

## HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

### Fostemsavir for HIV-1 infection for heavily treatment-experienced adults

<b>NIHRIO ID</b>	27354	<b>NICE ID</b>	10264
<b>Developer/Company</b>	ViiV Healthcare UK Ltd	<b>UKPS ID</b>	653090

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials.
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### SUMMARY

Fostemsavir is in clinical development for human immunodeficiency virus-1 (HIV-1) infection in heavily treatment-experienced adults. HIV is a virus that damages the cells in the immune system and weakens the body's ability to fight everyday infections and diseases. HIV infection is incurable but there are effective treatments that enable most infected people to live a healthy life. Antiretroviral (ARV) medicines are used to treat HIV. However, poor adherence and the subsequent development of drug resistance is one reason why HIV treatment can fail. A drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs. For highly treatment-experienced patients who have failed on a number of treatment regimens and have limited treatment options, complex regimens including drugs to which the virus is partially resistant may be required.

Fostemsavir is given orally as a tablet. It is an ARV medicine that prevents HIV from attaching to host cells. It acts by binding to a specific protein on the surface of the virus which prevents the virus from attaching to the host immune cells. This first-in-class mechanism of action has the potential to have full activity against HIV strains that have developed resistance. If licensed, fostemsavir will offer a treatment option for patients with HIV-1 infection in heavily treatment-experienced adults who have limited treatment options available.

*This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.*

## PROPOSED INDICATION

Treatment of HIV-1 infection in heavily treatment-experienced adults with multi-drug resistance.<sup>a</sup>

## TECHNOLOGY

### DESCRIPTION

Fostemsavir (GSK3684934) is an investigational drug and belongs to a group of HIV drugs called gp120 attaching inhibitors. Fostemsavir is a prodrug, which means that it is an inactive drug. Once taken, fostemsavir does not work until the body converts it into an active form called temsavir.<sup>1</sup> Temsavir inhibits the binding of the HIV virus to host white blood cells through blocking the HIV gp120 receptor.<sup>2</sup> On binding, the virus cannot effectively attach to the host CD4+ receptor to complete the fusion and entry process.<sup>3</sup>

Fostemsavir is currently in clinical development for the treatment of HIV-1 infection in heavily treatment-experienced adults with multi-drug resistance. In the phase III clinical trial (BRIGHTE, NCT02362503) fostemsavir 600mg tablets are administered twice daily for up to 48 weeks or longer.<sup>4</sup>

### INNOVATION AND/OR ADVANTAGES

Fostemsavir is a first-in-class attachment inhibitor with a novel mechanism of action that demonstrates virologic activity in HIV-infected treatment-experienced individuals.<sup>5-7</sup> In the absence of effective binding of HIV gp120 with the host CD4 receptor, HIV does not enter the host cell. Because fostemsavir has a novel mechanism of action, the drug is expected to have full activity against HIV strains that have developed resistance to other classes of antiretroviral medications.<sup>5</sup>

Overall results from the BRIGHTE trial indicated at week 96 found that 60% of randomly assigned patients achieved virologic suppression, which was an increase of 6% from week 48, despite continued attrition. Results also showed an increase in CD4 among randomly assigned patients with baseline CD4 <200 cells/ $\mu$ L, levels increased to  $\geq$ 200 in 67% and increased from <50 to  $\geq$ 200 cells/ $\mu$ L in 56%, mean was 205 cells/ $\mu$ L.<sup>8</sup> A subgroup analysis based on demographic factors showed that virologic responses at week 96 increased from 48 and were comparable across most groups.<sup>9</sup>

Immunologic improvements were also comparable across all subgroups, including a mean increase of 240 cells/ $\mu$ L in participants with baseline CD4 counts <20 cells/ $\mu$ L. Further, 46% of patients with CD4 counts <20 cells/ $\mu$ L had a severe adverse event, whereas 27% of patients with CD4 counts  $\geq$ 200 cells/ $\mu$ L had a severe adverse event.<sup>9</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Fostemsavir does not currently have Marketing Authorisation in the EU/UK for any indication.

