Research Letter

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Coformulated bictegravir, emtricitabine, tenofovir alafenamide after initial treatment with bictegravir or dolutegravir and emtricitabine/tenofovir alafenamide

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A phase 2, randomized, active-controlled study of initial antiretroviral therapy with bictegravir or dolutegravir in combination with emtricitabine and tenofovir alafenamide showed excellent efficacy. After 60 weeks of blinded treatment, participants switched to a single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide. Switching maintained viral suppression in all participants who remained on the study through 12 weeks in the open-label phase, and was safe and well tolerated.

Bictegravir (BIC) is a novel, once-daily integrase strand transfer inhibitor (INSTI) with excellent antiviral potency the longest plasma half-life of any INSTI as well as the longest dissociation half-life from the HIV-1 integrase-DNA complex [1–4]. *In vitro*, BIC retains activity against many HIV-1 isolates that are resistant to raltegravir and elvitegravir, and some with resistance to dolutegravir (DTG) [4,5].

Study 1475 was a phase 2, multicenter, randomized, double-blind, active-control study that compared initial HIV-1 treatment with BIC 75 mg to DTG 50 mg, each in combination with coformulated emtricitabine 200 mg (F, FTC) and tenofovir alafenamide 25 mg (TAF). At 48 weeks, 97% of participants randomized to BIC and F/TAF versus 91% of participants on DTG and F/TAF had HIV-1 RNA below 50 copies/ml with similar safety and tolerability in both treatment arms [6]. Although the double blind phase of Study 1475 was ongoing, a single-tablet coformulation of BIC with FTC and TAF (B/F/TAF) was developed in preparation for phase 3 studies. When this formulation was optimized, it was shown that the single-tablet B/F/TAF containing 50 mg of BIC produced plasma BIC exposures equivalent to those seen with the 75-mg single-agent tablet used in phase 2 [7]. Therefore, the single-tablet coformulation of B/F/TAF 50/200/25 mg was selected for further clinical development in phase 3 studies. After all participants in Study 1475 completed 48 weeks, the study treatments were unblinded and ongoing participants in both groups were offered continued therapy with the fixed-dose combination B/F/TAF 50/200/25 mg beginning at week 60. Here we present our findings through week 72 of the study reporting on at least 12 weeks of follow-up after this switch to open-label B/F/TAF for participants randomized to DTG and F/TAF.

Ninety-two of 98 participants (94%) completed the blinded phase, all of whom switched to a fixed-dose combination of B/F/TAF, 62 from the BIC and F/TAF arm and 30 from the DTG and F/TAF arm. Data were collected until all participants completed at least 72 weeks of treatment including at least 12 weeks of open-label B/F/TAF. At the time of analysis, the median exposure to BIC including blinded and open-label treatment was 75 weeks (interquartile 18, 76).

At week 72, 91 of 92 participants (99%) who enrolled in the open-label phase remained on study and all had HIV-1 RNA suppressed less than 50 copies/ml. One other participant withdrew consent in the open-label phase prior to week 72 and had an HIV-1 RNA less than 50 copies/ml at the time of discontinuation. In the open-label phase, no subjects met criteria for confirmed virologic failure or resistance testing. Through 72 weeks, no subject treated with B/F/TAF developed resistance to any component of their antiviral regimen.

Adverse events were similar in the blinded and open-label treatment phases. Amongst the 62 subjects randomized to BIC and F/TAF who continued B/F/TAF in the open-label phase, there were 21 adverse events occurring in 16 participants (26%); 18 events were mild in severity (Grade 1), three were moderate in severity (back pain, diarrhea, and hemorrhoids all Grade 2), and none were judged to be related to medications by the investigator. No subject reported a Grade 3 or 4 adverse event. Nine of the 30 participants (30%) who switched to B/F/TAF from DTG and F/TAF reported at least one adverse event after switching, all were mild in severity (Grade 1). Two of these adverse events were judged by the investigator to be related to switching from DTG and F/TAF to B/F/TAF; diarrhea and nausea, which were both Grade 1 events, self-limited and resolved without treatment interruption. No adverse event led to interruption or discontinuation of B/F/TAF in the open-label extension phase. There were no drug-related serious adverse events in either the randomized or open-label extension phases.

An increase in serum creatinine was observed in both randomization arms during the blinded phase; median change at week 60 was 0.11 mg/dl in the BIC and F/TAF

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arm and 0.14 mg/dl in the DTG and F/TAF arm (P value = 0.47). There was no further increase in serum creatinine after switching from DTG and F/TAF to B/F/TAF. Five participants had a Grade 3 or 4 treatment emergent laboratory abnormalities in the B/F/TAF open-label phase. Four were transient elevations in serum creatine kinase that occurred after exercise in young male subjects; none were associated with a clinical adverse event or led to the interruption of B/F/TAF and all improved without intervention. The fifth was a woman with Grade 3 hematuria consistent with sample contamination during menstruation.

In summary, combination antiretroviral therapy with zB/F/TAF demonstrated durable efficacy and was well tolerated. Among 65 participants randomized to BIC and F/TAF, 61 completed 72 weeks of treatment with BIC and F/TAF followed by B/F/TAF, all were virologically suppressed. Four participants discontinued the study regimen, two had HIV-1 RNA less than 50 copies/ml when they chose to withdraw from participation, one was lost to follow-up and one had an adverse event that led to study discontinuation. No participant receiving BIC and F/TAF or B/F/TAF had treatment emergent resistance detected to any component of the antiretroviral regimen.

The early but promising results obtained in the present study show that switching to the B/F/TAF fixed-dose combination from DTG and F/TAF is effective at maintaining virologic suppression. All 30 subjects who switched to B/F/TAF from DTG and F/TAF remained suppressed 12 weeks later. The B/F/TAF fixed-dose combination was well tolerated after switching, and no participant discontinued treatment after switching to B/F/TAF from DTG and F/TAF.

Although it is important to interpret these findings in the context of the study's small size, and limited duration of follow-up, to date, this provides the first assessment of patients switched from DTG and F/TAF to B/F/TAF as well as the longest duration of follow-up reported to date for patients treated with the combination B/F/TAF.

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All authors were involved in development of the report, interpretation of data, and have read and approved the final version. P.E.S., E.D., G.C., D.W., P.B., R.D., A.M., and C.B. enrolled participants, analyzed data, independently interpreted results, and edited and approved the report. X.W. designed the study and analyzed data. Data were reviewed and interpreted by P.E.S., S.E.C., and A.C. The first draft was written by P.E.S. and S.E.C. All authors contributed to edits of the final report.

The current data were presented at IDWeek 2017, San Diego, 4–8 October 2017.

Conflicts of interest

P.E.S. has received research support from BMS, Gilead, GSK, and Merck; consulting fees from AbbVie, BMS, Gilead, GSK, Merck, and Janssen. E.D. has received research grant support from Abbott Laboratories, Achillion Pharmaceuticals, Avexa, BMS, Gilead, GSK, Idenix, Janssen, Merck, Sangamo, Taimed, and Tobira; and consulting fees as a member of advisory boards for Gilead and Janssen. G.C. reports grants and personal fees from Gilead, GSK, Pfizer, Janssen, Sangamo, and Merck. D.W. reports research support from Gilead, ViiV, Tobira, and Kowa, and honoraria for advisory or speaker services from BMS, ViiV, Gilead, Janssen, and Merck. P.B. reports grants from Gilead. X.W., S.E.C., and A.C. are employees of Gilead and hold stock interest in the company.

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