Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan
All Wales Therapeutics & Toxicology Centre

Evidence Status Report: gilteritinib for maintenance therapy after haematopoietic stem cell transplant for acute myeloid leukaemia in adults with FLT3-ITD mutation and evidence of measurable residual disease before or after transplant **(OW36)**

Report prepared by the All Wales Therapeutics and Toxicology Centre **October 2026**

Key findings

Licence status
Gilteritinib is not licensed for maintenance therapy after haematopoietic stem cell transplant (HCT) for acute myeloid leukaemia (AML) in adults with FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) mutation and evidence of measurable residual disease (MRD), measured before or after transplant. Its use for this indication is off label.

Clinical evidence
The main evidence comes from a pre-specified subgroup analysis of the MORPHO study, a randomised controlled trial of gilteritinib compared with placebo as maintenance therapy after HCT for FLT3-ITD AML. Results showed that gilteritinib significantly improved relapse-free survival in patients who had detectable MRD before or after HCT.

Safety
No new safety signals have been observed for gilteritinib.

Patient factors
Clinical experts consider gilteritinib to be more potent and better tolerated than sorafenib. Sorafenib is associated with significant toxicity resulting in dose interruptions and discontinuations; unplanned hospital visits and additional monitoring are required for those patients who experience toxicity. Clinical experts expect a reduced incidence of dose interruptions and unplanned hospital visits if using gilteritinib instead of sorafenib. Therapy targeted by MRD measurements would mean only those patients expected to derive benefit would receive maintenance treatment.

Cost-effectiveness
An AWTTC literature review did not identify any studies relevant to the cost-effectiveness of gilteritinib versus sorafenib in the target population.

An AWTTC cost analysis compares gilteritinib versus sorafenib in the target population. The base case suggests an incremental cost of [commercial in confidence text removed] per patient.

AWTTC considers the most plausible incremental cost range to be between [commercial in confidence text removed] and [commercial in confidence text removed] per patient, given that these estimates reflect the three-year and 40-year time horizons they are both plausible in the NHS Wales context.

Threshold analysis indicates that a gain of [commercial in confidence text removed] QALYs is required over a three-year time horizon, for gilteritinib to be considered cost-effective. AWTTC consider the required QALY gain to be implausible based on current available evidence.

AWTTC considers the most plausible QALY gain to be between 0.02 and 0.03, over the three-year time horizon, with the range reflecting the base-case and scenario analysis utility value inputs.

The model has several limitations: it is underpinned by a naïve treatment comparison, there are issues with the generalisability of the evidence, and the data are subject to statistical limitations. It is unknown what impact these limitations have on the findings aside from an increase in uncertainty.

Budget impact
AWTTC estimates that two patients are eligible to receive treatment with gilteritinib in Wales in Year 1, increasing to four patients in Year 5. The base case suggests an additional cost [commercial in confidence text removed] in Year 1, increasing to [commercial in confidence text removed] in Year 5. The base case also predicts additional NHS resource use or NHS resource savings valued at £39,249 over the five-year period, resulting from an increase in secondary care costs.

The budget impact relies on clinical expert opinion to inform patient numbers and supplement published data on dose intensity and discontinuation, introducing uncertainty and the potential for bias.

Welsh commercial access agreements
The marketing authorisation holder has agreed that gilteritinib can be made available at a discount under the current simple Patient Access Scheme for this off-label indication.

Impact on health and social care services
Clinicians in Wales highlight the limited capacity in haematology units and the additional burden that unplanned visits and monitoring place on the service. A better tolerated treatment option such as gilteritinib is expected to reduce the frequency and duration of unscheduled care.

Innovation and/or advantages
Gilteritinib is a type 1 FLT3 tyrosine kinase inhibitor (TKI) that clinicians expect to be more efficacious and less toxic than sorafenib, which is a type 2 FLT3 TKI. Gilteritinib allows for a targeted approach to maintenance treatment for only those patients with measurable pre-HCT or post-HCT MRD who are most likely to benefit.

Background

The integration of targeted FLT3 TKIs into standard chemotherapy regimens has significantly improved outcomes for patients with FLT3-mutated AML[1].

In 2022 the off-label use of the FLT3 TKI sorafenib was supported through the One Wales Medicines process for maintenance treatment after HCT to reduce the risk of

relapse[2]. In 2024, results were published from the MORPHO clinical trial, a study that explored the use of gilteritinib, a FLT3 TKI, as maintenance treatment after HCT in FLT3-ITD AML[3]. A pre-specified subgroup analysis of the study results showed evidence for targeting only those patients who had detectable measurable residual disease (MRD) either before or after the HCT[3].

