CLINICAL PRIORITIES ADVISORY GROUP
18 07 2022

Agenda Item No	2.2
National Programme	Blood and Infection PoC
Clinical Reference Group	HIV
URN	2108

Title
Fostemsavir for multi-drug resistant HIV-1 infection (Adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend the relative priority

Proposition
For routine commissioning This clinical commissioning policy proposition is for the use fostemsavir and is for individuals with MDR HIV-1 infection who have limited or no therapeutic options, and therefore a fully viral suppressive regimen cannot be constructed. These individuals might have some ART options which are fully or partially active, but the virus will not be controlled and they will have a detectable virus within their blood tests. If a regimen of different active drugs cannot be constructed, it may lead to virological failure which in turn leads to immunosuppression, morbidity and mortality as well as the risk of onward transmission Fostemsavir is a new drug, which is the first to belong to this class of drugs for HIV treatment. The active metabolite of fostemsavir is temsavir, which is a HIV-1 gp120-directed attachment inhibitor. Fostemsavir has a unique mechanism of action, binding directly to the HIV viral envelope gp120, close to the CD4 binding site, locking gp120 into a closed state. This prohibits the conformational change necessary for initial interaction between the virus and OFFICIAL 4 CD4 cell-surface receptors, thereby preventing attachment and subsequent entry into host T cells and other immune cells. Fostemsavir has no in-vitro cross-resistance with other antiretroviral classes, and is active against CCR5-tropic, CXCR4-tropic, and dual-tropic strains of HIV-1. It is proposed that fostemsavir will be added to an optimised background ART regimen and initiated under the advice of a HIV specialist multidisciplinary team, in

line with the British HIV Association (BHIVA) guidelines (BHIVA. 2016) for the treatment of individuals with multiple class virological failure (with or without) extensive drug resistance.

Clinical Panel recommendation
Select appropriate option (*delete prompt and all not applicable statements*): The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement *(To be copied and pasted from evidence reviewer's CPAG Summary Report for Clinical Panel (delete this prompt))*
Clinical effectiveness	
Critical outcomes	
Virological suppression[1]: virologic response (HIV-1 RNA <40 copies/mL) **Certainty of evidence:** Moderate to very low	This outcome is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. When virological suppression is achieved, an individual has negligible ability to transmit the virus to others and low risk of disease progression. If virological failure is seen, consideration is given to alter the current ART regimen to achieve viral suppression. Two papers reporting the multicentre, two-cohort, phase three clinical trial known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for the proportion (%) of patients who had a virological response following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Virologic response was defined as HIV-1 RNA <40 copies/mL and measured up to 96 weeks. In adults with no fully active, approved ARV options •Kozal et al 2020 (n=99) reported that following additional treatment with fostemsavir, 37% of patients had a virological response at week 24 and 38% at week 48. Of the 15 patients who received ibalizumab in their initial OBT, 8 (53%) had a virological response at weeks 24 and 48. No measures of statistical significance were reported. (**VERY LOW**) •Lataillade et al 2020 (n=99) reported that 35% of patients had a virological response following additional treatment with fostemsavir at week 72 and 37% at week 96. No measures of statistical significance were reported. (**VERY LOW**) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=272) reported that overall following additional treatment with fostemsavir, 53% of patients had a virological response at week 24 and 54% at week 48. (**LOW**) •Kozal et al 2020 (n=272) reported that following additional treatment with fostemsavir, 57% of patients receiving fostemsavir in the initial blinded phase (days 1-8) had a virological response at week 48 compared to 45% of patients

[1] In the intention-to-treat (ITT) population (all patients who had received at least one dose of a trial regimen), virologic response rate was determined using the Food and Drug Administration Snapshot algorithm, whereby patients who had missing HIV-1 RNA values or who changed the composition of their OBT were classified as having had virologic failure.

