A Phase 1b/2a study of the safety, pharmacokinetics and antiviral activity of BIT225 in patients with HIV-1 infection

John Wilkinson1*, Gary Ewart1, Carolyn Luscombe1, Kristin McBride1, Winai Ratanasuwan2, Michelle Miller1 and Robert L. Murphy3

1Biotron Limited, Suite 1.9, 56 Delhi Road, North Ryde, NSW 2113, Sydney, Australia; 2Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; 3Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

*Corresponding author. Tel: +61-2-8382-4945; Fax: +61-2-8382-4967; E-mail: jwilkinson@biotron.com.au

Received 6 July 2015; returned 16 August 2015; revised 8 October 2015; accepted 19 October 2015

Objectives: BIT225 (N-carbamimidoyl-5-(1-methyl-1H-pyrazol-4-yl)-2-naphthamide), a novel acyl-guanidine, is a novel antiviral drug that blocks Vpu ion channel activity and has anti-HIV-1 activity in vitro. The antiviral effect of BIT225 is most pronounced in cells of the myeloid lineage. With infected circulating monocytes and tissue-resident macrophages representing a key cellular reservoir of HIV-1, BIT225 has a potential role in the eradication of the virus from the host.

Patients and methods: BIT225-004 is a Phase 1b/2a, placebo-controlled, randomized study of the safety, pharmacokinetics and antiviral activity of BIT225 in 21 HIV-1-infected, ART-naive subjects. Twenty-one subjects were enrolled and received BIT225 (400 mg twice daily) or placebo treatment for 10 days (randomized 2:1). The anti-HIV-1 effect of BIT225 in the monocyte reservoir was measured in CD14+ monocytes isolated from the peripheral blood on days 1 (pre-dose), 5, 10 and 20; isolated monocytes were co-cultured ex vivo with MT4 T cells. De novo HIV-1 replication was measured by p24 activity of released virus into the culture supernatant to day 25 of co-culture. In addition, monocyte samples were collected for analysis by RT–PCR total HIV-1 DNA single-copy assay.

Results: Measurement of HIV-1 directly within the patient’s monocyte population indicated that BIT225 treatment significantly reduced the viral burden in myeloid lineage cells, which was more evident in those individuals with the highest viral loads. In addition, BIT225-treated subjects demonstrated a significantly reduced level of monocyte activation (sCD163) compared with the placebo controls.

Conclusions: This study’s unique design demonstrates that BIT225 can significantly reduce the dissemination of HIV-1 from infected monocytes. This has important ramifications for diminishing the seeding/re-seeding of the viral reservoir.

Introduction

BIT225 (N-carbamimidoyl-5-(1-methyl-1H-pyrazol-4-yl)-2-naphthamide) is a first-in-class antiviral drug that blocks Vpu ion channel activity, resulting in disrupted HIV-1 assembly within the host cell and a substantial loss of infectivity of the progeny virus.1 - 4 BIT225 demonstrates encouraging anti-HIV-1 activity in primary human CD14+ monocyte-derived macrophages (MDMs) and significantly reduces virus release from MDMs with a mean (±SE) effective concentration (EC50) of 2.25 ± 0.23 μM and a mean (±SE) toxic concentration (TC50) of 284 μM.3 While BIT225 demonstrates anti-HIV-1 activity in T cells,3 the effects are greater in cells of the myeloid lineage as a result of differences in viral assembly and release. In CD4+ T cells HIV-1 assembles at the plasma membrane,5 whereas in macrophages assembly is within internal multi-vesicular bodies (MVBs), where progeny viruses accumulate in high numbers and possess markers of these compartments.5 - 8

Viral reservoirs are a significant obstacle to the eradication of HIV-1 infection. Despite the availability of combination ART to HIV-1 infected individuals, HIV-1 avoids eradication through the establishment and survival of latently infected cellular reservoirs.9 - 12 While the majority of latently infected cells are found within the resting CD4+ T cells, predominantly central and transitional memory subsets,11 monocytes and macrophages of the myeloid lineage also contribute to the overall reservoir.12 - 16 While there is evidence that circulating monocytes are infected,12,15,17 they generally only reside in the periphery for around a day before entering the tissues and differentiating into macrophages, although recently it has been reported that macrophages within the periphery in addition to those in the various organs are capable of self-renewal...
without additional monocyte input. This result in the establishment of a long-lived HIV-1 myeloid cell reservoir within the periphery, bone marrow MDMs, perivascular macrophages and microglia, which can act as additional reservoirs of virus able to infect surrounding cells. Evidence suggests that monocytes, macrophages, dendritic cells and haematopoietic stem cells can also be latently infected, with additional support in the simian immunodeficiency virus model for latent infection.

