

Fostemsavir: A novel multidrug-resistant HIV-1 infection therapy

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Abstract: Fostemsavir (Rukobia, ViiV Healthcare), is a prodrug of temsavir, an uncommon pyridine complicates with cogent liveliness against HIV-1. Fostemsavir, the first nuncupative attachment inhibitor, was ratified and granted the therapy designation by the Food and Drug Administration (FDA) for use in association with other antiretroviral agents for the treatment of HIV-1 infection in adults. As absorption of temsavir is not altered with increased gastric pH, patients may take acidic concealing agents such as famotidine during fostemsavir therapy. Temsavir is primarily metabolized through hydrolysis but also via cytochrome P-450 (CYP) oxygenation; therefore, coadministration of fostemsavir with firm CYP3A inducers such as rifampin, carbamazepine, phenytoin, mitotane, enzalutamide, or St John's plant is contraindicated because it may result in significantly lower temsavir exposure, which can eventually impair virologic response. The most common adverse reactions combined with fostemsavir use embody nausea, scour, bother, abdominal smart, indigestion, labor, rash, and sleep disturbance.

1. Introduction

The U.S. Food and Drug Administration (FDA) has approved Rukobia (Fostemsavir), developed by ViiV Healthcare. This is a new class of antiretroviral drugs for people with HIV who have tried multiple HIV drug therapies and have not been successfully treated due to drug resistance, intolerance or safety. Rukobia is an HIV-1 treatment that works differently from other HIV-1 treatments by stopping the virus from attaching to your CD4+ T-cells. Fostemsavir is a "first-in-class" HIV attachment inhibitor. It is a pro-drug of Temsavir. It can bind the gp120 subunit of the HIV-1 envelope glycoprotein GP160 complex to block the interaction between virus and cell CD4 receptor, thus preventing the virus from infecting host cells. Rukobia is not for use alone. Rukobia will be given along with an HIV-1 treatment regimen recommended by the doctor. It was developed by ViiV Healthcare to be used in combination with other antiviral drugs to treat adults infected with multidrug-resistant HIV-1. Fostemsavir has previously been granted breakthrough therapy designation and fast track status by the US FDA. Its new drug application was also granted priority review status.

2. Structure and Mechanism or fostemsavir

Fostemsavir tromethamine is a prodrug of temsavir, an HIV-1 gp120-directed attachment inhibitor. The chemical name of fostemsavir tromethamine is (3-((4-benzoyl-1-piperazinyl) (oxo)acetyl)-4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c] pyridin-1-yl) methyl dihydrogen phosphate, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). The empirical formula is C₂₅H₂₆N₇O₈P•C₄H₁₁NO₃. The molecular weight is 704.6 g/mol (583.5 as free acid). It has the following structural formula:

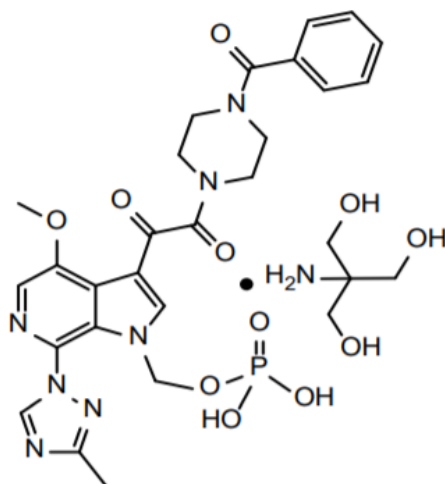


Figure 1. Structure of Fostemsavir.

3. Pharmacodynamics and Pharmacokinetics

Before Fostemsavir is a phosphonoxy methyl prodrug, which is hydrolyzed by alkaline phosphatase in the gastrointestinal tract to Temsavir (active part) to exert pharmacological effects. Fostemsavir is usually not detected in plasma, indicating that the conversion of Fostemsavir to Temsavir mainly occurs before entering the blood circulatory system. The pharmacokinetics of Temsavir are similar in healthy people and HIV-1 infected subjects [1].