	initially receiving placebo. No measures of statistical significance were reported. (**MODERATE**) •Lataillade et al 2020 (n=272) reported that 53% of patients had a virological response following additional treatment with fostemsavir at week 72 and 60% at week 96. No measures of statistical significance were reported. (**LOW**) **One multicentre, two-cohort phase three clinical trial (known as the BRIGHTE study) with 371 patients provided moderate to very low certainty evidence that the proportion (%) of patients who had a virological response increased over time (up to 96 weeks) following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (randomised cohort). The proportion (%) of patients who had a virological response following additional treatment with fostemsavir remained comparable at each timepoint in patients with no remaining ARV options (non-randomised cohort). No measures of statistical significance were reported for either cohort at any timepoint.**
Virological suppression: virologic failure (HIV-1 RNA ≥400 copies/mL)[2] **Certainty of evidence:** Low to very low	This outcome is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. When virological suppression is achieved, an individual has negligible ability to transmit the virus to others and low risk of disease progression. If virological failure is seen, consideration is given to alter the current ART regimen to achieve viral suppression. Two papers reporting the multicentre, two-cohort, phase three clinical trial known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for virologic failure following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Virologic failure was defined as HIV-1 RNA ≥400 copies/mL or HIV-1 RNA level above the Nadir (i.e. ≥40 copies/mL) and measured up to 96 weeks. In adults with no fully active, approved ARV options •Kozal et al 2020 (n=99) reported virologic failure following additional treatment with fostemsavir in 46% patients when defined as HIV-1 RNA ≥400 copies/mL and 53% when defined as HIV-1 RNA ≥40 copies/mL at 48 weeks. No measures of statistical significance were reported. (**VERY LOW**)

[2] Before 24 weeks, virologic failure was defined as an HIV-1 RNA value of at least 400 copies/mL after previous confirmed suppression to <400 copies/mL or an increase of at least 1.0 $\log_{10}$ in the HIV-1 RNA level above the nadir (that is, ≥40 copies/mL). During or after 24 weeks, virologic failure was defined as an HIV-1RNA level of at least 400 copies/mL

	•Lataillade et al 2020 (n=99) reported virologic failure following additional treatment with fostemsavir in 49% patients when defined as HIV-1 RNA ≥400 copies/mL at96 weeks. No measures of statistical significance were reported. (**VERY LOW**) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=272) reported virologic failure following additional treatment with fostemsavir in 18% patients when defined as HIV-1 RNA ≥400 copies/mL and 38% when defined as HIV-1 RNA ≥40 copies/mL at 48 weeks. No measures of statistical significance were reported. (**LOW**) •Lataillade et al 2020 (n=272) reported virologic failure following additional treatment with fostemsavir in 23% patients, when defined as HIV-1 RNA ≥400 copies/mL at 96 weeks. No measures of statistical significance were reported. (**LOW**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence that virologic failure rates remained similar across different timepoints up to 96 weeks following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and patients with one or two fully active ARVs remaining. No measures of statistical significance were reported**.
Reduction in viral load (change in HIV-1 RNA log10) **Certainty of evidence:** Moderate	This outcome is important to patients as it reflects a measure of clinical effectiveness of the treatment. A reduction in viral load correlates with reducing the risk HIV transmission to others and a lower risk of disease progression. One paper reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020) provided evidence for the reduction in viral load following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=270)[3]. Reduction in viral load was defined as change in HIV-1 RNA log10and measured from day 1 to 8. In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=270)7reported a mean[4](SE) reduction from baseline to day 8 in HIV-1 RNA level of 0.79 (0.05) log10copies/mL in the fostemsavir group and 0.17 (0.08) log10copies/mL in the placebo group. This reflected a statistically significant benefit of fostemsavir compared with

[3] Two patients (both from the fostemsavir treatment group) had missing Day 1 HIV-1 RNA values and were not included in the analysis.