Blocking viral replication within cells of the myeloid lineage often requires higher concentrations of antiretroviral drugs to penetrate these cell types compared with CD4+ T cells, making these cells an enduring reservoir during ART. Anatomical sanctuary sites exist, such as brain-resident macrophages, where drug penetration is poor and evaluating drug efficacy is challenging. Infected cells within these reservoir sites may be responsible for the persistent viraemia observed in some individuals on long-term ART. HIV-1 has been shown to replicate in CD14+ monocytes in vivo, even in those individuals receiving ART, and when therapy is discontinued in virally suppressed patients infectious virus originating from monocytes can be recovered. Further supporting the continued low-level viral replication in some of the treated individuals is the ongoing presence of two long terminal repeat (LTR) circles in CD14+ monocytes, although this finding remains contentious. Despite long-term ART, increased immune activation persists and results in increased mortality. The permanently elevated levels of immune activation are further indication of ongoing viral replication even in the presence of ART.

Here, we report on the antiviral effects of BIT225 in the setting of a Phase 1b/2a clinical trial conducted at Siriraj Hospital, Bangkok, Thailand, in HIV-1-positive individuals. Using a novel co-culture assay that measures infectious virus from patient CD14+ monocytes, and directly quantifying total HIV-1 DNA with RT–PCR, we demonstrated that treatment with BIT225 significantly reduced the level of HIV-1 within these cells. Our findings demonstrated that even a short, i.e. 10 day, treatment with BIT225 resulted in a decrease in monocyte immune activation, as measured by sCD163. These results provide evidence that BIT225 can target and reduce the viral burden in cells of the myeloid lineage in a clinical setting.

Methods

**Trial design**

Participants were recruited at a single site, Siriraj Hospital, in Bangkok, Thailand. The primary objective was the evaluation of the safety and tolerability of 400 mg of BIT225 twice daily compared with placebo in male and female individuals aged 18–65 years with HIV-1 infection (viral load >5000 copies/mL; CD4+ count >350 cells/μL) that were ART-naive or treatment-experienced patients that had received no antiretroviral treatment within 90 days of study screening.

**HIV-1 RNA plasma viral load assay**

Blood samples for HIV-1 plasma viral load were collected at the pre-screen and on days 1 (pre-dose) 2, 5, 10, 11 and 20. HIV-1 RNA was quantified using the COBAS TaqMan HIV-1 assay (Roche Diagnostics). Absolute CD4+ T cell counts were determined by flow cytometry on days 0, 5, 10 and 20.

**CD14+ monocyte isolation and co-culture assay**

For all patients, blood was collected on days 1 (pre-dose), 5 and 10 of dosing and at a follow-up visit 10 days after treatment (day 20). Plasma and CD14+ monocytes were isolated from the 21 study participants by magnetic bead sorting (Miltenyi Biotech, Gladbach, Germany) at each of these four timepoints. In real time, freshly isolated CD14+ monocytes were combined with uninfected MT4 T cells and co-cultured ex vivo for 25 days to amplify virus originating from the isolated monocyte cells. HIV-1 replication in the culture supernatant was determined by p24 ELISA (Perkin Elmer, MA, USA) after 5, 10, 15, 20 and 25 days of co-culture. Thus, for each individual, four cocultures were set up and sampled over a 25 day period for HIV-1 that originated from the infected individuals’ circulating monocytes.

**Total HIV-1 DNA quantification in monocytes**

Total HIV-1 DNA was extracted from isolated CD14+ monocytes collected at days 1 (pre-dose) 5, 10 and 20 using the Qiagen DNeasy Blood and Tissue Kit (Hilden, Germany) according to the manufacturer’s instructions. Total HIV-1 DNA was quantified by a real-time PCR assay specific for clade E HIV-gag using the clade E SK145 (5′-AGTGGGGGAGACCAGGACATGGAAAT-3′) and clade E SKC118 (5′-TAGTAGTCTCTGGTCTACACCT-3′) primers and incorporated a fluorescent locked nucleic acid (LNA) probe, SKLNA2-3 (5′-6-FAM AT[CA]A[TT]GAGGAA[GC]T[GC]-BHQ-1-3′; with LNAs shown in brackets). A TOPO cloned patient insert plasmid was used as a 10-fold serially diluted standard curve from 107 to 102 copies.

