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 guidelines1-3. Three INSTIs are currently approved: raltegravir (RAL), elvitegravir (E VG), and dolutegravir (DTG). RAL requires twice-daily administration, and E VG requires pharmaco-enhancement for once-daily dosing, which creates more potential drug-drug interactions. RAL and E VG have overlapping resistance profiles. BIC is being developed as a single-tablet regimen for the treatment of HIV-1 infection4-6.

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-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

Patients with chronic HIV-1 infection, HIV-1 RNA ≤10,000–≤500,000 copies/mL, and CD4 cell count >200/μL, who were ARV naive or previously treated, INSTI naive, and off of any ARV treatment for 3 weeks were eligible to enroll

− Patients were required to have no genotypic or phenotypic resistance to any INSTI at screening

− In Part 1, 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, 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

− 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–≤500,000 copies/mL, and CD4 cell count ≥200/μL, who were ARV naive or previously treated, INSTI naive, and off of any ARV treatment for 3 weeks were eligible to enroll

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− Within each cohort, patients were again randomized 4:1 to receive active BIC or matching PBO

Results, cont.

− 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 studied received therapy 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 placebo (PBO) group

− Within each cohort, patients were randomized 1:1 to receive active BIC or matching PBO

− AEs were coded using MedDRA Version 17.1

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 day 10 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


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