P0223

The Safety and Tolerability of ABI-5366, a Novel, Oral, Long-Acting HSV Helicase-Primase Inhibitor in Participants With Recurrent Genital Herpes

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Conclusions

- ABI-5366 was safe and well tolerated at all dose levels when evaluated in both weekly dosing regimens and a 1-month alternative regimen
- There were no significant differences in the proportions of participants experiencing treatment-emergent adverse events or laboratory abnormalities 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
- Results from this study support the potential development of ABI-5366 as a novel suppressive therapy for recurrent genital herpes

Plain Language Summary

- Many people with recurrent genital herpes still have “breakthrough” outbreaks, even when they are taking daily medicine to suppress the outbreaks
- Better suppressive treatment options are needed for patients with recurrent genital herpes
- ABI-5366 is an oral medicine that is currently being developed to suppress recurrent genital herpes
- In this study, ABI-5366 was safe and well tolerated at all tested doses when it was given either weekly or as a 1-month alternative
- No participants had severe adverse events related to the medicine, most changes in lab tests were mild, and no participants had to stop taking the medicine because of adverse events

Introduction

- Herpes simplex virus type 2 (HSV-2) is the predominant cause of recurrent genital herpes (RGH), with approximately 520 million people aged 15 to 49 years estimated to have HSV-2 globally[1,2]
- Breakthrough recurrences are common in people receiving suppressive treatment with nucleoside analogues[3,4]
- There remains an unmet need for more effective suppressive therapies that reduce recurrences and transmission of herpes simplex virus (HSV) and can be administered long term in patients with RGH
- ABI-5366[a] is an investigational, orally administered, long-acting inhibitor of the HSV helicase-primase complex under development as a suppressive therapy for RGH
- A Phase 1b study in participants who are seropositive for HSV-2 with RGH assessed the safety, pharmacokinetics, and antiviral activity of ABI-5366; safety and tolerability results are reported here

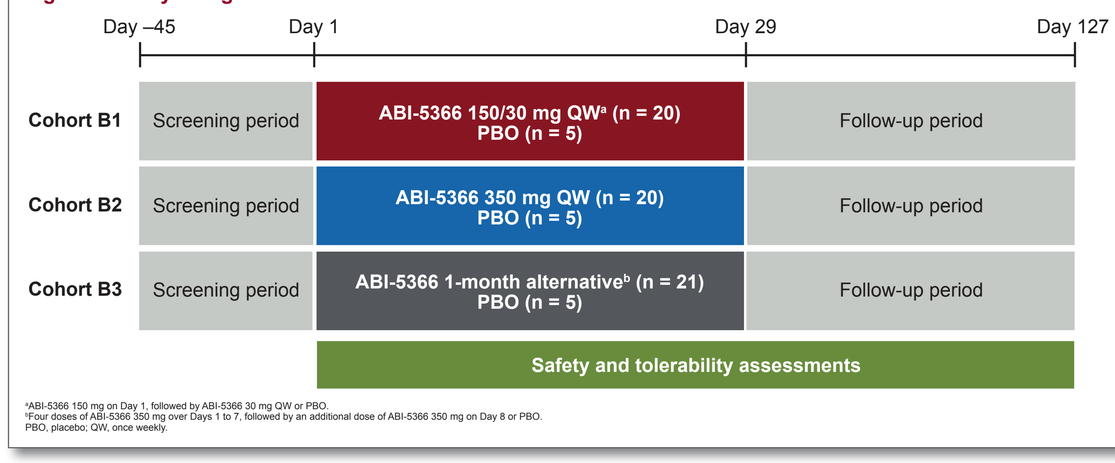
Objectives

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

Methods

- The safety and tolerability of ABI-5366 was assessed in a randomised, double-blinded, 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 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 combination of doses 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 potential once-monthly dosing in the future
- Safety and tolerability were assessed by physical examinations, adverse events, and laboratory parameters
- 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

- A total of 76 participants were enrolled across 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)
- Key safety and tolerability results are shown in **Table 1**
  - No Grade ≥3 treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, or serious TEAEs were observed
  - Most treatment-emergent laboratory abnormalities (TELabs) were Grade 1 or 2 in severity
  - Three Grade 3 TELabs were observed, including decreased neutrophils (subsequently normalised) in 1 participant receiving placebo,increased creatine kinase (exercise related) in 1 participant receiving 150/30 mg QW, and increased (preexisting) cholesterol levels in 1 participant receiving 350 mg QW
  - None of the Grade 3 TELabs were reported as adverse events