Total HIV-1 DNA copies were normalized using the Applied Biosystems (CA, USA) TaqMan β-actin detection reagents with a FAM-labelled probe. The standard curve was constructed from purified human Buffy coat DNA.

The assay was performed on a Bio-Rad iQ-5 multi-colour real-time PCR detection system (CA, USA), and consisted of 1 cycle of 95°C for 3 min followed by 45 cycles of 95°C for 15 s and 60°C for 1 min. All standard
dilutions and patient samples were run in triplicate and quantified total HIV-1 DNA was expressed as copies/500 ng DNA.

**Monocyte activation markers**

Levels of plasma sCD163 were quantified by ELISA according to the manufacturer’s recommendations (Trillium Diagnostics, Bangor, ME, USA). Plasma samples at days 1 (pre-dose), 5, 10 and 20 were batch tested in addition to 11 healthy HIV-1 seronegative individuals, to determine a normal range for this biomarker.

**Statistical analysis**

Pharmacokinetic parameters were derived from plasma sample data using non-compartmental methods employing WinNonlin® Phoenix version 6.3 (Pharsight, St Louis, MO, USA). Computer software (Statview 4.5; Abacus, Berkeley, CA, USA) was used for all statistical calculations. Comparisons between BIT225 and placebo controls were carried out by use of the Mann–Whitney U-test, with a significance cut-off of P<0.05, unless otherwise stated.

**Results**

**Study participants**

Twenty-one individuals were enrolled in the study and the two treatment arms were comparable for baseline characteristics (Table 1 and Figure S1, available as Supplementary data at JAC Online).

**Safety**

Adverse events (AEs) were reported from day 1 (time of administration of BIT225) to day 20. The majority of AEs were mild (Grade 1) in severity (Table S1), with the most frequently occurring AEs being headache (85.7% with BIT225 versus 28.6% with placebo), nausea (57.1% with BIT225 versus 28.6% with placebo) and vomiting (35.7% with BIT225 versus 14.3% with placebo).

A total of four BIT225-treated subjects experienced a Grade 2 AE; no subject experienced a Grade 3 AE. Although in most subjects the reported AEs were transient and self-limiting, two individuals prematurely discontinued BIT225, both due to headache, nausea and vomiting after the first dose (Grades 1 and 2).

**Pharmacokinetic analysis**

**Plasma**

The pharmacokinetics of BIT225 400 mg were assessed following single and repeated doses. Significant plasma concentrations were attained on day 1 after a single dose. AUC(0–12) values indicated an ~3-fold accumulation from day 1 to 10 and moderate inter-subject variability was observed in C_{min} and C_{max}. C_{max} averaged (±SE) 2110±239 ng/mL on day 1 and increased to an average of 4770±569 ng/mL on day 10. The median T_{max} for day 1 was 4.0 h (IQR 3–4 h) and on day 10 it was 3.5 h (IQR 0.5–4.5 h).

As calculated from the day 10 data, the mean (±SE) steady-state C_{max} was 4770±569 ng/mL and mean C_{min} was 3390±488 ng/mL (Figure S2). These are equivalent to ~16 µM (C_{max}) and ~11 µM (C_{min}) (the mol. wt of BIT225 is 293.32). The steady-state plasma concentration of BIT225 in the treated individuals was therefore at least five times the EC_{50} value for BIT225, 2.25±0.23 µM, as determined for BIT225 in vitro, using in HIV-1_{Bal}–infected MDMs.

The terminal half-life was calculated from the observed terminal phase rate constant estimated by linear regression through at least three data points in the terminal phase of the log concentration–time profile using data for the last dose on day 10. The pharmacokinetic sampling on day 1 was of insufficient duration and frequency to enable accurate determination of terminal half-life, hence it was calculated from the day 10 data. The half-life had a mean of 16.7 ± 3.0 h and ranged from 6.76 to 40.1 h.

