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Safety and Tolerability of GS-1179, a Novel, Oral, Long-Acting HSV Helicase-Primase Inhibitor for Recurrent Genital Herpes: Results From a Phase 1b Study

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Conclusions

- When administered at 50, 20, or 10 mg once-weekly, GS-1179 was generally safe and well tolerated in participants seropositive for herpes simplex virus type 2 with recurrent genital herpes
- Treatment-emergent adverse events and laboratory abnormalities were reported at similar rates among participants receiving once-weekly GS-1179 up to 50 mg compared with those receiving placebo
- Most treatment-emergent adverse events and all treatment-emergent laboratory abnormalities were Grade 1 or 2
 - One serious treatment-emergent adverse event of abdominal pain occurred in a participant receiving GS-1179 10 mg; this event was not related to the study drug
- No treatment-emergent adverse events leading to premature treatment discontinuation or death occurred
- These data support the continued development of GS-1179 as a long-acting suppressive therapy for recurrent genital herpes

Plain Language Summary

- Recurrent genital herpes is a common infection caused by herpes simplex virus type 2 that can lead to episodes of sores or blisters in the genital area
- While current antiviral medicines are safe, people often experience breakthrough episodes while taking them
 - Better medicines with proven safety are needed to suppress breakthrough episodes in people with recurrent genital herpes
- GS-1179 is a new medicine that is being developed for recurrent genital herpes
- In this study, once-weekly GS-1179 was generally safe and well tolerated at 3 different doses in people with herpes simplex virus type 2 and recurrent genital herpes

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Introduction

- Herpes simplex virus type 2 (HSV-2) affects an estimated 520 million people aged 15 to 49 years globally and is the most common cause of recurrent genital herpes (RGH)[1,2]
- Nucleoside analogs, which inhibit the viral polymerase, can be administered episodically during recurrences or daily as suppressive therapy for RGH[3]
 - As nucleoside analogs are only partially effective at preventing breakthrough recurrences and transmission, there remains an unmet need for novel, potent HSV-2 therapies for individuals with RGH[3,4]
- Herpes simplex virus (HSV) helicase-primase inhibitors target the viral helicase-primase complex, which is essential for viral replication[5,6]
- GS-1179 is an investigational, long-acting HSV helicase-primase inhibitor in development as a suppressive therapy for RGH
- A Phase 1b study evaluated the safety and tolerability of once-weekly (QW) GS-1179 50, 20, or 10 mg compared with placebo