Clinical experts in Wales said they would prefer to give gilteritinib rather than sorafenib for maintenance treatment of FLT3-ITD AML after HCT because of fewer adverse effects and better tolerability of gilteritinib. Clinical experts maintain that treating patients with MRD would limit the cohort of patients eligible for FLT3 TKI treatment and would reduce the number of patients receiving unnecessary maintenance treatment.

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from gilteritinib. The All Wales Medicines Strategy Group's Scrutiny Panel agreed that gilteritinib was suitable for assessment through the One Wales medicines process. The request for consideration is supported by the South Wales Blood and Transplant team.

Target group

The indication under consideration is off-label maintenance therapy after HCT for AML in adults with FLT3-ITD mutation and evidence of MRD, before or after transplant.

Marketing authorisation status: off label

Gilteritinib is not licensed for maintenance therapy after HCT in adults with FLT3-ITD AML and evidence of MRD, before or after transplant.

Gilteritinib is licensed and recommended by NICE as monotherapy for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation[4,5].

[commercial in confidence text removed]

Dosing information

The licensed dose of gilteritinib is 120 mg once daily; in the absence of a response after 4 weeks of treatment the dose may be increased to 200 mg once daily[4]. For off-label use as maintenance treatment after HCT, clinicians in Wales propose a dose of 120 mg once daily for two years, the same dosing regimen as used in the MORPHO clinical trial.

Clinical background

Acute myeloid leukaemia (AML) is a cancer of the blood and bone marrow, specifically the white blood cells (monocytes and granulocytes) that come from myeloid stem cells[6]. Acute leukaemia means that the disease progresses quickly and aggressively and usually requires immediate treatment[6]. Symptoms of AML develop over a few weeks and become worse over time; symptoms include anaemia, tiredness, breathlessness, bleeding problems and serious infections[6]. The risk of

developing AML increases with age; it is most common in people aged over 75 years[6].

Many patients with AML have alterations in a gene called FLT3, which are linked to poor outcomes[1]. The most common genetic alteration subtype is FLT3- ITD. A meta-analysis showed that FLT3-ITD occurs in approximately 23% of all AML cases in Europe[7].

FLT3-ITD-mutated AML is characterised by higher leukocyte counts, an increased risk of relapse, and a shorter overall survival compared to patients with wild-type FLT3[1]. In 2022 the European LeukaemiaNet changed the risk classification of FLT3-ITD in AML. The FLT3-ITD allelic ratio (ratio of mutated to wild-type alleles classified as high or low) is no longer considered in the risk classification[8]. AML with mutated nucleophosmin (NPM1) with FLT3-ITD and AML with wild type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) are categorised in the intermediate-risk group[8]. Chemotherapy followed by allogeneic HCT in first complete remission is standard of care for these patients.

Treatment of leukaemia is given in two phases: intensive induction chemotherapy to kill cancer cells in the blood and bone marrow, followed by consolidation chemotherapy[6]. If there is a high risk of the AML returning, patients are offered a bone marrow or a stem cell transplant[6]. Maintenance treatment is recommended after HCT or consolidation chemotherapy; clinicians in Wales have requested to use gilteritinib off-label to treat patients with MRD after transplant.

Measurable residual disease (MRD) refers to the presence of leukaemic cells below the threshold of detection by conventional morphological methods[9]. Patients whose disease achieved a complete response by morphological assessment alone can still have leukaemic cells in their bone marrow. NHS Wales MRD testing is conducted by the Cancer Genetics Service at Guy's Hospital by high sensitivity FLT3-ITD next-generation sequencing (NGS) with a sensitivity of 10^{-6}.

The introduction of FLT3 TKIs has significantly reshaped the management of AML with FLT3 mutations[1]. FLT3 TKIs include first-generation inhibitors sorafenib, midostaurin, and the more potent, selective second-generation inhibitors gilteritinib and quizartinib[1]. Sorafenib is not licensed in the UK for the treatment of AML. Quizartinib is licensed in the UK and recommended by NICE for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive AML[10].

Gilteritinib acts by inhibiting receptor signalling and proliferation in cells that exogenously express FLT3 and specifically induces apoptosis in leukemic cells expressing ITD mutation of FLT3[4].

Incidence/prevalence

Welsh Cancer Intelligence and Surveillance Unit data for the incidence of AML show an annual average of 96 newly diagnosed cases in Wales, during 2019 and 2021–2022[11]. If 23% of these are AML with FLT3-ITD[7], this would give an annual average of 22 newly diagnosed cases of FLT3-ITD AML in Wales.