**Table 1. Baseline characteristics of the study participants**

<table>
<thead>
<tr>
<th>Treatment group (no. of subjects)</th>
<th>BIT225 (n=14)</th>
<th>placebo (n=7)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>7 (50.0)</td>
<td>3 (42.9)</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>male</td>
<td>7 (50.0)</td>
<td>4 (57.1)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Withdraw</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Age (years), mean (SD):</td>
<td>32.1 (11.5)</td>
<td>25.6 (5.0)</td>
<td>29.9 (10.2)</td>
</tr>
<tr>
<td>Race, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>12 (85.7)</td>
<td>7 (100)</td>
<td>19 (90.5)</td>
</tr>
<tr>
<td>white</td>
<td>2 (14.3)</td>
<td>0</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD):</td>
<td>59.4 (7.9)</td>
<td>60.7 (9.4)</td>
<td>59.8 (8.2)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD):</td>
<td>22.3 (2.4)</td>
<td>22.4 (3.1)</td>
<td>22.3 (2.5)</td>
</tr>
<tr>
<td>Plasma viral load (copies/mL), median (IQR):</td>
<td>29049 (11 846–53553)</td>
<td>27897 (18 580–57698)</td>
<td>27897 (12 007–53644)</td>
</tr>
<tr>
<td>Log_{10} viral load (copies/mL), median (IQR):</td>
<td>4.46 (4.07–4.73)</td>
<td>4.45 (4.24–4.75)</td>
<td>4.45 (4.08–4.73)</td>
</tr>
<tr>
<td>CD4 count (cells/mm³), median (IQR):</td>
<td>428 (335–562)</td>
<td>482 (463–563)</td>
<td>451 (337–584)</td>
</tr>
</tbody>
</table>

The treated and placebo groups were comparable for baseline characteristics.
**CSF**

BIT225 was measured in CSF in two patients at ~4–5 h after the day 10 dose. CSF concentrations were 87.8 and 24.4 ng/mL in the two patients and the respective CSF/plasma ratios were 2.5 and 1.5%, indicating that BIT225 penetrates the blood–brain barrier.

**Plasma HIV-1 viral load and CD4+ T cell count**

BIT225 had no significant effect upon patient HIV-1 viral load or CD4+ T cell count. The mean plasma HIV-1 level in the placebo arm was relatively stable: it was 38341 copies/mL pre-dose, peaked at 50913 copies/mL on day 5 and returned to 32778 copies by day 20, 10 days post-therapy. Similarly, in the BIT225-treated cohort, excluding the two individuals that withdrew prior to day 5, mean copy number was 51494 copies/mL pre-dose and peaked on day 20 with 69677 copies/mL. Mean CD4+ T cell counts remained relatively constant throughout the study period in both cohorts, with the placebo arm fluctuating from +5 to −67 cells/mm³ and from +32 to −97 cells/mm³ with respect to baseline.

**Antiviral activity in myeloid cells**

**Total HIV-1 DNA as determined by RT–PCR**

Total HIV-1 DNA could only be detected at all four timepoints in the isolated monocytes from 6 of the 12 individuals receiving BIT225 (2 additional subjects withdrew from the study and were excluded from these analyses due to incomplete sample sets). In individuals where a signal was absent at one or more of the timepoints, the level of virus detected was generally low (<200 copies/500 ng) in these cells.

The placebo cohort demonstrated a significantly higher pre-dose total HIV-1 DNA copy number in the monocyte cells. HIV-1 DNA copy number in the placebo cohort was 7851 ± 2981 compared with 1493 ± 593 copies/500 ng in the BIT225-treated patients (P = 0.02). In the control group, the HIV-1 DNA copy number in the isolated monocytes remained stable throughout the study, with 7851 ± 2981, 6000 ± 4731, 6974 ± 3836 and 7098 ± 3066 copies/500 ng at pre-dose and days 5, 10 and 20, respectively (n = 7). In contrast, there was a reduction in total HIV-1 DNA copy number in the monocytes from the drug cohort during the course of treatment with BIT225 at day 10 (P = 0.09). The mean (±SE) total HIV-1 copy number in the BIT225-treated group was 1493 ± 593, 1414 ± 655, 547 ± 157 and 1419 ± 1183 copies/500 ng DNA at pre-dose and days 5, 10 and 20, respectively (Figure 1).

Analysis of individual responses from each subject demonstrated that three of the six BIT225-treated individuals demonstrated significant reductions in total HIV-1 DNA levels within their monocytes; the other three subjects’ responses remained unchanged. Of note, these three individuals with the greatest observable BIT225-induced effects also demonstrated the highest levels of HIV-1 within the circulating monocytes pre-dose. This suggests that a drug response can be detected provided there is a high detectable level of virus at the initiation of therapy for BIT225 to act upon (Figure 2).

