

Fostemsavir, a Drug with Novel Mechanism for the Treatment of HIV-1 Infection

Raman Palanisamy Priyadharsini, C. M. Divyashanthi, Dhivya Elango

Department of Pharmacology, JIPMER, Karaikal, Puducherry, India

Abstract

HIV is a global problem with increased mortality and morbidity. The highly active antiretroviral therapy is effective in reducing the HIV RNA and improving the immune response. The drugs in the current regimen have certain disadvantages such as adverse effects, drug intolerance, and drug resistance. Since there is a demand for identifying the drugs with new mechanism of action, the compounds which target the viral gp120 receptor were screened and the most suitable drug among them was identified. In a Phase II and Phase III trial, the drug BMS-663068 fostemsavir was found to be efficacious in reducing the viral RNA levels. The drug is a prodrug that gets converted into metabolite temsavir BMS-626529. The preferred dose is 600 mg orally 12 hourly in patients who had undergone many treatment schedules with multidrug-resistant infection and those who cannot tolerate the drug regimen due to resistance and safety issues. The drug is metabolized by CYP3A4 and has drug interactions with CYP3A4 inducers and inhibitors. This review mainly comprises the mechanism of action, clinical trials, pharmacological properties, and adverse effects of the drug fostemsavir.

Keywords: BMS-663068, fostemsavir, gp120 inhibitor, HIV, novel drugs, temsavir

INTRODUCTION

As per the WHO, it was estimated that 38 million people in the world were affected with HIV in 2019.^[1] The major treatment approach is highly active antiretroviral therapy (HAART), and the major goals of HAART include suppression of viral replication and recovery of the immune system. HIV being a highly threatening disease-causing immunosuppression requires the treatment with multiple drug regimens for quite a long duration. The currently preferred drug groups used for the treatment include nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry inhibitors. The treatment with such drugs can lead to severe adverse effects, drug interactions, lack of adherence, and drug resistance. The later treatment options for the treatment-experienced patients are very less. There is a need for new drugs with novel mechanisms of action in patients who had undergone multiple treatments. Fostemsavir is a prodrug that gets converted to temsavir which exhibits a novel mechanism by inhibiting the attachment of the virus to CD4 cells. The drug was identified to be specifically used in HIV-1 who had undergone many drug treatments. The drug

does not affect the human cells, and it is active against X4, R5, and R5 × 4 HIV-1.^[2]

MECHANISM OF ACTION

The entry inhibitors include various drug classes such as CCR5 antagonists, Gp120 antagonists, GP41 antagonists, and CD4 antagonists. The viral glycoproteins such as gp120 and gp41 attach to the CD4 cell receptor which brings about the conformational changes in the gp120 exposing the target chemokine receptor-binding domains that bind to major co-receptors CXCR4 and CCR5. The entry begins with the attachment of gp120 to the CD4 cell followed by the formation of loop structure by gp120, CD4 cell, and co-receptor and gp41 penetrating the cell membrane. A series of the compounds such as BMS-488403, BMS-378806, and

Address for correspondence: Raman Palanisamy Priyadharsini, Department of Pharmacology, JIPMER, Karaikal, Puducherry, India.
E-mail: drpriya.rp@gmail.com

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Table 1: Summary of the trials