[4] Mean adjusted by Day 1 $\log_{10}$HIV-1 RNA.

	placebo (a between group difference of -0.63 log10copies/mL [95% CI -0.81 to -0.44]; p<0.0001)[5].(**MODERATE**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided moderate certainty evidence from 201 patients with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes, that at day 8 of treatment there was a statistically significant reduction in viral load in patients receiving blinded fostemsavir compared to patients receiving blinded placebo.**
Important outcomes	
Mortality **Certainty of evidence:** Low to very low	Mortality is important to patients as individuals with advanced HIV have a high mortality rate due to progressive viral replication and advanced immunosuppression. Interventions which improve the survival outcome are important markers of effective HIV treatment. Three papers reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Ackerman et al 2021, Kozal et al 2020, Lataillade et al 2020) provided evidence for mortality rates following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Mortality was measured up to 96 weeks. In adults with no fully active, approved ARV options •Kozal et al 2020 (n=99) reported 14 (14%) deaths at week 48 following additional treatment with fostemsavir. (VERY LOW) •Lataillade et al 2020 (n=99) reported 17 (17%) deaths at week 96 following additional treatment with fostemsavir. (VERY LOW) •Ackerman et al 2021 (n=99) reported 15 (15%) deaths at week 96 following additional treatment with fostemsavir. (VERY LOW) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=272) reported 11 (4%) deaths at week 48 following additional treatment with fostemsavir. (LOW) •Lataillade et al 2020 (n=272) reported 12 (4%) deaths at week 96 following additional treatment with fostemsavir. (LOW) •Ackerman et al 2021 (n=272) reported 9 (3%) deaths at week 96 following additional treatment with fostemsavir. (LOW)

[5] Different p-values were reported in the main text (Kozal 2020, pg. 1234) and supplementary appendix (Table S3, pg. 11) and the figure reported in this evidence review has been taken from the appendix.

	One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence for rates of mortality following additional treatment with fostemsavir. However, there were unexplained discrepancies in rates of mortality reported at week 48 (Kozal et al 2020) and week 96 (Ackerman et al 2021), with more deaths reported at 48 weeks compared to 96 weeks. In addition, the two publications (Ackerman et al 2021, Lataillade et al 2020) reported different mortality rates at week 96. The authors did not provide explanations for the discrepancies in reported death rates at similar timepoints.
Important outcomes	
Increase in baseline CD4+ cell counts (cells/mm^3) **Certainty of evidence:** Low to very low	Increase in CD4+ counts is important to patients as it reflects the overall immune function of a person living with HIV. The CD4+ measurements are critical in establishing thresholds for initiation and discontinuation of opportunistic infection prophylaxis. Increased CD4+ counts correlate with the reduced risk of disease progression and reduced rates of death. One paper reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020) provided evidence for CD4+ T-cell counts (cells/mm3) following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options(non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). CD4+ T-cell counts were measured at 24, 36 and 48 weeks. In adults with no fully active, approved ARV options •Kozal et al 2020 (n=87) reported a mean CD4+ T-cell count of 41 cells/mm3at 24 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. (**VERY LOW**) •Kozal et al 2020 (n=83) reported a mean CD4+ T-cell count of 60 cells/mm3 at 36 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. (**VERY LOW)** •Kozal et al 2020 (n=83) reported a mean CD4+ T-cell count of 64 cells/mm3at 48 weeks following additional treatment with fostemsavir. This reflected a mean increase over time of 63.5 cells/mm3. No measures of statistical significance were reported. (**VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=247) reported a mean CD4+ T-cell count of 90 cells/mm3at 24 weeks following additional treatment with