Fostemsavir has been designated a Breakthrough Therapy by the US FDA<sup>10</sup>

<sup>a</sup> Information provided by ViiV Healthcare UK Ltd on UK PharmaScan

### DISEASE BACKGROUND

The human immunodeficiency virus (HIV) is a virus that damages the cells in the immune system and weakens the body's ability to fight everyday infections and disease. Acquired immune deficiency syndrome (AIDS) is the name used to describe a number of potentially life-threatening infections and illnesses that happen when the immune system has been severely damaged by the HIV virus.<sup>11</sup>

There are two main types of HIV – HIV-1 (the most common) and HIV-2 (relatively uncommon and less infectious). The strains of HIV-1 can be classified into four groups. Of these, M is the 'major' group and is responsible for the majority of the global HIV epidemic.<sup>12</sup>

The ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs is called HIV drug resistance. The consequences of HIV drug resistance include treatment failure and further spread of drug-resistant HIV. This can compromise the effectiveness of the limited therapeutic options to reach the last 90 targets (of achieving viral suppression) and further reduce HIV incidence, mortality and morbidity.<sup>13</sup>

Most people diagnosed with HIV in the UK acquire the virus through unprotected vaginal or anal sex. Also, HIV infection can be transmitted through unprotected oral sex and sharing sex toys with someone infected with HIV.<sup>14</sup> Other risk factors for getting HIV includes sharing needles, syringes and other injecting equipment; transmission of the virus from mother to baby before or during birth or by breastfeeding; receiving unsafe injections, blood transfusions (now very rare in the UK); experiencing accidental needle stick injuries, including among health workers.<sup>14,15</sup>

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months, many are unaware of their status until later stages.<sup>15</sup> Most people experience a short flu-like illness two to six weeks after HIV infection, which lasts for a week or two. After these symptoms disappear, HIV may not cause any symptoms for many years, although the virus continues to damage the immune system.<sup>11</sup> Consequently, an individual can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea and cough. Without treatment, they could also develop severe illnesses such as tuberculosis, cryptococcal meningitis, severe bacterial infections and cancers such as lymphomas and Kaposi's sarcoma, among others.<sup>15</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

In 2017, 4,363 people were newly diagnosed with HIV and it was estimated that there were 101,600 people living with HIV in the UK.<sup>16</sup> In 2017, 92% (Credible interval (CrI) 88 to 94%) of the estimated 101,600 (CrI 99,300 to 106,400) people living with HIV infection in the UK were diagnosed, 98% of people diagnosed were receiving treatment and 97% of people receiving treatment were virally suppressed. Overall, 87% of people living with HIV in the UK were estimated to have an undetectable viral load and therefore unable to pass on the infection.<sup>17</sup>

Of the 87,057 people attending for care in 2015, 97% were retained in care 2 years later in 2017.<sup>17</sup> In the UK, the population of people living with diagnosed HIV infection (93,385) is growing older and diversifying. In 2017, 98% of people receiving care were on antiretroviral treatment, and 97% on treatment had an undetectable viral load.<sup>17</sup> Among drug-experienced patients, the prevalence of HIV resistance to any drug class fell markedly from 72.4% in 2002 to 30% in 2014.<sup>18</sup>

In 2017, 428 people with HIV infection died from any cause and over half of the deaths (62%) were among people aged 50 years and over. The crude overall mortality rate among those aged 15 to 59 years who had their HIV infection diagnosed promptly (CD4 cell count  $\geq 350$  cells/mm<sup>3</sup>) was 1.22 per 1,000 compared to 1.66 per 1,000 in the general population of the same age group.<sup>17</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

While there's no cure for HIV, there are very effective treatments that enable most people with the virus to live a long and healthy life. HIV is treated with antiretroviral medications, which work by stopping the virus replicating in the body. This allows the immune system to repair itself and prevent further damage. A combination of HIV drugs is used because HIV can quickly adapt and become resistant.<sup>19</sup> Such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.<sup>20</sup>