Study	Population	Intervention	Comparator	Outcome
Initial trials	Healthy volunteers <i>n</i> =88 BMS-663068	BMS-663068 Dose ranging from 20 to 2000	-	Plasma half-life 3.2-4.5 h with immediate release and 7-14 h with extended release
	HIV-infected patients <i>n</i> =30	BMS-488403 800 mg 1800 mg 12 received 800 mg 12 received 1800 mg 6 received placebo days monotherapy	-	Reduction in HIV RNA (Hanna)
Phase IIa	HIV-infected patients	BMS-663068 600 mg + RTV 100 mg every 12 h BMS-663068 1200 mg + RTV 100 mg every bedtime BMS-663068 1200 mg + RTV 100 mg every 12 h BMS-663068 1200 mg + RTV 100 mg every morning BMS-663068 every 12 h	-	Reduction in RNA levels
Phase IIb	Treatment-experienced patients <i>n</i> =251	Ratio 1:1:1:1 <i>n</i> =200 Fostemsavir various doses for 7 days After 7 days fostemsavir as add-on to tenofovir + raltegravir	RTV-boosted ATV for the initial 7 days <i>n</i> =51 After 7 days ATZ/r as add-on to tenofovir + raltegravir	A decrease from 0.69 to 1.44 log ₁₀ copies/ml
Phase III	Multidrug-resistant HIV patients	Randomized cohort (3/4th population) And nonrandomized cohort	Randomized cohort (1/4 th population)	Decrease in the RNA level after 8 days of fostemsavir group compared to placebo
Drug-drug interaction study	Healthy volunteers	Totally 3 groups BMS-663068 600 mg BD BMS-663068 600 mg BD + RTV 100 mg QD BMS-663068 600 mg BD + ATV 300 mg QD plus RTV 100 mg QD	1 group ATV 300 mg QD plus RTV 100 mg QD	RTV alone increases the concentration

ATV=Atazanavir, RTV=Ritonavir

BMS-663068 (fostemsavir) were tested in various *in vitro* studies and animal studies. The drug fostemsavir acts by binding to the gp120 in the virus envelope and thus targeting the viral entry into the CD4 cell.^[3]

PRECLINICAL STUDIES

The study reported by Fanglin *et al.* reported that the compound BMS-378806 was found to be effective against HIV-1 affected cell lines without causing cytotoxicity. This was the compound initially identified, and it had favorable pharmacological properties such as better oral bioavailability, reduced protein binding, and good safety profile.^[4]

In vitro studies demonstrated the efficacy of the compound in HeLa cells infected with viral DNA. HeLa cells expressing CCR5 receptor and CD4 protein were exposed to the viral DNA containing HIV-1 *LAI-Δenv-luc* and *env* gene. A high-throughput screening was developed to evaluate the effect of the test compounds in the viral-infected HeLa cells. A wide variety of compounds were screened, and a chemical compound indole glyoxamide derivative was identified. The drug temsavir was identified in the process, and its phosphonoxyethyl derivative fostemsavir was further developed.^[5] Fostemsavir was effective at EC₅₀ of 0.7 nmol/L in HIV_{LA1} infection, 0.01 nmol/L in

HIV-susceptible infection, and 2 μmol/L in less susceptible HIV infection.^[6]

EARLY TRIALS

The compounds initially evaluated had some disadvantages. Although BMS-378806 was identified with some good, favorable pharmacological properties, the drug had a short half-life, and the target concentration was not achieved. Another related compound BMS-488403 exerted *in vitro* antiviral activity, and prolonged half-life was tested in various studies.

BMS-488403

A double-blinded randomized ascending dose study was conducted among HIV-infected patients with doses of drug BMS-488403 800 mg and 1800 mg with a high-fat meal [Table 1]. A total number of 30 patients were randomized into three groups in the ratio of 4:4:1. Among 30 patients, 12 received 800 mg of the drug, 12 received 1800 mg of the drug, and 6 received a placebo. The plasma HIV RNA levels were reduced after 8 days of monotherapy. Although the compound reduced the RNA levels, further development of the compound was stopped because of limited oral bioavailability.^[7]

BMS-663068 (fostemsavir)

The drug (BMS-663068) was tested in healthy volunteers of age ranging from 18- to 45-year-old people. A double-blinded

placebo-controlled trial was conducted using single and multiple ascending doses in 88 healthy volunteers. The doses used were ranging from 20 mg to 2000 mg combined with ritonavir or used alone in an immediate-release formulation and extended-release formulation.

The doses used were as follows:

- 100 mg immediate release 8 hourly
- 200 mg immediate release 8 hourly
- 600 mg extended release plus ritonavir every 12 hourly
- 1200 mg extended release every 12 hourly
- 1200 mg extended release plus ritonavir 100 mg every 12 hourly.

The drug was converted to active form BMS-626529 (temsavir) immediately. The time taken to attain the maximum levels with the immediate-release formulation and extended-release formulation is 1.5–2 h and 4–5 h, respectively. The steady-state concentration levels were achieved on days 2 and 3^[8] (levels with ritonavir).

