P0220

Virologic Analyses Following Treatment With ABI-5366, a Novel, Oral, Long-Acting HSV Helicase-Primase Inhibitor in Participants Seropositive for HSV-2 With Recurrent Genital Herpes

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Conclusions

- Administration of ABI-5366 350 mg in both a weekly dosing regimen and a 1-month alternative regimen significantly reduced the rates of herpes simplex virus type 2 shedding in the genital area and genital lesions, as well as mean herpes simplex virus 2 DNA levels
- There were no significant differences in virologic responses or lesion occurrence across key subgroups, including those defined by frequency of genital lesion occurrence, use of suppressive therapy at screening, and seropositivity for both herpes simplex virus type 1 and herpes simplex virus type 2 or herpes simplex virus type 2 only

Plain Language Summary

- Herpes simplex virus type 2 is a common virus that can cause repeated genital herpes outbreaks
- Current medicines must be taken daily and do not fully prevent genital herpes outbreaks for many people
- ABI-5366 is a new medicine being developed to help prevent outbreaks, with dosing that may be as infrequent as once a week or once a month
- In this study, people with herpes simplex virus type 2 and recurrent genital herpes were given ABI-5366 or placebo (a pill with no medicine) for 29 days
- People taking 350 mg of ABI-5366 as a weekly dose or as a 1-month alternative had much less virus detected on genital swabs, fewer genital lesions, and lower overall virus levels compared with those taking placebo

Introduction

- Globally, approximately 520 million people aged 15 to 49 years have herpes simplex virus type 2 (HSV-2), which is the leading cause of recurrent genital herpes (RGH)[1,2]
- Standard-of-care, once-daily suppressive treatment with nucleoside analogues is often suboptimal, with many individuals continuing to experience breakthrough recurrences[3,4]
- ABI-5366[a] is an oral, long-acting inhibitor of the herpes simplex virus (HSV) helicase-primase complex that is currently under development as a chronic suppressive therapy for RGH
- A Phase 1b study assessed the safety, pharmacokinetics, and antiviral activity of ABI-5366 in participants seropositive for HSV-2 with RGH; results from the virologic analyses are reported here

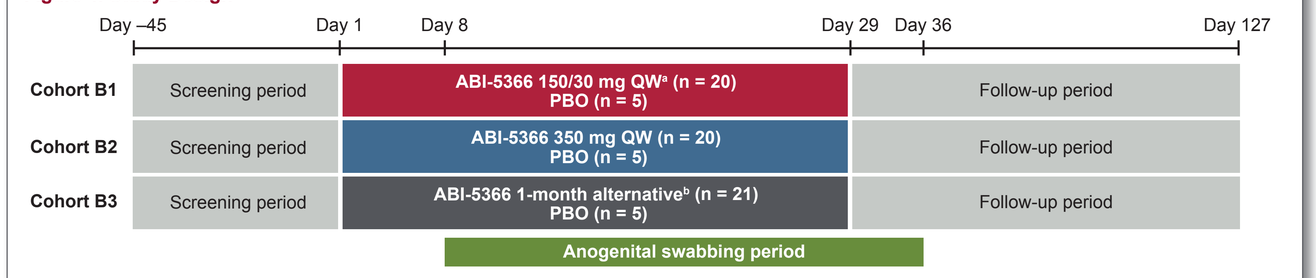
Objectives

- To investigate the antiviral efficacy of ABI-5366 in participants seropositive for HSV-2 with RGH
- To investigate the antiviral efficacy of ABI-5366 across subgroups defined by frequency of genital herpes lesion outbreaks, use of suppressive therapy at screening, and seropositivity for both HSV type 1 (HSV-1) and HSV-2 or HSV-2 only

Methods

- ABI-5366-101 is a randomised, double-blind, placebo-controlled, Phase 1b study (ClinicalTrials.gov Identifier: NCT06385327) conducted in participants seropositive for HSV-2 with RGH (**Figure 1**)
- Three multiple-dose cohorts (Cohorts B1-B3) have been enrolled
  - In each cohort, participants were randomised 20:5 to receive ABI-5366 or placebo for up to 29 days, with up to an additional 98 days of follow-up
  - Cohort B1 received ABI-5366 150 mg on Day 1 and ABI-5366 30 mg once weekly (QW) on Days 8, 15, 22, and 29; Cohort B2 received ABI-5366 350 mg QW on Days 1, 8, 15, 22, and 29; and Cohort B3 received 4 doses of ABI-5366 350 mg over Days 1 to 7 and an additional dose of ABI-5366 350 mg on Day 8
  - The dose combination used in Cohort B3 was designed to maintain the target minimum concentration of ABI-5366 over a month, representing a 1-month dose. The goal was to generate pharmacokinetic data to evaluate the feasibility of a potential once-monthly dose in the future
- Anogenital swabs were collected from participants twice daily over a 4-week period from Day 8 to 36
  - In the case of lesion occurrence, a separate lesion swab was collected twice daily until lesion resolution
- HSV DNA was quantified from the anogenital and lesion swabs using a validated real-time polymerase chain reaction assay
- The highest HSV DNA value across all swabs collected at a single time point was used for statistical analysis purposes
- Subgroup analyses were performed based on the frequency of genital herpes lesion occurrence (≤6 or >6 lesion occurrences in the past 12 months or in the 12-month period prior to initiating suppressive therapy), suppressive therapy at screening (yes or no), and HSV type (both HSV-1 and HSV-2 or HSV-2 only)
  - Suppressive therapy (systemic and topical) was discontinued beginning 7 days prior to Day 1 dosing through Day 36