In patients with multi-drug resistant HIV-1 who have received multiple HIV treatments, Fostemsavir (600 mg each time, 2 times a day) is administered in combination with other antiretroviral drugs. 2~3 d Tensa vir blood drug after administration The concentration reaches a steady state. The cumulative ratio is 1.1 to 1.7. The maximum plasma concentration (C) of Temsavi at steady state is 1770 ng/mL, the area under the steady-state curve (AUC.) during the dosing interval (12 h) is 12 900 ng·h·mL', and the medication is taken for 12 hours. The posterior blood concentration (C) was 478 ng/mL [2].

Fostemsavir single-dose administration studies show that the absolute bioavailability of Temsavir is 26.9%, and the time (t) to reach the peak blood concentration is 2h. The plasma protein binding rate of Temsavir is 88.4% (mainly bound to serum albumin), the blood-plasma ratio is 0.74, and the steady-state volume of distribution (V) is 29.5 L. Temsavir hydrolyzed by esterase accounted for 36.1%. Cytochrome P450 (cytochrome P450.CYP) oxidation accounted for 21.2%. Uridine diphosphate glucuronosyltransferase (urine diphosphate glucuronosyltransferase, UGT) metabolism accounted for <1%. Temsavir clearance rate (CL) and apparent clearance rate (CL F) were 17.9 and 66.4L/h, respectively, and the average half-life was 11h. 51% of Temsavir is ultimately excreted in urine (prototype drug content <2%), and 33% is excreted in feces (prototype drug content is 1.1%).

Factors such as age, gender, race, etc. have no significant effect on the pharmacokinetics of Temsavir. Patients with mild, moderate, and severe liver damage do not need to adjust the dose of Fostemsavir. Patients with mild, moderate or severe renal impairment, patients with end-stage renal insufficiency and patients undergoing hemodialysis also do not need to adjust the dose.

4. Dosage and administration

According to the remaining treatment plan, HIV-1 patients were divided into two groups. The first group included patients who could still accept a completely active drug in at least one but no more than two types of anti-reverse viruses. Then, the group's participants were randomly assigned to receive blind treatment, fostemsavir Sven (600 mg/ oral, two times a day) or a comforter. Their current plans ranged from the first day to the eighth day. After that, all the patients received open-label fostemsavir and OBT treatment [3].

18 clinical trials organized by Research and development companies conducting FTR to treat HIV-1 infected subjects, 17 of which have all been completed by the time of FDA approval for marketing. The trials contain 1340 subjects: 665 subjects with 14 trials from phase I, 304 subjects with 2 trials from phase II, 371 subjects with 1 trial from phase III.

5. Trail

5.1 Trial I

Trial I AI438011 was a phase 2b clinical trial number NCT01384734, randomized, active-controlled, blinded-to-FTR-dose trial. The trial was done at 53 hospitals and outpatient clinics from 10 countries in South America, North America, Europe and Africa [4]. The double-blind positive and placebo-controlled trial was conducted in heavily treated HIV-1-infected patients enrolling 581 subjects for screening and 254 met the clinical trial criteria. Subjects were randomly divided into 5 groups according to the ratio of 1:1:1: 1:1. Four FTR groups: A (n=52) with dose of 400 mg, bid, B (n=50) with dose of 800 mg, bid, C (n=51) with dose of 600 mg, qd, D (n=50) with dose of 1200 mg, qd, and one control group E (n=51) with dose of 300 mg ritonavir-boosted atazanavir and 100 mg of ritonavir, qd, lasting for 48 weeks treatment.

The number of evaluable cases was 251: Group A (n = 50), Group B (n = 49), Group C (n = 51), Group D (n = 50), and Group E (n = 51). The number of patients who did not continue treatment due to lack of efficacy was 0%, 2 (4.1%), 0%, 1 (2.0%) and 0%. No virological data were available at week 48, and treatment could not be continued due to adverse effects or death in 1 (2.0%), 2 (4.1%), 0%, 1 (2.0%), and 2 (3.9%) cases; for other reasons, treatment could not be continued in 2 (4.1%), 0%, 1 (2.0%), and 2 (3.9%) cases. 2 (4.0%), 5 (10.2%), 3 (5.9%), 0% and 5 (9.8) were unable to continue treatment for other reasons; 1 (2.0), 0%, 0%, 0% and 0% continued to participate in the trial despite the loss of data during the window period [4].