Recommendations for treatment of individuals diagnosed with HIV-1 in the UK issued by the British HIV Association (BHIVA) show that overall, therapy selection in patients with MDR HIV-1 is complex and individualised, and must consider, among others, contraindications and drug-drug interactions (ARV and concomitant medication), tolerability, cross-resistance within ARV classes; viability of CCR5-antagonists in only a proportion of patients, viral load and Page 5 of 13 CD4+ cell count, treatment history, drug resistance profile, adherence, as well as future salvage regimens.<sup>21</sup>

### CURRENT TREATMENT OPTIONS

BHIVA recommend patients with extensive drug resistance are switched to a new antiretroviral therapy regimen containing at least two preferably three fully active agents with at least one active ritonavir-boosted protease inhibitor (PI/r) such as twice-daily darunavir/r and one agent with a novel mechanism [an integrase inhibitor (INI), maraviroc or enfuvirtide] with etravirine an option based on viral susceptibility and extensive drug resistance including reduced darunavir susceptibility receive dolutegravir as the INI. Individuals with extensive drug resistance including reduced darunavir susceptibility receive dolutegravir as the INI.<sup>21</sup>

### PLACE OF TECHNOLOGY

If licensed fostemsavir will provide a treatment option for HIV-1 infection in heavily treatment-experienced adults with multi-drug resistance who have limited treatment option available.

## CLINICAL TRIAL INFORMATION

Trial	BRIGHT, <a href="#">NCT02362503</a> ; A1438-047, <a href="#">EudraCT 2014-002111-41</a> ; aged $\geq 18$ years; Fostemsavir (various regimens) phase III
Sponsor	ViiV Healthcare
Status	Ongoing
Source of Information	Trial registry, <sup>4,22</sup> Manufacturer, <sup>23</sup>

<b>Location</b>	EU (incl UK), USA, Canada and other countries
<b>Design</b>	Randomised, parallel assignment, double-blinded
<b>Participants</b>	n= 371 (planned); aged ≥ 18 years; chronic HIV-1 infection; AVR experienced baseline resistance, intolerability, and/or contraindications to AVR; failing current regimen with a confirmed plasma HIV-1 RNA ≥ 400 c/mL
<b>Schedule</b>	<p>Patients were randomly allocated 3:1 fostemsavir or placebo</p> <ul style="list-style-type: none"> <li>• Experimental : A1: Fostemsavir <ul style="list-style-type: none"> <li>○ Phase 1: Fostemsavir 600 mg tablets orally twice daily for 8 days.</li> <li>○ Phase 2: Fostemsavir 600 mg tablets orally twice daily for 48 weeks or longer</li> </ul> </li> <li>• Active Comparator : B1: Placebo + fostemsavir <ul style="list-style-type: none"> <li>○ Phase 1: Placebo twice daily for 8 days</li> <li>○ Phase 2: Fostemsavir 600 mg tablets orally twice daily for 48 weeks or longer</li> </ul> </li> <li>• Experimental: Fostemsavir <ul style="list-style-type: none"> <li>○ Fostemsavir 600 mg tablets orally twice daily for 48 weeks or longer</li> </ul> </li> </ul>
<b>Follow-up</b>	Up to 96 weeks or longer
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Mean change in logarithm to the base 10 (<math>\log^{10}</math>) HIV-1 ribonucleic acid (RNA) from day 1 at day 8-randomised cohort [Time frame: day 1 and day 8]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Percentage of participants with HIV-1 RNA decreases from day 1 that exceed 0.5 <math>\log^{10}</math> c/mL and 1.0 <math>\log^{10}</math> c/mL at day 8-randomised cohort [Time frame: day 1 and day 8]</li> <li>• Percentage of participants with HIV-1 RNA &lt;40 c/mL at weeks 24 and 48-randomised cohort [Time frame: weeks 24 and 48 ]</li> <li>• Number of participants with on-treatment serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation (AELD)-randomised cohort [Time frame: up to week 48 analysis cut-off date]</li> <li>• Number of participants with toxicity grade increase in clinical chemistry results to grade 3-4 relative to baseline-randomised cohort [Time frame: baseline and up to week 48 analysis cut-off date]</li> <li>• Number of participants with toxicity grade increase in haematology results to grade 3-4 relative to baseline-randomised cohort [Time frame: baseline and up to week 48 analysis cut-off date]</li> <li>• Number of participants with Centers for Disease Control (CDC) class C events-randomised cohort [Time frame: up to week 48 analysis cut-off date]</li> <li>• Change from day 1 in CD4+ T-cell count at day 8-randomised cohort [Time frame: day 1 and day 8]</li> <li>• Change in CD4+ T- cell count percentage from day 1 at day 8-randomised cohort [Time frame: day 1 and day 8]</li> <li>• Change from baseline in <math>\log^{10}</math> HIV-1 RNA for fostemsavir when given with OBT through week 48-randomised cohort [Time frame: baseline and up to week 48]</li> <li>• Change from baseline in CD4+ T-cell count through week 48-Randomised cohort [Time frame: baseline and up to week 48]</li> <li>• Change from baseline in CD4+ T-cell count percentage through week 48 [Time frame: baseline and up to week 48]</li> <li>• Number of participants with treatment-emergent viral genotypic substitution of Interest in the GP160 domain as a measure of genotypic resistance-randomised cohort [Time frame: week 48]</li> </ul>