The proarrhythmic property of fostemsavir was studied in Phase I randomized double-blinded trial at therapeutic doses and supratherapeutic doses. The therapeutic dose used was 1200 mg BID, and the supratherapeutic dose used was 2400 mg BID. There was no prolonging of QT interval at therapeutic doses, whereas there is the prolongation of QT interval at supratherapeutic doses.^[9]

PHASE II A STUDY (PROOF-OF-CONCEPT STUDY)

BMS-663068 (fostemsavir)

The safety, pharmacodynamics, and pharmacokinetics of BMS-663068 were identified by a Phase I study. The HIV-1-infected patients were randomized into five treatment groups in an open-label multiple-dosing study, i.e.,

- BMS-663068 600 mg + ritonavir 100 mg every 12 h
- BMS-663068 1200 mg + ritonavir 100 mg every bedtime
- BMS-663068 1200 mg + ritonavir 100 mg every 12 h
- BMS-663068 1200 mg + ritonavir 100 mg every morning
- BMS-663068 every 12 h.

The effect of fostemsavir is assessed by a dose-ranging Phase IIb study in which 7 days of fostemsavir monotherapy resulted in a decrease in RNA levels from 0.7 to 1.5 log₁₀ c/mL in treatment-experienced patients.^[10]

PHASE IIb (ANALYZED AT 24 WEEKS, 48 WEEKS, AND 96 WEEKS)

The inclusion criteria included patients with high levels of plasma RNA, CD4 cells more than 50 cells/mm³, and patients with HIV-1 genotype and phenotype who are susceptible to atazanavir, raltegravir, and tenofovir disoproxil fumarate. A Phase II randomized multinational trial was conducted, in which the treatment experienced patients (n = 251) were allocated in a ratio of 1:1:1:1 in the following treatment arms (fostemsavir 400 mg twice daily, 800 mg thrice daily, 600

mg QD, 1200 mg QD) and they were compared with the another treatment arm, i.e., ritonavir boosted atazanavir (ATZ/r) therapy. The patients were treated with fostemsavir for 7 days, and after that, all the patients were receiving either fostemsavir (n = 200) or Ritonavir boosted atazanavir (ATZ/r) (n = 51) as an add-on therapy to raltegravir and tenofovir disoproxil fumarate.^[11] The HIV RNA levels decrease from 0.69 log₁₀ copies to 1.44 log₁₀ copies/ml. The efficacy of fostemsavir was demonstrated which was comparable to that of atazanavir/ritonavir combination as an add-on therapy to raltegravir and tenofovir.

PHASE III TRIAL (BRIGHT E TRIAL)

The Phase III trial which was conducted in 23 countries included multidrug-resistant HIV patients more than or equal to 18 years of age. The trial started with 731 patients satisfying the eligibility criteria among which 360 patients were excluded for various reasons. The treatment failure was confirmed by plasma RNA levels, and the study was conducted for a total duration of 48 weeks. At least four drug treatments are already exhausted in these patients, i.e. every agent in each class is removed as a therapeutic option to be combined with fostemsavir. The patients were divided into two cohorts: the first cohort is the randomized cohort (n = 272) with one or two available fully active drug options and the second cohort (n = 99) with no active drug options. The three-fourth and one-fourth population of the randomized cohort received fostemsavir + failing regimen and fostemsavir + placebo for 96 weeks. The nonrandomized cohort received only the fostemsavir for 96 weeks. The primary endpoint is the decrease in RNA levels after 8 days of fostemsavir therapy. The mean reduction in the RNA levels after 8 weeks of fostemsavir is 0.17 ± 0.08 log₁₀ copies/ml in the placebo group and 0.79 ± 0.05 log₁₀ copies/ml.^[12,13]

A study also reported the use of fostemsavir in 32 HIV-negative patients who are taking opioid antagonists as a treatment for substance use. The drug fostemsavir was given for a total duration of 10 days in patients receiving methadone and patients receiving a combination of buprenorphine and naloxone. The opioid antagonists did not affect the concentration of fostemsavir in the blood, and there were no serious adverse effects.^[14]