5.2 Trial II

BRIGHTHE, clinical trial number NCT02362503, was a Phase 3, international, double-blind, placebo-controlled trial that evaluated the efficacy and safety of RUKOBIA in patients with HIV-1 who were heavily treatment-experienced (HTE) with limited treatment options remaining. All patients in BRIGHTHE: were failing on their current ARV regimens with viral loads of ≥ 400 copies/mL and had ≤ 2 classes of ARVs remaining at baseline due to resistance, intolerability, contraindication, or other safety concerns. (Cited from <https://www.rukobiahcp.com/clinical-trial/>) 731 patients were recruited for this trial, and 371 patients were eligible if screened. The subjects were divided into 2 groups. group A (n = 272), was randomized 3:1 into 2 groups, group A1 (n = 69), and group A2 (n = 203). For the first 8 days, group A1 was blinded to the placebo and ineffective treatment option, and group A2, blinded to the FTR 600 mg, bid and ineffective treatment option, and from day 9 both A1 and A2 received blind FTR 600 mg, bid, effective therapy, until 64 weeks. Group 2 (n = 69), a non-randomized group with no effective antiretroviral drug (ARV) options at all, multi-resistant patients with HIV-1 RNA ≥ 400 copies per ml, received open-blind FTR 600 mg, bid, effective therapy from day 1 until 64 weeks.

Overall, 371 of the 731 patients had received treatment: 272 in a random queue and 99 in a nonrandom queue. At the end of the data analysis in the forty-eighth week, 57 out of 272 patients in the random queue (21%) and 32 out of 99 patients in the nonrandom queue (32%) had been withdrawn from the test. In the 8-day double-blind random queue study, the rate of adverse events in the two groups was similar to that of serious ones. The most common drug-related adverse events between level 2 and level 4 were nausea (4%) and diarrhea (3%). The adverse event caused 27 patients (7%) to stop the trial treatment. Most of the adverse events that led to the withdrawal of medicine were related to infection. During the test, the rate of abnormalities in the clinical related laboratory was very low, and there was no important safety signal related to the abnormality in ECG. This indicated that the drug was relatively safe. In the random queue, 49 out of 272 patients (18%) met the standard of poisoning failure as defined in the plan in the forty-eighth week. In the nonrandom queue study, 46

out of 99 patients (46%) had a virus failure at 48 weeks. In this limited test which involved multiple drug resistance HIV-1 infection in adults, after several days of single functional treatment, fostemsavir was better than the previous one. All the patients in the test had already used up all the approved drugs in at least four types of anti-reverse viruses, and the number of CD4+T cells was low. In a random group of patients whose HIV-1 RNA level was higher than 1000 copies /ml at the baseline, which was a common standard for other tests of the HIV-1 infected patients with drug resistance, the average level of the HIV-1 RNA from the baseline to the eighth day was reduced to /ml at the baseline in the HIV-1 group, and there was no copy of HIV-1 RNA at the eighth day in the comforter group. At the same time, 68% of the patients in the random queue had HIV-1 RNA levels lower than 0.5 log₁₀ copy /ml. The systematic evaluation of HIV clinical test data showed that the decrease of HIV-1 RNA level was related to meaningful clinical practice. The benefits of HIV-1 infection. In the random group, the percentage of patients who had a 48-week patient poison response was 54% after being given an open sign of fostemsavir and an optimal background treatment. Although the patient continued to lose the test due to other factors, the twenty-fourth week to the forty-eighth week's relief rate showed continuous relief. In the random queue, whether the patient used one or two kinds of antipyretics in the initial background treatment, the rate of suppression was similar. All in all, they found that among the adults who had received multiple types of HIV-1 infection treatment, the average change of the HIV-1 RNA level of fostemsavir from the baseline to the eighth day in the random queue was better than that of the condoms. The treatment lasted for 48 weeks, which supported the further development of the treatment of fostemsavir as a patient with HIV-1 infection [5].