	fostemsavir. No measures of statistical significance were reported. (**LOW**) •Kozal et al 2020 (n=234) reported a mean CD4+ T-cell count of 110 cells/mm3at 36 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. (**LOW**) •Kozal et al 2020 (n=228) reported a mean CD4+ T-cell count of 139 cells/mm3at 48 weeks following additional treatment with fostemsavir. This reflected a mean increase over time of 139 (SD 135) cells/mm3. No measures of statistical significance were reported. (**LOW**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence that there were important improvements in CD4+ T-cell counts following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining from baseline through to 48 weeks. No measures of statistical significance were reported.**
Quality of life **Certainty of evidence:** Low to very low	Quality of life is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. One paper reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Lataillade et al 2020) provided evidence for quality of life following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Quality of life was measured using the FAHI score and EQ-5D-3L up to week 96. In adults with no fully active, approved ARV options •Lataillade et al 2020 reported a positive change following additional treatment with fostemsavir from baseline to week 96 in mean total score (4.9 [95% CI -1.8 to 11.5]) and in subscales for physical wellbeing (1.7 [95% CI -0.2 to 3.6]) and emotional wellbeing (1.6 [95% CI -0.6 to 3.8]). (**VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Lataillade et al 2020 reported a positive change following additional treatment with fostemsavir from baseline to week 96 in mean total score (5.3 [95% CI 2.0 to 8.5]) and in subscales for physical wellbeing (2.1 [95% CI 1.1 to 3.2]) and emotional wellbeing (3.0 [95% CI 1.9 to 4.1]). (**LOW**)

	One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence that there were positive changes (indicating benefit) in QoL following additional treatment with fostemsavir, measured by the overall FAHI score and the physical and emotional wellbeing scores at 96 weeks for both adults with MDR HIV-1 with one or two fully active ARVs remaining and adults with MDR HIV-1 with no remaining ARV options. No measures of statistical significance were reported. However, both cohorts reported little (or small negative) changes in the function or global wellbeing, social wellbeing, and cognitive function subscales for the FAHI. QoL measured using EQ-5D-3L showed a small positive improvement following additional treatment with fostemsavir in adults with MDR HIV-1 with one or two fully active ARVs remaining at 96 weeks, but this was not reflected in adults with MDR HIV-1 with no remaining ARV options. No statistical data or measures of statistical significance were reported for these subscales.
Treatment failure **Certainty of evidence:** Low to very low	This outcome is important to patients as it reflects the effectiveness of the intervention. Clinical conditions occur in advanced HIV disease as a consequence of failure to achieve viral suppression and with advanced immunosuppression. These conditions are associated with significant patient morbidity and mortality. One paper reporting the multicentre, two-cohort, phase three clinical trial (Ackerman et al 2021) provided evidence for treatment failure following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Treatment failure was defined as withdrawal due to lack of treatment efficacy[6] and measured at 96 weeks. In adults with no fully active, approved ARV options •Ackerman et al 2021 (n=99) reported withdrawal due to lack of treatment efficacy in six patients at 96 weeks following additional treatment with fostemsavir. (**VERY LOW**) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •The randomised cohort, including adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes (Ackerman et al 2021) (n=272) reported withdrawal due to lack of treatment efficacy in

[6] Change in OBT due to lack of efficacy was classified as treatment failure (Ackerman et al 2021).

	12 patients at 96 weeks following additional treatment with fostemsavir. (**LOW**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence that withdrawal due to lack of efficacy was low in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining up to 96 weeks following additional treatment with fostemsavir**.
Treatment adherence **Certainty of evidence:** Low to very low	Adherence to treatment is an important to patients as it provides an indication of how the treatment is tolerated. Effective treatment requires long-term therapy with ART regimens to achieve viral suppression and immune regulation. If a treatment has adherence challenges it can increase the risk of treatment failure and add to viral resistant strain development and transmission. One paper reporting the multicentre, two-cohort, phase three clinical trial (Ackerman et al 2021) provided evidence for treatment adherence following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Treatment adherence was defined in the study as withdrawal due to non-adherence and measured at 96 weeks. In adults with no fully active, approved ARV options •Ackerman et al 2021 (n=99) reported withdrawal due to treatment non-adherence in six (6%) patients at 96 weeks following additional treatment with fostemsavir. (**VERY LOW**) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Ackerman et al 2021 (n=272) reported withdrawal due to treatment non-adherence in 11 (4%) patients at 96 weeks following additional treatment with fostemsavir. (**LOW**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence that rates of withdrawal due to treatment non-adherence were low (between 4% and 6%) in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining up to 96 weeks following additional treatment with fostemsavir.**
Safety	
Adverse events	Safety of fostemsavir is an important to patients as it allows comparison of interventional approaches. Two papers reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020)