FOOD AND DRUG ADMINISTRATION APPROVAL AND COMPASSIONATE USE

The Food and Drug Administration approved the drug (Rukobia) on fast-track approval on July 2, 2020, in HIV patients who had a poor response to multiple treatments.^[15,16] Fostemsavir is also prescribed for compassionate usage in individuals with multidrug-resistant HIV infection.^[17]

DRUG PROPERTIES

Pharmacokinetics

The active metabolite of fostemsavir is temsavir which is

metabolized by CYP3A4. The drug also serves as a substrate for P-glycoprotein and BCRP. The plasma half-life ranged from 3.2 to 4.5 h with the immediate-release formulation and 7–14 h with the extended-release formulation, respectively.^[18]

Dosage and formulation

The dose preferred is 600 mg oral extended-release tablets every 12 h in treatment-experienced patients with multidrug resistance.^[18]

Adverse effects and contraindications

The drug concentrations of the temsavir increase with the concomitant use of P-glycoprotein inhibitors, BCRP inhibitors, and CYP3A4 inhibitors. The CYP3A4-inducing drugs such as rifampicin, carbamazepine, and phenytoin decrease the therapeutic effects of the drug. The most common adverse effects include diarrhea, nausea, headache, fatiguability, night sweats, and cold sore elevation of liver enzymes which occurred in 8.5%–18% of patients.^[3,19]

Drug interactions and resistance

The concurrent use of drugs such as CYP3A4 inhibitors/inducers, P-gp inhibitors, and BCRP inhibitors increases the concentration of temsavir resulting in toxicity and better avoided. The plasma concentration of the substrates of the OATP and BCRP is increased when along with fostemsavir, and the dose of such drugs is reduced. The drug can be combined with other anti-HIV drugs without dose adjustment, whereas with drugs such as HMG-CoA inhibitors and ethinylestradiol supplements, dose adjustment is required.^[20] The potential drug–drug interactions of fostemsavir with other anti-HIV drugs such as ritonavir and atazanavir were evaluated in the study which involved healthy volunteers randomized into four groups. The combination of the drugs atazanavir/ritonavir with fostemsavir increased the parameters such as C_{max}, area under the curve (AUC), and C₁₂ of temsavir (BMS) by 68%, 54%, and 57%, respectively. The drug ritonavir increased the values of C_{max}, AUC, and C₁₂ of temsavir (BMS) by 53%, 45%, and 44%, respectively.^[21] The Los Alamos HIV database was used to assess the fostemsavir resistance using 1997 gp120 sequences, and it was identified that the prevalence of drug resistance mutations is less with HIV-1 subtype.^[22]