	<ul style="list-style-type: none"> <li>Number of participants with indicated fold change ratio (FCR) using the Monogram Phenosense Entry assay-randomised cohort [Time frame: week 48]</li> </ul>
<b>Key Results</b>	<ul style="list-style-type: none"> <li>At week 96, 60% of patients receiving fostemsavir plus optimized background therapy (OBT) in the randomised cohort (n=163/272) achieved virologic suppression (HIV-1 RNA &lt;40 copies per millilitre [c/mL]), an increase of 6% from week 48 results</li> <li>Patients in the randomised cohort showed continued immunologic improvement through week 96 as demonstrated by an increase in CD4+ T-cell counts (mean change from baseline of +205 cells per microliter [cells/μL], a mean increase of 66 cells/μL from week 48)</li> <li>At week 96 in the randomised cohort, 67% of patients with a baseline CD4 &lt;200 cells/μL increased to a CD4 ≥200 cells/μL, and 56% of patients with a baseline CD4 &lt;50 cells/μL increased to a CD4 ≥200 cells/μL</li> </ul>
<b>Adverse effects (AEs)</b>	<ul style="list-style-type: none"> <li>Almost all patients who received fostemsavir experienced at least one adverse event</li> <li>The most common of adverse events were nausea, diarrhoea and headache</li> <li>34% patients experienced at least one serious adverse event (SAE)</li> <li>3% of SAEs were related to the study medication with few SAEs (1%) leading to discontinuation of study medication</li> </ul>
<b>Expected reporting date</b>	Study completion date December 2024

## ESTIMATED COST

The cost of fostemsavir is not known yet.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- No relevant guidance identified

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Human Immunodeficiency Virus Services (Adults). B06/S/a.
- NHS England. Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 infection (all ages). B06/P/a. January 2019.
- NHS England. Clinical Commissioning Policy: Use of cobicistat as a booster in treatment of HIV infection (all ages). F03/P/b. July 2015 – updated September 2018.
- NHS England. Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents. 16043/P. July 2016.
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- NHS England. Clinical Commissioning Policy: Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults. F03/P/a. 2015.

## OTHER GUIDANCE

- European AIDS Clinical Society (EACS). Guidelines. Version 10.0 November 2019.<sup>24</sup>
- British HIV Association (BHIVA), British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update).<sup>21</sup>

## ADDITIONAL INFORMATION

## REFERENCES

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