Figure 1. Study Design



[a]ABI-5366 150 mg on Day 1, followed by ABI-5366 30 mg QW or PBO.
[b]Four doses of ABI-5366 350 mg over Days 1 to 7, followed by an additional dose of ABI-5366 350 mg on Day 8 or PBO.
PBO, placebo; QW, once weekly.

Results

- Seventy-six participants were enrolled across all cohorts; 61 were assigned to ABI-5366 (20 participants each in the 150/30 mg QW and 350 mg QW cohorts and 21 participants in the 1-month alternative cohort), and 15 were assigned to placebo (5 in each cohort)
  - One participant in the 1-month alternative cohort discontinued the study without any postdose HSV DNA or diary data collected and was excluded from the efficacy analysis
- Significant reductions in HSV-2 shedding and high viral load shedding rates were observed for the 350 mg QW and 1-month alternative cohorts compared with placebo (P <0.05 for all; **Tables 1** and **2**)
- Subclinical shedding rates were significantly reduced for the 350 mg QW cohort (P <0.05) compared with placebo
- Significant reductions in mean HSV-2 DNA levels for positive anogenital swabs were observed in both the 350 mg QW and 1-month alternative cohorts compared with placebo (P <0.01), with reductions of 2.1 and 1.0 $\log_{10}$ copies/mL, respectively
- Rates of genital lesions and virologically confirmed genital lesions were also significantly reduced for both the 350 mg QW and 1-month alternative cohorts compared with placebo (P <0.05 for all)

Table 1. Antiviral Activity and Clinical Outcomes by Cohort

	PBO (n = 15)	150/30 mg QW[a] (n = 20)	350 mg QW (n = 20)	1-Month Alternative[b] (n = 20)
HSV-2 overall shedding rate, %[c]	14.9	14.5	0.9	3.5
High viral load shedding rate, %[d]	11.8	9.4	0.2	2.2
HSV-2 subclinical shedding rate, %[e]	4.0	7.8	0.5	2.7
Mean (SD) $\log_{10}$ HSV-2 copies/mL	5.5 (1.54)	5.0 (1.64)	3.3 (0.87)	4.5 (1.47)
Overall genital lesion rate, %[f]	18.3	11.5	1.1	6.5
Virologically confirmed HSV-2 genital lesion rate, %[g]	16.2	11.5	0.5	2.0

[a]ABI-5366 150 mg on Day 1, followed by ABI-5366 30 mg QW. [b]Four doses of ABI-5366 350 mg over Days 1 to 7, followed by an additional dose of ABI-5366 350 mg on Day 8. [c]HSV-2 shedding rate was calculated as the number of positive HSV-2 anogenital swabs divided by the total number of swabs collected. [d]High viral load shedding rate was calculated as the number of positive HSV-2 anogenital swabs with HSV-2 >10^4 copies/mL divided by the total number of swabs collected. [e]HSV-2 subclinical shedding rate was calculated as the number of positive HSV-2 anogenital swabs when lesions were not present divided by the total number of swabs collected when lesions were not present. [f]Genital lesion rate was calculated as the number of days with genital lesions present divided by the total number of days assessed. [g]Virologically confirmed lesion rate was calculated as the number of days with genital lesions associated with positive HSV-2 anogenital swabs present divided by the total number of days assessed.
HSV-2, herpes simplex virus type 2; PBO, placebo; QW, once weekly.