6. Safety profile and adverse effects

In these two studies, fostemsavir demonstrated strong tolerance. In the patients with kidney damage and liver damage, no death or clinical change was found in the clinical laboratory, ECG, vital signs or physical examination. In the study of kidney damage, one of the subjects in group E (ESRD) began to experience two SAE (pneumonia and pneumonia) 8 days after a single dose of medicine in the first stage, which had nothing to do with the research medicine. These SAEs caused subjects to stop the study. No other SAE or discontinuation due to AE occurred during the study of renal impairment. A total of 31 AES from 10 subjects (33.3%) were reported, and the incidence of treatment AES did not seem to increase with the increase of the severity of the renal injury. The most common adverse reaction was diarrhea (3 subjects, 1 in groups a, C and E), nausea (2 subjects in Group E) and sleepiness (2 subjects in group A). Treatment emergent AES (2 subjects each) are usually reported. A. All AES in groups C and D were considered to be mild in intensity, and there was no AE in group B. Two subjects in Group E experienced treatment emergent AES of moderate (nausea, vomiting, earache) or severe (pneumonia, pulmonary edema) intensity. All the subjects reported abdominal pain, dry mouth, vomiting, fatigue and headache. All the AE was solved at the end of the study. In the study of liver damage, SAE, serious AE or AE induced drug withdrawal did not happen during the treatment. A total of 11 AES from 9 subjects (30.0%) were reported, and the incidence of AES did not seem to increase with the increase of the severity of the liver injury. The most frequently reported AE was headache (6 cases in normal liver function group, 3 cases in mild group and 1 case in moderate group), and the other 1 case in each group reported AE. Headache, flatulence and flushing were considered to be related to the drug research. All AEs were resolved at the end of the study [6].

In another phase III experiment enrolled 371 participants, 272 in a random queue, and 99 in a nonrandom queue. On the data deadline of the ninety-sixth week (August 14, 2018), 213 players (78%) in the random queue and 61 players (62%) in the nonrandom queue were still in the research. Withdrawal from the study was most commonly due to lack of efficacy (n=12), non-compliance (n=11), death (n=9), and death (n=15), lack of efficacy (n=6), and non-compliance in a nonrandomized cohort (n=6). Adverse events led to the withdrawal of seven and four participants, respectively. One participant in the placebo group withdrew before starting the open-label fostemsavir treatment and was not included in the safety population. Of all participants, 22% were women, 22% were black / African Americans, and 44% were over the age of 50 [7].

These experimental results support the clinical safety of fostemsavir in the treatment of HIV.

7. Efficacy

The BRIGHT (NCT02362503) experiment evaluated the safety and effectiveness of this drug. Researchers conduct experiments in 22 countries around the world. This is a multi-center Phase III clinical trial. The researchers selected 371 adult patients who had failed previous treatments. The median age is 49 years old (range 17-73) males account for 78%. 85% of the volunteers had received no less than 5 HIV treatments before.

According to the types of remaining treatments available, patients were enrolled into 2 cohorts. In a randomized cohort (n=272), patients have the full activity to class 1 antiretroviral drugs but not more than class 2. The study randomized patients at a ratio of 3:1, and received Fostemsavir (600 mg each time, 2 times a day, n=203) or placebo (n=69) based on the existing treatment plan for 8 days, and then received Open-label Fostemsavir combined with optimized background therapy. In a non-randomized cohort (n=99), patients who were not fully active against optional antiretroviral drugs received open-label Fostemsavir (600 mg each time, twice a day) plus optimized background therapy. The primary endpoint of the trial is the average reduction in the logarithmic number of HIV-1 nucleic acids on day 8 compared to day 1 in patients in the randomized cohort. Key secondary endpoints include the proportion of patients who achieved a virological response (HIV-1 RNA<40 copies/mL) at the 24th, 48th, and 96th weeks of treatment, and the change in CD4+T cell count.

Day 8. The reduction of HIV-1 RNA level in the Fostemsavir group (0.79 log copies/mL) in the random cohort was 0.63 log₁₀ copies/mL (95% CI: -0.81~-0.44:P) higher than that of the placebo group (0.17 log₁₀ copies/mL); P<0.001). In the Fostemsavir group, the rate of viral load reduction from baseline >0.5 log₁₀ copies/mL and >1 log₁₀ copies/mL was 65% (131/203) and 46% (93/203), respectively, while the placebo group was 19% (13/69) and 10% (7/69). At week 24 and week 48, the proportion of patients with the virological response (HIV-1 RNA<40 copies/mL) in the random cohort was 53%; at week 96, the proportion of patients with virological response was 60%. The average CD and T cell count also gradually increased during treatment, from 90 cells/mm at the 24th week to 205 cells/mm³ at the 96th week. In the non-randomized cohort. 37% of subjects reached HIV-1 RNA <40 copies/mL CD at Week 24 and Week 96, and the average change in T cell count from baseline increased over time: Week 24 It was 41 pieces/mm. The 96th week was 119 pieces/mm³ [5].