Certainty of evidence: Moderate to very low	provided evidence for safety outcomes following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). In adults with no fully active, approved ARV options •Kozal et al 2020 (n=99) reported that 97% of patients had had at least one adverse event at 48 weeks following additional treatment with fostemsavir (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache); 85% were assessed as grade 2 to 4 adverse events; 22% as drug-related grade 2 to 4 adverse events; 47% as grade 3or 4 adverse events; and 13% resulted in discontinuation of trial drug. (**VERY LOW**) •Lataillade et al 2020 (n=99) reported similar findings at week 96; 98% of patients had had at least one adverse event following additional treatment with fostemsavir (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache); 22% were assessed as drug-related grade 2 to 4 adverse events; and 12% resulted in discontinuation of trial drug. (**VERY LOW**) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=272) reported that 43% of patients receiving blinded fostemsavir and 35% of patients receiving blinded placebo had had at least one adverse event up to day 8 (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache). (**MODERATE**) •Kozal et al 2020 (n=272) reported that, following additional treatment with fostemsavir, 91% of patients had had at least one adverse event at week 48(the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache);76% were assessed as grade 2 to 4 adverse events; 20% as drug-related grade 2 to 4 adverse events; 26% as grade 3 or 4 adverse events; and 5% resulted in discontinuation of trial drug. (**LOW**) •Lataillade et al 2020 (n=272) also reported similar findings at 96 weeks follow-up; 92% of patients had had at least one adverse event (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache);21% were assessed as drug-related grade 2 to 4 adverse events; and 5% resulted in discontinuation of trial drug. (**LOW**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided moderate to very low certainty evidence for safety. Adverse event rates were reported to be similar during the 8-day double-blind period of the**

	randomised cohort between the two treatment groups (fostemsavir versus placebo; 43% and 35%, respectively). Overall, most patients in both cohorts reported having at least one adverse event up to 96 weeks follow-up. Higher rates of grade 3 or 4 adverse events and events leading to discontinuation were reported in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options compared to adults with MDR HIV-1 with one or two fully active ARVs remaining
Serious adverse events (not including death) **Certainty of evidence:** Low to very low	Two papers reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for safety outcomes following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272).In adults with no fully active, approved ARV options •Kozal et al 2020 (n=99) reported that 30% of patients had had at least one serious adverse event at 48 weeks following additional treatment with fostemsavir;14% were assessed as CDC Class C AIDS-defining events; and 3% were assessed as drug-related. (**VERY LOW**) •Lataillade et al 2020 (n=99) reported that 48% of patients had had at least one serious adverse event at 96 weeks following additional treatment with fostemsavir; 15% were assessed as CDC Class C AIDS-defining events; and 3% were assessed as drug-related. (**VERY LOW**) In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes •Kozal et al 2020 (n=247) reported that 27% of patients had had at least one serious adverse event at 48 weeks following additional treatment with fostemsavir;9% were assessed as CDC Class C AIDS-defining events; and 3% were assessed as drug-related. (**LOW**) •Lataillade et al 2020 (n=272) reported that 34% of patients had had at least one serious adverse event at 96 weeks following additional treatment with fostemsavir;8% were assessed as CDC Class C AIDS-defining events; and 3% were assessed as drug-related. (**LOW**) **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided low to very low certainty evidence for safety. Serious adverse events did not include deaths and the authors reported that the majority of serious adverse events were associated with infections or complications associated with advanced AIDS. Rates of serious adverse events following additional treatment with fostemsavir increased from 48 to 96 weeks in both cohort populations; from 27% to 34% respectively in heavily**