Table 2. Percent Rate Reductions for Each Outcome for the ABI-5366 350 mg QW and 1-Month Alternative Cohorts Versus PBO

	350 mg QW (n = 20)	P Value[a]	1-Month Alternative[b] (n = 20)	P Value[a]
Reduction in HSV-2 overall shedding rate, %	94	<0.01	76	<0.01
Reduction in high viral load shedding rate, %	98	<0.05	81	<0.01
Reduction in HSV-2 subclinical shedding rate, %	88	<0.05	33	NS
Reduction in mean (SD) $\log_{10}$ HSV-2 copies/mL	–2.1	<0.01	–1.0	<0.01
Reduction in overall genital lesion rate, %	94	<0.01	65	<0.05
Reduction in virologically confirmed HSV-2 genital lesion rate, %	97	<0.05	88	0.01

[a]Statistical analysis was conducted using Poisson regression models, and the corresponding P values were estimated accordingly.
[b]Four doses of ABI-5366 350 mg over Days 1 to 7, followed by an additional dose of ABI-5366 350 mg on Day 8.
HSV-2, herpes simplex virus type 2; NS, not significant; PBO, placebo; QW, once weekly.

- Antiviral activity and clinical outcomes stratified by the frequency of genital herpes lesion occurrence, suppressive therapy at screening, and HSV type are shown in **Tables 3** to **5**
- While limited by the number of participants, numerical reductions in virologic and clinical outcomes were generally observed across most subgroups
- Most participants (55/75 [73%]) had ≤6 genital herpes lesion occurrences within the previous 12 months or in the 12-month period prior to initiating suppressive therapy (**Table 3**); virologic responses and lesion occurrence across cohorts were generally similar when stratified by frequency of lesion occurrence

Table 3. Antiviral Activity and Clinical Outcomes by Cohort and Frequency of Genital Herpes Lesion Occurrence

	≤6 Genital Herpes Lesion Occurrences[a]				>6 Genital Herpes Lesion Occurrences[a]			
	PBO (n = 11)	150/30 mg QW[b] (n = 13)	350 mg QW (n = 16)	1-Month Alternative[c] (n = 15)	PBO (n = 4)	150/30 mg QW[b] (n = 7)	350 mg QW (n = 4)	1-Month Alternative[c] (n = 5)
HSV-2 overall shedding rate, %[d]	14.2	16.1	1.1	1.9	16.8	11.4	0.4	9.6
High viral load shedding rate, %[e]	10.8	9.8	0.2	1.1	14.6	8.8	0	6.6
HSV-2 subclinical shedding rate, %[f]	4.3	8.9	0.5	1.8	3.1	5.9	0.4	6.2
Mean (SD) $\log_{10}$ HSV-2 copies/mL	5.5 (1.61)	4.8 (1.63)	3.4 (0.91)	4.2 (1.45)	5.7 (1.38)	5.5 (1.59)	2.8 (NA)	4.7 (1.48)
Overall genital lesion rate, %[g]	19.1	12.6	1.4	5.7	16.2	9.3	0	9.5
Virologically confirmed HSV-2 genital lesion rate, %[h]	16.3	12.6	0.7	1.4	16.2	9.3	0	4.3

[a]Genital herpes lesion occurrences were in the past 12 months or in the 12-month period prior to initiating suppressive therapy. [b]ABI-5366 150 mg on Day 1, followed by ABI-5366 30 mg QW. [c]Four doses of ABI-5366 350 mg over Days 1 to 7, followed by an additional dose of ABI-5366 350 mg on Day 8. [d]HSV-2 shedding rate was calculated as the number of positive HSV-2 anogenital swabs divided by the total number of swabs collected. [e]High viral load shedding rate was calculated as the number of positive HSV-2 anogenital swabs with HSV-2 >10^4 copies/mL divided by the total number of swabs collected. [f]HSV-2 subclinical shedding rate was calculated as the number of positive HSV-2 anogenital swabs when lesions were not present divided by the total number of swabs collected when lesions were not present. [g]Genital lesion rate was calculated as the number of days with genital lesions present divided by the total number of days assessed. [h]Virologically confirmed lesion rate was calculated as the number of days with genital lesions associated with positive HSV-2 anogenital swabs present divided by the total number of days assessed.
HSV-2, herpes simplex virus type 2; NA, not applicable; PBO, placebo; QW, once weekly.