Ten days of BIT225 treatment resulted in a 2.7-fold decrease or 63% reduction in the mean total HIV-1 DNA copy number in the monocytes of the BIT225-treated individuals (n = 6) compared with baseline (P = 0.09; Figure 3). The three treated individuals with the highest total HIV-1 DNA copy number pre-dose demonstrated a significant 3.3-fold or 70% reduction following treatment with BIT225, with a mean (±SE) decrease in monocyte HIV-1 copy number from 2733 ± 459 to 830 ± 199 copies/500 ng (P = 0.05).

**HIV-1 co-culture transfer assay**

The amount of virus originating from the CD14+ monocytes in the placebo group (n = 7) remained constant throughout the study, with no differences observed in the HIV-1 replication rate in the co-cultures at the four sampled timepoints: pre-dose and days 5, 10 and 20 (Figure 3). In the BIT225-treated arm (n = 12), a reduced amount of virus was detected in the isolated patient monocytes that were collected after 5 and 10 days of drug treatment, compared with pre-dose levels. This lower level of virus in the co-cultured cells was evident at days 5 and 10 of BIT225 therapy and persisted to day 20, 10 days after the drug was stopped. This is indicative of less HIV-1 present within the myeloid
compartment in the drug-treated patients and a post-drug treat-
ment effect after cessation of BIT225 treatment on day 10.

To further analyse the BIT225 antiviral effect, the 12
BIT225-treated patients were split into two groups on the basis
of their pre-dose plasma HIV-1 RNA viral loads relative to the
median cohort HIV-1 RNA viral load at that timepoint. Group A
included subjects with higher viral loads (>log10 4.43) and
Group B those with lower viral loads (<log10 4.43) at study
entry. Subjects with the highest viral loads had a significant reduc-
tion in virus in their CD14+ monocytes following treatment with
BIT225. In this group, monocytes isolated at day 5 demonstrated
significantly less virus within the co-cultures at days 15 and 20
of culture (P=0.05 and 0.04, respectively) and there was a
general trend of less HIV-1 originating from monocytes during
BIT225 therapy, even 10 days following the cessation of
BIT225 (Figure 4a). In contrast, analysis of virus levels within the
monocytes of treated individuals with lower plasma viral loads
(Group B) remained constant throughout the study (Figure 4b).

These data are similar to previous findings with the HIV-1 total
DNA assay on HIV-1 infected monocytes, where a high level of
virus before treatment allowed a measurable drug response
after treatment (Figure 3).

Figure 3. Reduction in virus burden within CD14+ monocytes following treatment. Although the levels of HIV-1 within the monocyte population
remained steady throughout the trial in the placebo arm (left panel), a reduction in the amount of HIV-1 within the monocytes of individuals
receiving BIT225 treatment was observed (right panel). The mean p24 titres in co-culture supernatants are shown (with SE bars) for monocytes
isolated pre-dose, on day 5 of treatment and on day 10 and 10 days following treatment for the placebo- and BIT225-treated individuals.

Figure 4. BIT225 therapy results in a significant reduction in HIV-1 within the CD14+ monocytes of (a) patients with higher viral loads (Group A; n=6)
compared with (b) those with lower viral loads (Group B; n=6). Individuals with higher levels of plasma HIV-1 at baseline demonstrated a greater
responses following 10 days of BIT225.
reasonably high plasma viral loads (days 5, 10 and 20, respectively. Despite enrolled individuals having healthy controls throughout the course of the study (Figure 5). Plasma sCD163 levels were comparable to those in uninfected relatively constant across the four timepoints, with 1275 + 736 dose to 1802 (n with the mean (SE bar) for HIV-1-uninfected controls (normal range: + 0.04) elevated from +0.53). Treatment with BIT225 (n=12) resulted in a significant (P=0.04) decrease in sCD163 levels, from 1992 ± 187 ng/mL pre-dose to 1802 ± 184 ng/mL at day 5, the level normalizing at day 10 to 2087 ± 163 ng/mL. At day 20, 10 days after BIT225 cessation, sCD163 levels were significantly (P=0.04) elevated from baseline, (2187 ± 205 ng/mL), suggesting the resumption of HIV-1 replication within this myeloid population.