	treatment-experienced adults with MDR HIV-1 with no remaining ARV options and from 30% to 48% respectively in adults with MDR HIV-1 with one or two fully active ARVs remaining.
Abbreviations AIDS –acquired immune deficiency syndrome, ART –antiretroviral therapy, ARV –antiretroviral, CDC –Centres for Disease Control and Prevention, CI –confidence interval, FAHI –functional assessment of HIV infection, HIV –human immunodeficiency virus, MDR –multidrug resistance, N/A –not applicable, OBT –optimised background therapy, RNA –ribonucleic acid, SD –standard deviation, SE –standard error, VAS –visual analogue scores.	

In the Population what is the cost effectiveness of the Intervention compared with Comparator?

Cost effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Subgroup-baseline characteristics **Certainty of evidence:** Very low	One paper reporting the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) reported outcomes following additional treatment with fostemsavir in subgroups of patients with one or two fully active ARVs remaining (Kozal et al 2020) (n=272) At week 48: •Kozal et al 2020 reported virologic response (HIV-1 RNA <40 copies/mL) following additional treatment with fostemsavir in pre-specified subgroups (n=272). The proportion (%) of patients who had a virological response at week 48 were similar across most subgroups but were higher for patients aged 50 years or older (59%), females (61%), and patients self-reported as black race (65%); higher response rates were reported among patients who had one fully active antiretroviral drug in their initial OBT(56%). In contrast, patients who had a high baseline viral load (≥100,000 copies/mL) or a low baseline CD4+ T-cell count (<20 cells/mm3) showed a reduced response rate (35% for both subgroups).No statistical measures were reported. **There was evidence that that the proportion (%) of patients who had a virological response varied for some pre-specified baseline characteristic subgroups. In adults with MDR HIV-1 with one or two fully active ARVs remaining, the rate of virologic response (HIV-1 RNA <40 copies/mL) was higher in older patients, females, patients self-reported as black race, and patients who had one fully active ARV drug**

	in their initial OBT. Reduced response rates were reported in patients who had a high baseline viral load (≥100,000 copies/mL) or a low baseline CD4+ T-cell count (<20 cells/mm^3).
Subgroup – baseline viral load (copies/mL) **Certainty of evidence:** Very low	One paper reporting the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for virologic response following additional treatment with fostemsavir in subgroups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Lataillade et al 2020) (n=272). At week 96: •Lataillade et al 2020 reported virologic response (HIV-1 RNA <40 copies/mL) following additional treatment with fostemsavir in subgroups of patients by baseline viral load (copies/mL) (n=272). The lowest virological response rate was reported in patients with baseline viral loads of ≥100,000 copies/mL (49%). By comparison, the response rate in patients with baseline viral loads of <1,000 copies/mL was 74%. No statistical measures were reported. •Virologic response rates at week 96 were similar across most baseline subgroups, including between patients with one or two fully active antiretrovirals in their initial OBT. **There was evidence that the proportion (%) of patients who had a virological response was similar for most pre-specified baseline characteristic subgroups. The randomised cohort reported lowest response rates in patients with baseline viral loads of ≥100,000 copies/mL.**
Subgroup – baseline HIV-1 RNA >1,000 copies/mL **Certainty of evidence:** Moderate	One paper reporting the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for reduction in viral load following additional treatment with fostemsavir in subgroups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Kozal et al 2020) (n=239). Reduction in viral load was defined as change in HIV-1 RNA log10and measured from day 1 to 8. At day 8: •There was a mean (SE) reduction from baseline to day 8 in HIV-1 RNA level of 0.86 (0.05) log10copies/mL in the fostemsavir group and 0.20 (0.09) log10copies/mL in the placebo group within a subgroup of patients with baseline HIV-1 RNA >1,000 copies/mL(n=239). This reflected a between group difference of -0.66 log10copies/mL [95% CI-0.87 to -0.46]; p=n/a (Kozal et al 2020). •There was no effect on between-group differences in the decrease in HIV-1 RNA level on the basis of age, gender, race, or geographic region.