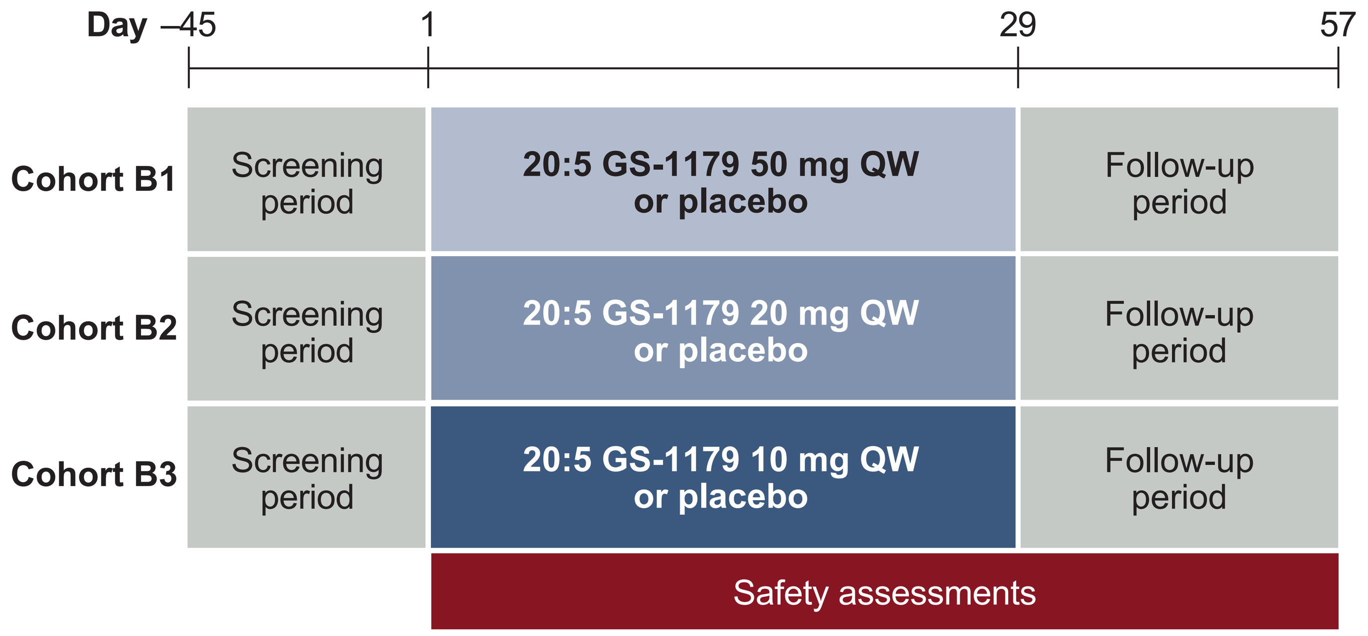
Objective

- To investigate the safety and tolerability of GS-1179 in participants who are seropositive for HSV-2 with RGH

Methods

- This randomized, blinded, placebo-controlled study (ClinicalTrials.gov Identifier: NCT06698575) enrolled participants who were seropositive for HSV-2 with RGH (**Figure 1**)
 - Eligible participants had 4 to 9 clinical RGH episodes within the past 12 months if not currently on suppressive therapy, or within the 12 months prior to initiation of suppressive therapy
 - Exclusion criteria included current coinfection with HIV, hepatitis B virus, hepatitis C virus, acute hepatitis A virus, or acute hepatitis E virus and any clinically significant medical, behavioral, or mental condition, or pharmacologic or surgical treatment that may interfere with safety assessments or the absorption, distribution, and/or elimination of the study drug or make the individual unsuitable for study participation
- Participants were randomized 20:5 to receive QW GS-1179 (50 mg [cohort B1], 20 mg [cohort B2], or 10 mg [cohort B3]) or placebo for 29 days
 - Dose levels were determined based on emergent safety, tolerability, and available pharmacokinetic data from completed cohorts in a concurrent single-ascending dose study of GS-1179
- Participants were monitored through Day 57 for safety evaluations, including treatment-emergent adverse event (TEAE) reporting, laboratory testing, and physical examinations

Figure 1. Study Design



Day –45
1
29
57
Cohort B1
Screening period
20:5 GS-1179 50 mg QW or placebo
Follow-up period
Cohort B2
Screening period
20:5 GS-1179 20 mg QW or placebo
Follow-up period
Cohort B3
Screening period
20:5 GS-1179 10 mg QW or placebo
Follow-up period
Safety assessments

QW, once weekly.

Results

Participants

- Overall, 73 participants were enrolled in 3 dosing cohorts with placebo controls
 - One participant was lost to follow-up, and 1 participant discontinued the study for reasons not related to adverse events or study treatments
 - One participant was assigned to receive placebo within cohort B2 but did not receive treatment
 - All participants who received treatment (n = 72) were evaluated for safety outcomes (**Table 1**)

TEAEs

- TEAEs were reported in 18/20 (90%), 15/20 (75%), and 12/18 (67%) participants receiving GS-1179 50, 20, and 10 mg, respectively, and in 12/14 (86%) participants receiving placebo (**Table 2**)
- Most TEAEs were Grade 1 or 2
 - One participant receiving GS-1179 10 mg experienced a Grade 3 TEAE of headache, and 1 participant receiving GS-1179 10 mg experienced a Grade 3 serious TEAE of abdominal pain that was considered not related to the study drug by investigators
 - One participant receiving placebo experienced a Grade 3 TEAE of migraine
 - No Grade 4 TEAEs were reported
- The most common TEAEs were headache (in 45%, 10%, and 39% of participants receiving GS-1179 50, 20, and 10 mg, respectively, and in 7% of participants receiving placebo) and upper respiratory tract infection (in 10%, 5%, and 11% of participants receiving GS-1179 50, 20, and 10 mg, respectively, and in 29% of participants receiving placebo)
- Treatment-related TEAEs occurred in 8/20 (40%), 7/20 (35%), and 5/18 (28%) participants receiving GS-1179 50, 20, and 10 mg, respectively, and in 4/14 (29%) participants receiving placebo
 - The most common treatment-related TEAE was headache (in 30%, 10%, and 22% of participants receiving GS-1179 50, 20, and 10 mg, respectively, and in 0 participants receiving placebo)
 - Most treatment-related headache TEAEs resolved by the end of study follow-up
- No TEAEs leading to premature discontinuation of treatment or death occurred