CONCLUSION

Although many compounds that inhibit viral gp120 were investigated, BMS-663068 was finally successful till Phase III trial and got approved for use in heavily treatment-experienced patients who had multidrug resistance. The drug is marketed under the name Rukobia and further postmarketing studies are required to identify the efficacy and long-term adverse effects.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. HIV/AIDS. Available from: <https://www.who.int/news-room/fact-sheets/detail/hiv-aids>. [Last accessed on 2020 Nov 02].
2. Najjar A, Najjar A, Karaman R. Newly developed prodrugs and prodrugs in development; an insight of the recent years. *Molecules* 2020;25:884.
3. Venanzi Rullo E, Ceccarelli M, Condorelli F, Facciola A, Visalli G, D'Aleo F, *et al.* Investigational drugs in HIV: Pros and cons of entry and fusion inhibitors (Review). *Mol Med Rep* 2019;19:1987-95.
4. Lin PF, Blair W, Wang T, Spicer T, Guo Q, Zhou N, *et al.* A small molecule HIV-1 inhibitor that targets the HIV-1 envelope and inhibits CD4 receptor binding. *Proc Natl Acad Sci U S A* 2003;100:11013-8.
5. Meanwell NA, Krystal MR, Nowicka-Sans B, Langley DR, Conlon DA, Eastgate MD, *et al.* Inhibitors of HIV-1 attachment: The discovery and development of temsavir and its prodrug fostemsavir. *J Med Chem* 2018;61:62-80.
6. Zhang X. Anti-retroviral drugs: Current state and development in the next decade. *Acta Pharm Sin B* 2018;8:131-6.
7. Hanna GJ, Lalezari J, Hellinger JA, Wohl DA, Nettles R, Persson A, *et al.* Antiviral activity, pharmacokinetics, and safety of BMS-488043, a novel oral small-molecule HIV-1 attachment inhibitor, in HIV-1-infected subjects. *Antimicrob Agents Chemother* 2011;55:722-8.
8. Nettles R, Chien C, Elefant E, Wang X, Chung E, Zhu L, *et al.* Single and multiple dose pharmacokinetics and safety in non HIV infected healthy subjects dosed with BMS 663068, an oral HIV attachment inhibitor. *Proceedings of the 12th International Workshop on Clinical Pharmacology of HIV Therapy*; 2011. April 13 15; Miami, Florida, USA.
9. Lagishetty C, Moore K, Ackerman P, Llamoso C, Magee M. Effects of temsavir, active moiety of antiretroviral agent fostemsavir, on QT interval: Results from a phase I study and an exposure-response analysis. *Clin Transl Sci* 2020;13:769-76.
10. Nettles RE, Schürmann D, Zhu L, Stonier M, Huang SP, Chang I, *et al.* Pharmacodynamics, safety, and pharmacokinetics of BMS-663068, an oral HIV-1 attachment inhibitor in HIV-1-infected subjects. *J Infect Dis* 2012;206:1002-11.
11. Lataillade M, Zhou N, Joshi SR, Lee S, Stock DA, Hanna GJ, *et al.* Viral drug resistance through 48 weeks, in a phase 2b, randomized, controlled trial of the HIV-1 attachment inhibitor prodrug, fostemsavir. *J Acquir Immune Defic Syndr* 2018;77:299-307.
12. Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina JM, *et al.* Fostemsavir in adults with multidrug-resistant HIV-1 infection. *N Engl J Med* 2020;382:1232-43.
13. Cahn P, Fink V, Patterson P. Fostemsavir: A new CD4 attachment inhibitor. *Curr Opin HIV AIDS* 2018;13:341-5.
14. Moore K, Magee M, Sevinisky H, Chang M, Lubin S, Myers E, *et al.* Methadone and buprenorphine pharmacokinetics and pharmacodynamics when coadministered with fostemsavir to opioid dependent, human immunodeficiency virus seronegative participants. *Br J Clin Pharmacol* 2019;85:1771-80.
15. Markham A. Correction to: Fostemsavir: First approval. *Drugs* 2020;80:1615.
16. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. PubChem Compound Summary for CID 11319217, Fostemsavir. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Fostemsavir>. [Last accessed on 2021 Mar 01].
17. Cambou MC, Landovitz RJ. Novel antiretroviral agents. *Curr HIV/AIDS Rep* 2020;17:118-24.
18. Hiryak K, Koren DE. Fostemsavir: A novel attachment inhibitor for patients with multidrug resistant HIV 1 infection. *Ann Pharmacother* 2021;55:792-7.

19. Fostemsavir Uses, Side Effects and Warnings Drugs.com. Available from: <https://www.drugs.com/mtm/fostemsavir.html>. [Last accessed on 2020 Nov 06].
20. Moore KP, Mageau AS, Magee M, Gorycki PD, Ackerman P, Llamoso C. Fostemsavir drug – Drug interaction profile, an attachment inhibitor and oral prodrug of temsavir, for heavily treatment experienced HIV-1-infected patients. *Open Forum Infect Dis* 2019;6:867.
21. Zhu L, Hruska M, Hwang C, Shah V, Furlong M, Hanna GJ, *et al.* Pharmacokinetic interactions between BMS-626529, the active moiety of the HIV-1 attachment inhibitor prodrug BMS-663068, and ritonavir or ritonavir-boosted atazanavir in healthy subjects. *Antimicrob Agents Chemother* 2015;59:3816-22.
22. Bouba Y, Berno G, Fabeni L, Carioti L, Salpini R, Aquaro S, *et al.* Identification of gp120 polymorphisms in HIV-1 B subtype potentially associated with resistance to fostemsavir. *J Antimicrob Chemother* 2020;75:1778-86.