	There was evidence that reduction in viral load was similar between patients receiving fostemsavir or placebo up to 8 days for subgroups based on baseline characteristics, although a difference between treatment groups was reported between patients with baseline HIV-1 RNA >1,000 copies/mL.
Subgroup – baseline characteristics and viral susceptibility and availability to initial OBT[7&8]	One paper reporting the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for the virologic response (HIV-1 RNA <40 copies/mL) and increases in CD4+ T-cell count following additional treatment with fostemsavir in subgroups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Ackerman et al 2021) (n=272). At week 96: •Subgroup outcomes for virologic response (HIV-1 RNA <40 copies/mL)following additional treatment with fostemsavir in patients by initial OBT:OSS-new(Ackerman et al 2021) (n=272) showed that the lowest proportion (%) of patients who had virological response was in patients with an OSS-new score of 0 for their initial OBT (31% at 96 weeks) compared to patients with an OSS-new score of >2 (88% at 96 weeks). •There was no clear association between increased virologic response rate at week 96 and S-GSS, GSS, PSS, OSS or #FAA. •In the randomised cohort, increases in CD4+ T-cell count from baseline to week 96 following additional treatment with fostemsavir were generally similar across subgroups (Ackerman et al 2021) (n=213), with the exception of a greater mean increase among patients aged less than 35 years compared with those aged 35 to less than 50 years [292 cells/µL; 95% CI 225 to 359 vs 166 cells/µL; 95% CI 133 to 199] and patients from Europe [306 cells/µL; 95% CI 219 to 392] compared with those from North America [147 cells/µL; 95% CI 112 to 182]. •Subgroup outcomes for CD4+ T-cell count (cells/µL)for patients by viral susceptibility to initial OBT(Ackerman et al 2021) (n=213) showed comparable outcomes for #FAA, S-GSS, GSS, PSS, OSS, and OSS-new. •Patients with CD4+ T-cell count <20 cells/µL at baseline had a mean increase of 240 cells/mm3to week 96.There was evidence that the OSS-new score was associated with virologic response rates following additional treatment with fostemsavir, but there was no clear association between S-GSS, GSS, PSS, OSS or

[7] For genotypic susceptibility scores (GSS), phenotypic susceptibility scores (PSS) and overall susceptibility scores (OSS), each ARV agent in the OBT was assigned a susceptibility rating based, respectively, on the genotypic susceptibility rating (GSR), phenotypic susceptibility rating (PSR) or net susceptibility rating (OSR) results from the Monogram assays (1.0 = full activity, 0.5 = partial activity, 0 = resistance) and the susceptibility ratings were summed. 'OSS-new' was a variation of OSS in which ARV agents previously used by the patient contributed an OSR of 0. Stanford GSS (SGSS) was determined using the Stanford University HIV Drug Resistance Database algorithm applied to sequence data from the Monogram genotypic assays (Ackerman et al 2021).

[8] Number of fully active ARVs according to study entry criteria (#FAA), including availability in terms of the patients' tolerance to, eligibility for, and willingness to take the FAA (Ackermanet al 2021).

	#FAAand virologic response rates. CD4+ T-cell counts were generally similar across subgroups, with the exception of age and geographical location, and CD4+ T-cell counts increased up to week 96 in patients with CD4+ T-cell count <20 cells/μL at baseline but no measures of statistical significance were reported. **There was evidence that the OSS-new score was associated with virologic response rates following additional treatment with fostemsavir, but there was no clear association between S-GSS, GSS, PSS, OSS or #FAAand virologic response rates. CD4+ T-cell counts were generally similar across subgroups, with the exception of age and geographical location, and CD4+ T-cell counts increased up to week 96 in patients with CD4+ T-cell count <20 cells/μL at baseline but no measures of statistical significance were reported.**
Subgroup – baseline CD4+ T-cell count (copies/μL) **Certainty of evidence:** Low	One paper reporting the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for the increases in CD4+ T-cell count (cells/μL) following additional treatment with fostemsavir in subgroups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Lataillade et al 2020) (n=213). At week 96 •increases in CD4+ T-cell count(cells/μL) from baseline to week 96, following additional treatment with fostemsavir, were generally similar across subgroups (Lataillade et al 2020) (n=213) including patients with <20 cells/μL at baseline. **There was evidence that CD4+ T-cell counts were generally similar across subgroups of patients by baseline CD4+ T-cell counts, with most patients maintaining or improving their CD4+ count category from baseline to week 96, following additional treatment with fostemsavir.**

