PW-030
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Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients

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Introduction

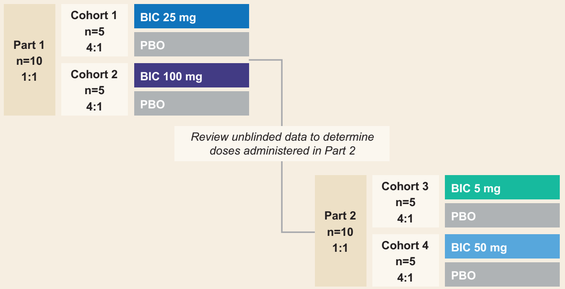
- Integrase strand transfer inhibitors (INSTIs) are a recommended class of antiretrovirals (ARVs) for treatment of HIV-1 in treatment guidelines[1,2]
- Three INSTIs are currently approved: raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG)
  - RAL requires twice-daily administration, and EVG requires pharmaco-enhancement for once-daily dosing, which creates more potential drug-drug interactions
  - RAL and EVG have overlapping resistance profiles
  - DTG is an unboosted INSTI that can be administered once daily
  - While DTG retains activity against most RAL- and EVG-resistant variants, it must be dosed twice daily in patients with known or suspected INSTI resistance, or when coadministered with cytochrome P450 or uridine diphosphate glucuronosyltransferase inducers
- Bictegravir (BIC; GS-9883) is a novel, potent, once-daily, unboosted INSTI with in vitro activity against most INSTI resistant variants
- BIC is currently in clinical development in combination with tenofovir alafenamide and emtricitabine as a single-tablet regimen for the treatment of HIV-1 infection[3-6]

Objectives

- To evaluate the short-term antiviral potency of BIC compared with placebo (PBO) once daily for 10 days at doses ranging from 5 to 100 mg in HIV-infected adults
- To characterize the pharmacokinetics (PK) of BIC following multiple daily doses in HIV-1-infected patients
- To characterize the dose-response relationship between BIC exposure and viral dynamics of HIV-1
- To assess for emergence of INSTI resistance mutations during 10 days of BIC monotherapy
- To investigate the safety and tolerability of BIC at doses of 5–100 mg compared with PBO

Methods

Study Design



- This was a double-blind, adaptive, sequential-cohort, placebo-controlled study of BIC monotherapy in HIV-1–infected patients (NCT02275065)
- Patients with chronic HIV-1 infection, HIV-1 RNA ≥10,000–≤400,000 copies/mL, and CD4 cell count >200/μL, who were ARV naïve or previously treated, INSTI naïve, and off of any ARV treatment for ≥12 weeks were eligible to screen
  - Patients were required to have no genotypic or phenotypic resistance to any INSTI at screening
- In Part 1, 10 patients were randomized 1:1 to Cohort 1 (BIC 25 mg) or Cohort 2 (BIC 100 mg)
  - Within each cohort, patients were assigned in a 4:1 ratio to receive active BIC or matching PBO
- Following review of data from Part 1, 10 patients were randomized 1:1 to Cohort 3 (BIC 5 mg) or Cohort 4 (BIC 50 mg)
  - Within each cohort, patients were again randomized 4:1 to receive active BIC or matching PBO
- Screening, baseline, and Day 11 samples for each patient were tested for genotypic and phenotypic resistance to reverse transcriptase, protease, and integrase (Monogram Biosciences, South San Francisco, CA)
- All patients received study medication in a fasted state for 10 days and were monitored for safety for an additional 7 days
- Virologic responses were compared between each BIC treatment group and the pooled placebo group using the t test at a 2-sided 0.05 significance level based on an analysis of variance model
- BIC PK parameters were listed and summarized by treatment group
- Safety data, including adverse events (AEs), laboratory data, and vital signs, were summarized by treatment
  - AEs were coded using MedDRA Version 17.1

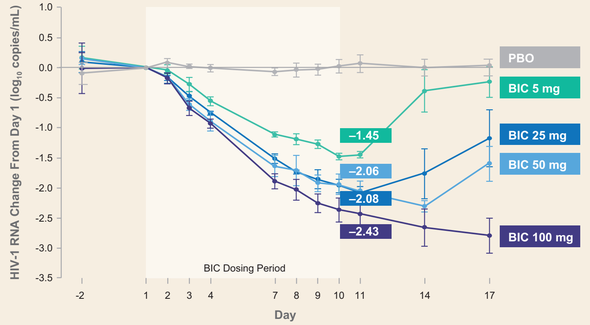
Results

Baseline Characteristics

Characteristic	BIC 5 mg n=4	BIC 25 mg n=4	BIC 50 mg n=4	BIC 100 mg n=4	PBO n=4
Mean age, y (range)	29 (25–34)	44 (29–59)	34 (19-44)	36 (26–48)	24 (21, 28)
Male, n	4	4	3	4	4
Race, n					
White	4	2	3	3	1
Black	0	1	1	1	3
Mean BMI, kg/m^2 (SD)	27.5 (5.35)	26.9 (2.23)	22.5 (3.64)	27.4 (3.84)	22.7 (2.45)
Mean HIV-1 RNA, $\log_{10}$ copies/mL (SD)	3.8 (1.02)	4.6 (0.50)	4.4 (0.46)	4.7 (1.04)	4.5 (0.41)
Mean CD4 count, /μL (SD)	520 (138)	329 (98)	445 (124)	410 (215)	507 (113)
ARV status, n					
ARV naive	3	3	4	2	4
ARV experienced	1	1	0	2	0

SD, standard deviation.

