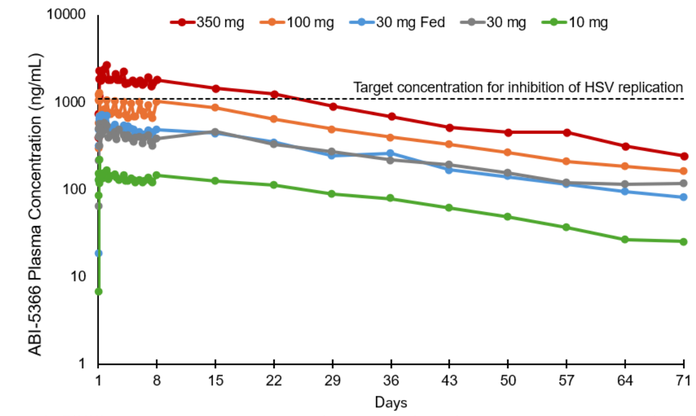
- There were no apparent dose-response relationships in the frequency or severity of treatment-emergent laboratory abnormalities.
- All treatment-emergent laboratory abnormalities were either Grade 1 or Grade 2 (**Table 3**). The exception was a single Grade 3 creatine kinase elevation in a participant receiving 10 mg ABI-5366. At Day 36, this participant had a transient Grade 3 creatine kinase elevation and Grade 1 alanine aminotransferase (ALT) elevation and was confirmed to have an increased exercise level. These elevations were not observed at any other visits
- The most common graded laboratory abnormality reported in participants receiving ABI-5366 and placebo was increases in serum cholesterol. Cholesterol increases occurred to a similar extent in participants receiving placebo
- Two Grade 1 elevations in ALT were observed in participants receiving ABI-5366, one at each of the 10 mg and 30 mg dose levels. These elevations were not considered related to ABI-5366, with further details on the elevations described below:
  - One participant who received a single dose of 10 mg ABI-5366 had a transient Grade 1 ALT increase along with a Grade 3 creatine kinase elevation associated with exercise at Day 36
  - Another participant who received a single dose of 30 mg ABI-5366 had slightly elevated ALT (47 U/L) at baseline, which continued to fluctuate during the study

Table 4. Pharmacokinetic Profile of ABI-5366

Pharmacokinetic Parameters	ABI-5366 10 mg (n=6)	ABI-5366 30 mg (n=6)	ABI-5366 100 mg (n=6)	ABI-5366 350 mg (n=6)	ABI-5366 30 mg FE (n=6)
T_{max}, hours, median (range)	4.0 (2.0–9.0)	18.0 (3.0–60.0)	4.0 (3.0–96.0)	4.0 (4.0–24.0)	5.5 (4.0–12.0)
$t_{1/2}$, hours	491.4 (36.5)	608.3 (28.6)	531.3 (25.5)	418.3 (32.4)	525.9 (30.5)
C_{max}, ng/mL	224.5 (52.4)	645.5 (44.8)	1393 (34.6)	2960 (32.9)	793.2 (41.4)
AUC_{24}, h·ng/mL	3444 (44.6)	11,150 (40.8)	19,660 (40.0)	48,690 (36.2)	13,510 (47.7)
AUC_{last},[a] h·ng/mL	134,000 (31.3)	419,200 (43.7)	805,300 (19.8)	1,582,000 (35.8)	456,600 (26.5)
C_{168h}, ng/mL	146.0 (29)	383.7 (35)	1014 (22)	1806 (53)	485.3 (38)

All values are mean (CV%) unless otherwise stated.
AUC_{24}, area under the curve from time 0 to 24 hours; AUC_{last}, area under the curve from time 0 to last measured; C_{168h}, concentration at 168 hours (Day 8) postdose; C_{max}, maximum concentration; CV, coefficient of variation; FE, food effect; $t_{1/2}$, terminal half-life; T_{max}, time to reach C_{max}

Figure 3. Mean Plasma Concentrations vs Time Following Single Doses of ABI-5366 (Semi-Log Scale)



- ABI-5366 was rapidly absorbed, with median time to maximum concentration of 4.0 to 18.0 hours (**Table 4**)
- Increases in ABI-5366 exposure appeared to be dose proportional in the 10 mg to 30 mg dose range and slightly less than dose proportional at the 100 mg and 350 mg dose levels (**Table 4**)
- Consumption of a high-fat meal did not appear to change ABI-5366 exposures at the 30 mg dose level
- The PK profile suggests intestinal reabsorption with a mean elimination half-life estimate of 20 days supportive of both once-weekly and once-monthly dosing regimens (**Table 4, Figure 3**)
- Based on these data, plasma trough concentrations following multiple dosing are projected to be in multiple-fold excess of the target efficacious concentration for the inhibition of HSV replication

Conclusions

- ABI-5366, a novel, oral, long-acting HSV helicase-primase inhibitor, was safe and well tolerated when administered orally as single doses up to 350 mg
- Plasma trough concentrations following multiple dosing are projected to be in multiple-fold excess of the target efficacious concentration for the inhibition of HSV replication
- The data indicate that ABI-5366 has the potential to provide potent suppression of HSV replication with weekly or monthly dosing
- The Phase 1b part of the study assessing multiple-dose administration in patients seropositive for HSV-2 with recurrent genital herpes is ongoing

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ACKNOWLEDGMENTS

We express our gratitude to all the patients, investigators, and site staff who participated in the study. This study was sponsored by Assembly Biosciences, Inc. Writing and editorial support were provided by Alisa Cario, PhD, of Red Nucleus, and were funded by Assembly Biosciences, Inc.

DISCLOSURES

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

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Presented at the STI & HIV 2025 World Congress; Montreal, Canada; July 26–30, 2025