Abbreviations

AIDS –acquired immune deficiency syndrome, ART –antiretroviral therapy, ARV –antiretroviral, CDC –Centres for Disease Control and Prevention, CI –confidence interval, #FAA -fully active antiretrovirals, FAHI –functional assessment of HIV infection, GSS –genotypic susceptibility score, HIV –human immunodeficiency virus, MDR –multidrug resistance, N/A –not applicable, OBT –optimised background therapy, OSS –overall susceptibility score, PSS –phenotypic susceptibility score, RNA –ribonucleic acid, SD –standard deviation, SE –standard error, S-GSS –standard genotypic susceptibility score

Patient Impact Summary
The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have moderate to severe problems in walking about OR are unable to walk about
- **ability to provide self-care:** Patients have moderate problems in washing or dressing OR are unable to wash or dress
- **undertaking usual activities:** Patients have moderate to severe problems in doing their usual activities OR are unable to do their daily activities
- **experience of pain/discomfort:** Patients have moderate to severe pain or discomfort
- **experience of anxiety/depression:** Patients are moderately to extremely anxious or depressed

Further details of impact upon patients:
People living with multi-drug resistant HIV-1 infection (MDR-HIV-1) have limited treatment options and the HIV virus, is not controlled (supressed). This means individuals have issues related to a poor functioning immune system (they are immunosuppressed) and they are at high risk of infection and developing serious health problems including certain types of cancers and AIDS defining illnesses.

Individuals living with MDR-HIV-1 infection have a significant morbidity (poor health) related to the immunosuppression as well as the drug treatments used to prevent infections (prophylactic medications). They also have a high chance of dying from a complication of HIV. If the virus is not supressed, they can also pass the HIV virus onto others. Individuals have complex health needs and require ongoing specialist team input. They need to take antiretroviral (ART) medication daily to control HIV-1 and/or take medications to prevent developing HIV complications such as infections if the immune levels are low.

As the virus is not controlled, individuals may develop health problems which can limit their participation and functioning in daily activities. This can also mean the individual may need to spend time in hospital, if they have serious infections. This can have a significant emotional and psychological impact for patients and their families. HIV currently does not have any cure, though normally, individuals with HIV will have a near normal life if the ART medication controls the virus. This is not the case with MDR-HIV-1 infection, which is difficult to treat. This can further exacerbate the psychological impact this diagnosis has.

Further details of impact upon carers:
Carers most likely will have been with the patient throughout their HIV journey, from the initial diagnosis, through trials of different ART medications and then potentially into the complications of immunosuppression.

This can place a significant emotional and psychological burden on patients, carers and their wider families as they may require more assistance, have greater care needs and require help to complete household activities. Patients and their families must also live with the uncertainty of MDR-HIV-1 infection and the limited treatment options.

Patients may have declining health, which can limit their ability to perform family roles such as caring responsibilities for children and work roles. This can place additional pressure on carers and wider families emotionally, physically and also financially.

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
Fostemsavir is recommended to be routinely commissioned in combination with an optimised background regimen of antiretroviral(s) therapy in accordance with the patient pathway for patients meeting the proposition's inclusion criteria. **Fostemsavir is licensed from 18 years therefore Trust policy regarding unlicensed medicines should apply.**

Considerations from review by National Programme of Care
The proposal has received the full support of the Blood and Infection PoC on 19 April 2022.