- Overall, 45/75 (60%) participants were receiving suppressive therapy at screening (**Table 4**); virologic responses and lesion occurrence across cohorts were generally similar when stratified by those who were receiving suppressive therapy at screening versus those who were not

Table 4. Antiviral Activity and Clinical Outcomes by Cohort and Suppressive Therapy at Screening

	Suppressive Therapy at Screening				No Suppressive Therapy at Screening			
	PBO (n = 8)	150/30 mg QW[a] (n = 12)	350 mg QW (n = 12)	1-Month Alternative[b] (n = 13)	PBO (n = 7)	150/30 mg QW[a] (n = 8)	350 mg QW (n = 8)	1-Month Alternative[b] (n = 7)
HSV-2 overall shedding rate, %[c]	16.2	15.3	1.5	5.4	13.5	13.1	0.2	0.3
High viral load shedding rate, %[d]	12.6	9.0	0.3	3.5	11.0	10.2	0	0
HSV-2 subclinical shedding rate, %[e]	3.4	7.5	0.7	4.2	4.7	8.3	0.2	0.3
Mean (SD) $\log_{10}$ HSV-2 copies/mL	5.5 (1.62)	4.9 (1.67)	3.2 (0.89)	4.5 (1.47)	5.6 (1.45)	5.3 (1.56)	4.0 (NA)	2.8 (NA)
Overall genital lesion rate, %[f]	22.6	11.6	1.9	10.0	13.3	11.2	0	0.5
Virologically confirmed HSV-2 genital lesion rate, %[g]	20.9	11.6	0.9	3.2	10.8	11.2	0	0

[a]ABI-5366 150 mg on Day 1, followed by ABI-5366 30 mg QW. [b]Four doses of ABI-5366 350 mg over Days 1 to 7, followed by an additional dose of ABI-5366 350 mg on Day 8. [c]HSV-2 shedding rate was calculated as the number of positive HSV-2 anogenital swabs divided by the total number of swabs collected. [d]High viral load shedding rate was calculated as the number of positive HSV-2 anogenital swabs with HSV-2 >10^4 copies/mL divided by the total number of swabs collected. [e]HSV-2 subclinical shedding rate was calculated as the number of positive HSV-2 anogenital swabs when lesions were not present divided by the total number of swabs collected when lesions were not present. [f]Genital lesion rate was calculated as the number of days with genital lesions present divided by the total number of days assessed. [g]Virologically confirmed lesion rate was calculated as the number of days with genital lesions associated with positive HSV-2 anogenital swabs present divided by the total number of days assessed.
HSV-2, herpes simplex virus type 2; NA, not applicable; PBO, placebo; QW, once weekly.

- At baseline, 37/75 (49%) participants were seropositive for both HSV-1 and HSV-2 and 38/75 (51%) were seropositive for HSV-2 only (**Table 5**); virologic responses and lesion occurrence across cohorts were generally similar when stratified by HSV type

Table 5. Antiviral Activity and Clinical Outcomes by Cohort and HSV Type

	Seropositivity for HSV-1 and HSV-2				Seropositivity for HSV-2 Only			
	PBO (n = 7)	150/30 mg QW[a] (n = 10)	350 mg QW (n = 11)	1-Month Alternative[b] (n = 9)	PBO (n = 8)	150/30 mg QW[a] (n = 10)	350 mg QW (n = 9)	1-Month Alternative[b] (n = 11)
HSV-2 overall shedding rate, %[c]	12.0	12.1	1.3	6.1	17.4	16.9	0.4	1.2
High viral load shedding rate, %[d]	10.7	7.7	0.3	4.1	12.8	11.3	0	0.5
HSV-2 subclinical shedding rate, %[e]	1.8	6.5	0.5	4.4	6.2	9.3	0.4	1.3
Mean (SD) $\log_{10}$ HSV-2 copies/mL	5.8 (1.36)	4.8 (1.53)	3.5 (0.82)	4.7 (1.47)	5.3 (1.62)	5.1 (1.71)	2.4 (0.52)	3.7 (1.33)
Overall genital lesion rate, %[f]	13.7	8.9	0.9	10.3	22.3	14.1	1.3	3.1
Virologically confirmed HSV-2 genital lesion rate, %[g]	12.3	8.9	0.9	4.2	19.7	14.1	0	0

[a]ABI-5366 150 mg on Day 1, followed by ABI-5366 30 mg QW. [b]Four doses of ABI-5366 350 mg over Days 1 to 7, followed by an additional dose of ABI-5366 350 mg on Day 8. [c]HSV-2 shedding rate was calculated as the number of positive HSV-2 anogenital swabs divided by the total number of swabs collected. [d]High viral load shedding rate was calculated as the number of positive HSV-2 anogenital swabs with HSV-2 >10^4 copies/mL divided by the total number of swabs collected. [e]HSV-2 subclinical shedding rate was calculated as the number of positive HSV-2 anogenital swabs when lesions were not present divided by the total number of swabs collected when lesions were not present. [f]Genital lesion rate was calculated as the number of days with genital lesions present divided by the total number of days assessed. [g]Virologically confirmed lesion rate was calculated as the number of days with genital lesions associated with positive HSV-2 anogenital swabs present divided by the total number of days assessed.
HSV, herpes simplex virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; PBO, placebo; QW, once weekly.

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