8. Drug Interaction

Fostemsavir active ingredient Temsavir has no inhibitory or inducing effect on the CYP enzyme system and UGT, but the drug is CYP3A4, P-sugar. Protein and breast cancer resistance protein (breast cancer resistance protein BCRP), and Temsavir and (or) its metabolites are BCRP and organic anion transporter 1B1 (organic anion transporter Inhibitor of transporting polypeptide 1B1, OATP1B1)/OATP1B3. Combined administration with CYP3A4:P-glycoprotein and/or BCRP inhibitor can increase the blood concentration of Temsavir, which has no clinical significance at the therapeutic dose.

Fostemsavir is administered simultaneously with the androgen receptor inhibitor enzalutamide, the anticonvulsants carbamazepine and phenytoin, the antimycobacterial drug rifampicin, the antitumor drug mitotane, or the Chinese herbal medicine Hypericum perforatum. The blood concentration of the active ingredient Temsavir Decreases. Fostemsavir may lose its therapeutic effect, and its combined use should be prohibited in clinical practice. Fostemsavir can increase the blood concentration of certain statins (including rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and simvastatin). When combined, statins should be administered at the lowest starting dose. And monitor the adverse events related to statins. When Fostemsavir and compound oral contraceptives containing ethinyl estradiol and norethindrone were administered at the same time, the exposure of ethinyl estradiol increased by 40%, but it had no significant effect on the level of norethindrone. When combined with Fostemsavir. The daily dose of ethinyl estradiol in oral contraceptives should not exceed 30 ug. For patients with

additional risk factors for thromboembolic events, caution is recommended [8]. Co-administration with Fostemsavir can increase the blood concentration of hepatitis C antiviral drugs glarevir and vocilvir, and the degree of increase is unpredictable: the increase of glaprevir plasma concentration may be related to the increase of alanine aminotransferase. Fostemsavir can prolong the QT interval, and the combined administration of drugs known to have the risk of torsade de pointes ventricular tachycardia may increase the risk of torsade de pointes ventricular tachycardia, and should be used with caution.[9]

9. Medication guide

Before taking Fostemsavir, tell your healthcare provider about all of your medical conditions, including if you: have or have had a heart problem, including a heart rhythm problem called QTc prolongation (irregular heartbeat). have or have had liver problems, including hepatitis B or C infection. Are pregnant or plan to become pregnant. It is not known if RUKOBIA will harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with Fostemsavir are breastfeeding or plan to breastfeed. Do not breastfeed if you take Fostemsavir. You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with Fostemsavir.

10. Conclusion

Fostemsavir was first approved on July 2, 2020 as a precursor to Temsavir. It is mainly used to treat infected adults who have received a variety of anti-HIV drugs. But these adults cannot be successfully treated with other therapies because of drug resistance, intolerance or safety concerns. Fostemsavir (FTR) is an attachment inhibitor that is active regardless of viral predisposition and has no cross-resistance to any existing ARV compounds. In a Phase 3 study, plasma viral RNA decreased by 1.21-1.73 log₁₀ copies/ mL from baseline after 8 days of functional monotherapy; At 48 weeks, up to 82% of patients treated with FTR and optimized background ARV achieved virologic suppression of fewer than 50 copies/mL.

The Phase III clinical trial of Fostemsavir is still in progress. The experiment started in February 2015 and is expected to end in 2024. The mechanism of more drug resistance, safety, and efficacy is still being studied. The critical point for drug resistance is still being explored. Fostemsavir, as an HIV-1 attachment inhibitor, has stifled the possibility of development from the beginning of the virus, and it is a brand-new achievement in both technical and ideological terms. This also brings more drug options for HIV patients, and brings hope and help to long-term HIV patients.

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