Mean Change (95% confidence interval) in HIV-1RNA



Virologic Responses to Bictegravir

	BIC 5 mg n=3*	BIC 25 mg n=4	BIC 50 mg n=4	BIC 100 mg n=4	PBO n=4
Mean $DAVG_{11}$, $\log_{10}$ copies/mL (SD)	-0.92 (0.10)	-1.33 (0.17)	-1.37 (0.31)	-1.61 (0.26)	-0.01 (0.14)
Pairwise p-value† vs:					
PBO	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.10	0.15		
Mean Δ HIV-1 RNA Day 11 from baseline, $\log_{10}$ copies/mL (SD)	-1.45 (0.10)	-2.08 (0.21)	-2.06 (0.35)	-2.43 (0.39)	0.08 (0.30)
Pairwise p-value† vs:					
PBO	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.11	0.09		
Mean max reduction from baseline HIV-1 RNA, $\log_{10}$ copies/mL (SD)	-1.52 (0.08)	-2.18 (0.24)	-2.31 (0.19)	-2.91 (0.53)	-0.12 (0.18)
Pairwise p-value† vs:					
PBO	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.004	0.01		
Patients ever achieving HIV-1 RNA <50 copies/mL by end of study, n (%)	0	0	1 (25)	2 (50)	0

*1 patient was excluded from virologic assessments as HIV-1 RNA on Day 1 was 173 copies/mL; †2-sided t test. $DAVG_{11}$, time-weighted average change from baseline to study Day 11.

Summary of Bictegravir Multiple-Dose PK Parameters

PK Parameter	BIC 5 mg n=4	BIC 25 mg n=4	BIC 50 mg n=4	BIC 100 mg n=4
Mean AUC_{τ}, h·ng/mL (%CV)	9983 (26.7)	48 950 (40.0)	87 538 (32.7)	178 902 (17.8)
Mean C_{τ}, ng/mL (%CV)	225.3 (37.5)	1052.3 (54.1)	2053.0 (47.6)	4520.0 (21.9)
Median $t_{½}$, h (Q1, Q3)	20.8 (17.2, 23.8)	15.9 (14.1, 19.4)	17.8 (15.5, 20.5)	20.9 (17.9, 24.5)
Median $_{pa}$IQ 95 (range)*	1.3 (0.9–2.1)	4.9 (4.4–11.7)	13.4 (5.3–18.6)	25.9 (23.0–36.9)

*Protein-adjusted 95% inhibitory quotient ($_{pa}$IQ95) based on observed steady-state concentration at end of dosing interval (C_{τ}) and in vitro protein-adjusted 95% inhibitory concentration for wild-type HIV-1 (162 ng/mL). AUC_{τ}, area under plasma concentration–time curve for dosing interval; %CV, coefficient of variation; Q, quartile; $t_{½}$, half-life.

Safety Summary

- There were no serious AE's or AE's leading to study drug discontinuation
- Headache (1 each in 5-, 25-, and 100-mg groups) and diarrhea (1 each in 5- and 100-mg groups) were the only AEs reported in >1 patient on BIC
- Most laboratory abnormalities were Grade 1. Only 2 patients had a Grade 2 abnormality:
  - 1 patient on PBO had Grade 2 amylase on Day 10
  - 1 patient in the BIC 5-mg arm had Grade 2 aspartate aminotransferase and creatine phosphokinase abnormalities on Day 17 attributed to crystal methamphetamine use

Conclusions

- BIC 10 day monotherapy led to rapid declines in HIV-1 RNA from baseline that were sustained through the treatment period with no viral breakthrough
- HIV-1 RNA decreases demonstrated a dose-response effect, and viral rebound after the treatment period was delayed to Day 14 in the 50-mg dose group and to Day 17 in the 100-mg group
- 3 patients (1 in 50 mg arm, 2 in 100 mg arm) had HIV-1 RNA <50 copies/mL by end of study
- No primary INSTI resistance mutations were selected following 10 days of monotherapy
- BIC was well-tolerated at all dose levels through 10 days of dosing
- BIC plasma exposure was linear and dose proportional at doses up to 100 mg

References

1. EACS Guidelines 8.0. http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf. October 2015; **2.** Panel on Antiretroviral Guidelines for Adults and Adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Jan 28, 2016; **3.** Jones G, et al. ASM Microbe 2016, poster 1673; **4.** Lazerwith SE, et al. ASM Microbe 2016, poster 414; **5.** Tsiang M, et al. ASM Microbe 2016, poster 1643; **6.** White K, et al. 14th European Meeting on HIV & Hepatitis 2016; abstr O-01.

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