Treatment-Emergent Laboratory Abnormalities

- Treatment-emergent laboratory abnormalities were reported in 7/20 (35%), 7/20 (35%), and 9/18 (50%) participants receiving GS-1179 50, 20, and 10 mg, respectively, and in 5/14 (36%) participants receiving placebo
 - All treatment-emergent laboratory abnormalities were Grade 1 or 2

Table 1. Participant Demographic and Baseline Characteristics

Characteristic	Placebo (n = 14)[a]	Cohort B1: GS-1179 50 mg QW (n = 20)	Cohort B2: GS-1179 20 mg QW (n = 20)	Cohort B3: GS-1179 10 mg QW (n = 18)
Age, years, mean (SD)	41.6 (10.9)	38.4 (12.4)	40.5 (9.9)	42.0 (10.9)
Sex at birth, male, n (%)	5 (36)	5 (25)	12 (60)	4 (22)
Race, White, n (%)	11 (79)	19 (95)	18 (90)	14 (78)
BMI, kg/m^2, mean (SD)	25.9 (3.8)	25.7 (4.0)	25.3 (3.0)	27.3 (3.8)
Time since RGH diagnosis, years, mean (SD)	13.1 (9.5)	10.2 (9.6)	11.3 (9.9)	12.9 (10.0)
Number of recurrences,[b] mean (SD)	6.0 (1.4)	6.1 (1.3)	5.3 (0.9)	5.8 (1.4)
On suppressive therapy at baseline,[c] n (%)	10 (71)	17 (85)	16 (80)	12 (67)
≥1 medical history condition at baseline, n (%)	13 (93)	18 (90)	20 (100)	18 (100)

[a]One participant assigned to receive placebo in cohort B2 did not receive treatment and was not evaluated.
[b]Number of recurrences was defined as the number of lesions in the past 12 months or prior to suppressive therapy.
[c]Participants discontinued suppressive therapies for RGH beginning 7 days prior to Day 1 dosing through Day 35.
BMI, body mass index; QW, once weekly; RGH, recurrent genital herpes.

Table 2. Summary of TEAEs

Participants With TEAE,[a] n (%)	Placebo (n = 14)[b]	Cohort B1: GS-1179 50 mg QW (n = 20)	Cohort B2: GS-1179 20 mg QW (n = 20)	Cohort B3: GS-1179 10 mg QW (n = 18)
Any TEAE	12 (86)	18 (90)	15 (75)	12 (67)
Grade ≥3 TEAE	1 (7)	0	0	2 (11)
Abdominal pain	0	0	0	1 (6)
Headache	0	0	0	1 (6)
Migraine	1 (7)	0	0	0
TEAE by preferred term occurring in ≥5% of participants overall				
Headache	1 (7)	9 (45)	2 (10)	7 (39)
Upper respiratory tract infection	4 (29)	2 (10)	1 (5)	2 (11)
Fatigue	0	2 (10)	3 (15)	0
Rash	1 (7)	3 (15)	0	0
Abdominal pain	1 (7)	0	2 (10)	1 (6)
Any treatment-related TEAE	4 (29)	8 (40)	7 (35)	5 (28)
Treatment-related TEAE by preferred term occurring in ≥5% of participants overall				
Headache	0	6 (30)	2 (10)	4 (22)
Any serious TEAE	0	0	0	1 (6)
TEAE leading to premature discontinuation of treatment	0	0	0	0
Death	0	0	0	0

[a]TEAEs were coded according to MedDRA Version 27.1.
[b]One participant assigned to receive placebo in cohort B2 did not receive treatment and was not evaluated.
MedDRA, *Medical Dictionary for Regulatory Activities*; QW, once weekly; TEAE, treatment-emergent adverse event.

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