In the placebo cohort (n=7), sCD163 plasma levels remained relatively constant across the four timepoints, with 1275 ± 141, 1263 ± 176, 1449 ± 238 and 1334 ± 196 ng/mL at pre-dose and days 5, 10 and 20, respectively. Despite enrolled individuals having reasonably high plasma viral loads (>log 3.5 copies/mL at entry), plasma sCD163 levels were comparable to those in uninfected healthy controls throughout the course of the study (Figure 5).

Quantification of monocyte activation

As a prelude to this study, a normal range of the activation marker sCD163 was determined in a cohort of 11 HIV-1-uninfected Caucasian individuals. The mean (+SE) sCD163 level was 1378 ± 151 ng/mL (range 680–2427 ng/mL) in this healthy cohort. The plasma level of the activation marker sCD163 was quantified in the individuals enrolled in the trial, at the four timepoints (pre-dose and days 5, 10 and 20) by ELISA. High plasma levels of sCD163 significantly correlated with higher HIV-1 viral loads pre-dose and throughout BIT225 therapy (P=0.0001, r=0.53). However, macrophages are widely acknowledged to be a major target for infection by HIV-1, with vaginal macrophages reported to be highly permissive and dendritic cells having been implicated in early infection within the mucosa and assisting in viral dissemination, rapidly transporting HIV-1 from the periphery to the lymph nodes, resulting in high levels of HIV-1 replication.24-26 By directly measuring total HIV-1 DNA within the circulating monocyte cells, the most accessible myeloid population, this study demonstrates that BIT225 reduces the viral burden in these cells following 10 days of treatment. The finding of a reduction in integrated virus within the CD14+ monocytes was supported using a co-culture assay to measure the release of infectious virions that originate from the CD14+ monocytes isolated from BIT225-treated individuals. Unsurprisingly, the activity of BIT225 was greatest in those individuals with a high viral burden at study entry, where an antiviral response could be clearly delineated from the limits of detection, i.e. the background of the assay. Further, the reduction in immune activation, as measured by the myeloid-specific marker sCD163, suggests a lower level of viral replication within these cells. The fact that virus can be detected within these circulating cells and that BIT225 has an effect is promising. Monocytes circulating in the periphery account for a small percentage of all myeloid cells and remain in circulation only briefly before extravasation and differentiation in the peripheral tissues, with macrophages found in every organ system.25,26 A drug targeting HIV-1 replication within the myeloid cells and limiting virus dissemination has a clear clinical benefit.

Despite combination ART reducing plasma HIV-1 RNA levels to below detection, cell-associated HIV-1 DNA can be detected in...
Clinical trial of BIT225 in HIV-1-seropositive individuals

most patients receiving ART. Interruption of treatment results in the rapid rebound of virus from latent reservoirs and from cells and/or sanctuary sites where drug penetration is poor. Current approaches employing latency-reversing or reactivation agents result in productive infection within these cells, with the potential to both reduce and re-seed the reservoir. The generation of large numbers of de novo virions, using agents such as vorinostat and romidepsin, requires effective ART that targets both T cell and myeloid infected cells to be fully effective and prevent a net increase in the reservoir size. By targeting the cells of the myeloid lineage and preventing seeding/re-seeding of the reservoirs, BIT225 has a potential role in the eradication strategy of HIV-1.

Acknowledgements

We would like to thank all patients who enrolled in this study and the clinical support staff at Siriraj Hospital and ACLIRES. We would also like to thank Professor Ruengpung Sutthent and her staff in the Department of Microbiology, Faculty of Medicine, for graciously allowing us access to their PC3 facility at Siriraj Hospital. Lastly, we are grateful for the assistance given by Dr Craig Witherington with the real-time co-culture assay.

Funding

This work was supported by Biotron Limited.

Transparency declarations

J. W., C. L., G. E., K. McB. and M. M. were all employed by Biotron Limited at the time of the study. R. L. M. is a Medical Consultant for Biotron Limited. There are no conflicts of interest for W. R.

Author contributions

W. R. was the principal investigator of the study and responsible for recruitment of patients. J. W., C. L., G. E., M. M and R. L. M. were involved with the design and implementation of the study. J. W. performed the co-culture and scCD163 assays and K. McB. performed the single copy RT–PCR assay.

Supplementary data

Figures S1 and S2 and Table S1 are available at JAC Online (http://jac.oupjournals.org/).

References

26 Shikuma CM, Nakamoto B, Shiramizu B et al. Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV. Antivir Ther 2012; 17: 1233–42.