Table 1. Summary of TEAEs and TELabs by Cohort

Participants With TEAE or TELab, n (%)	PBO (n = 15)	150/30 mg QW[a] (n = 20)	350 mg QW (n = 20)	1-Month Alternative[b] (n = 21)
Any TEAE	14 (93)	18 (90)	19 (95)	21 (100)
Grade ≥3 TEAE	0	0	0	0
Any treatment-related AE	6 (40)	6 (30)	3 (15)	7 (33)
Any TEAE leading to discontinuation of study drug	0	0	0	0
Any serious TEAE	0	0	0	0
Grade 2 TEAE by preferred term occurring in ≥2% of participants overall				
URTI	2 (13)	2 (10)	4 (20)	1 (5)
Headache	3 (20)	1 (5)	0	3 (14)
Viral URTI	1 (7)	0	2 (10)	0
Arthralgia	1 (7)	0	0	1 (5)
Back pain	2 (13)	0	0	0
Ligament sprain	1 (7)	1 (5)	0	0
LRTI	2 (13)	0	0	0
Any TELab	10 (67)	14 (70)	15 (75)	13 (62)
Grade ≥3 TELab	1 (7)	1 (5)	1 (5)	0
Grade ≥2 TELab by parameter occurring in ≥2% of participants overall				
Increased cholesterol	2 (13)	2 (10)	4 (20)	0
Increased triglycerides	1 (7)	1 (5)	1 (5)	0
Increased creatine kinase	0	1 (5)	0	1 (5)

[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.
AE, adverse event; LRTI, lower respiratory tract infection; PBO, placebo; QW, once weekly; TEAE, treatment-emergent adverse event; TELab, treatment-emergent laboratory abnormality; URTI, upper respiratory tract infection.

- Summaries of TEAEs and TELabs stratified by the frequency of genital herpes lesion occurrence, suppressive therapy at screening, and HSV type are shown in **Tables 2** to **4**
- While limited by the number of participants, TEAEs and TELabs were generally balanced across all subgroups, with no Grade ≥3 TEAEs, TEAEs leading to discontinuation of study drug, or serious TEAEs reported in any subgroups

Table 2. Summary of TEAEs and TELabs by Cohort and Frequency of Genital Herpes Lesion Occurrence

	≤6 Genital Herpes Lesion Occurrences[a]				>6 Genital Herpes Lesion Occurrences[a]			
Participants With TEAE or TELab, n (%)	PBO (n = 11)	150/30 mg QW[b] (n = 13)	350 mg QW (n = 16)	1-Month Alternative[c] (n = 16)	PBO (n = 4)	150/30 mg QW[b] (n = 7)	350 mg QW (n = 4)	1-Month Alternative[c] (n = 5)
Any TEAE	11 (100)	12 (92)	16 (100)	16 (100)	3 (75)	6 (86)	3 (75)	5 (100)
Grade ≥3 TEAE	0	0	0	0	0	0	0	0
Any treatment-related AE	5 (45)	4 (31)	3 (19)	5 (31)	1 (25)	2 (29)	0	2 (40)
Any TEAE leading to discontinuation of study drug	0	0	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0	0	0
Any TELab	8 (73)	9 (69)	12 (75)	11 (69)	2 (50)	5 (71)	3 (75)	2 (40)
Grade ≥3 TELab	1 (9)	1 (8)	1 (6)	0	0	0	0	0

[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.
AE, adverse event; PBO, placebo; QW, once weekly; TEAE, treatment-emergent adverse event; TELab, treatment-emergent laboratory abnormality.

Table 3. Summary of TEAEs and TELabs by Cohort and Suppressive Therapy at Screening

	Suppressive Therapy at Screening				No Suppressive Therapy at Screening			
Participants With TEAE or TELab, n (%)	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 = 8)
Any TEAE	7 (88)	11 (92)	11 (92)	13 (100)	7 (100)	7 (88)	8 (100)	8 (100)
Grade ≥3 TEAE	0	0	0	0	0	0	0	0
Any treatment-related AE	4 (50)	3 (25)	1 (8)	5 (38)	2 (29)	3 (38)	2 (25)	2 (25)
Any TEAE leading to discontinuation of study drug	0	0	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0	0	0
Any TELab	6 (75)	9 (75)	9 (75)	7 (54)	4 (57)	5 (63)	6 (75)	6 (75)
Grade ≥3 TELab	1 (13)	1 (8)	0	0	0	0	1 (13)	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.
AE, adverse event; PBO, placebo; QW, once weekly; TEAE, treatment-emergent adverse event; TELab, treatment-emergent laboratory abnormality.

Table 4. Summary of TEAEs and TELabs by Cohort and HSV Type

	Seropositivity for HSV-1 and HSV-2				Seropositivity for HSV-2 Only			
Participants With TEAE or TELab, n (%)	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 = 12)
Any TEAE	6 (86)	9 (90)	11 (100)	9 (100)	8 (100)	9 (90)	8 (89)	12 (100)
Grade ≥3 TEAE	0	0	0	0	0	0	0	0
Any treatment-related AE	2 (29)	3 (30)	3 (27)	5 (56)	4 (50)	3 (30)	0	2 (17)
Any TEAE leading to discontinuation of study drug	0	0	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0	0	0
Any TELab	4 (57)	6 (60)	7 (64)	6 (67)	6 (75)	8 (80)	8 (89)	7 (58)
Grade ≥3 TELab	0	1 (10)	1 (9)	0	1 (13)	0	0	0

[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.
AE, adverse event; HSV, herpes simplex virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; PBO, placebo; QW, once weekly; TEAE, treatment-emergent adverse event; TELab, treatment-emergent laboratory abnormality.

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