Clinicians in Wales estimate that each year an average of two patients with FLT3-ITD AML and evidence of MRD (MRD positive) before or after HCT would be eligible for maintenance treatment with gilteritinib.

Current treatment options and relevant guidance

Chemotherapy is the main treatment for AML; in some cases, intensive chemotherapy and radiotherapy may be needed, in combination with a bone marrow or stem cell transplant[6]. The first-line treatment of choice for newly diagnosed FLT3-ITD AML in patients who are fit enough is chemotherapy with the goal of complete remission. For younger patients, the treatment goal is for cure; for older patients, treatment aims to control the disease and improve overall survival and quality of life. For eligible patients at high risk of relapse, HCT may be given after induction and consolidation chemotherapy.

Allogeneic HCT in first complete remission is a cornerstone of therapy for FLT3-ITD AML[1]. Maintenance treatment is recommended after consolidation chemotherapy or HCT. Off-label sorafenib is the only available treatment in NHS Wales for maintenance treatment after HCT for patients with FLT3-ITD AML, under a One Wales recommendation[2].

In a modified-Delphi consensus on the management of FLT3-ITD, published in 2026, pre-transplant evaluation of MRD is recommended since it helps to define relapse risk and, therefore, it contributes to informing the decision about the most appropriate allogeneic transplantation platform for the individual patient[1]. Final statement 4.4 recommends that for patients with relapsed or refractory FLT3-mutated AML, gilteritinib should be considered as a bridge-to-transplant therapy and for post-transplant maintenance, given its clear therapeutic benefit in this setting of patients[1].

The National Comprehensive Cancer Network (NCCN) guideline on ‘Acute Myeloid Leukemia’ (version 3.2026) states that for post-allogenic HCT, in patients with FLT3-ITD AML in complete remission after HCT, gilteritinib, sorafenib, midostaurin and quizartinib are maintenance therapy options[9]. For patients with FLT3-ITD AML in first complete remission post-HCT, without MRD negativity pre-HCT, gilteritinib is preferred. Sorafenib is another post-HCT maintenance option for patients with FLT3-ITD AML. The guideline also states that the Panel recommends post-transplant maintenance with gilteritinib for patients with bone marrow FLT3-ITD MRD ≥ 10^{-6} by a highly sensitive NGS-based, targeted, deep-sequencing assay with a sensitivity level of ≤ 10^{-5} pre- or post-HCT[9].

In 2025, the European LeukemiaNet-DAVID MRD working group published a consensus update on MRD in AML[12]. Recommendation A15 states that FLT3 TKI maintenance treatment in FLT3-mutated AML after allogeneic HCT is effective in patients with FLT3-ITD and MRD positivity before and/or after allogeneic HCT (gilteritinib) and independent of MRD (sorafenib) and is recommended in these patients[12].

Best practice recommendations on MRD-guided interventions for AML, published by the European Society for Blood and Marrow Transplantation (EBMT) Practice Harmonisation and Guidelines Committee state that detectable MRD is a prognostic

factor for relapse after HCT[13]. For patients with FLT3-ITD AML with detectable MRD before HCT, FLT3 TKIs should be offered as maintenance therapy and gilteritinib might be preferred. The recommended duration of FLT3 TKI maintenance therapy is two years. However, treatment duration should be individualised based on tolerability and patient-specific factors. For patients with FLT3-ITD AML with detectable MRD after HCT, recommendations are more general and state that targeted pharmacological agents should be used in patients for whom these therapies are available[13].

Older guidance, published before results were available from the MORPHO study of gilteritinib maintenance treatment for FLT3-ITD AML after HCT, suggest the off-label use of sorafenib as post-HCT maintenance therapy independent of MRD status[8,14].

Summary of evidence on clinical effectiveness

The All Wales Therapeutics and Toxicology Centre (AWTTC) conducted a literature search to identify evidence for the use of gilteritinib and sorafenib (comparator treatment) for the maintenance treatment of AML in adult patients with evidence of minimal or measurable residual disease before or after HCT.

Searches of MEDLINE, Embase, the Cochrane Library and TRIP were conducted in early April 2026. The search terms used were: gilteritinib, sorafenib, acute myeloid leukaemia, AML, hematopoietic stem cell transplantation. The primary outcomes were: progression-free survival; relapse free survival; relapse rate; overall survival; adverse events; discontinuation rate; and quality of life. The MEDLINE search strategy was adapted to enable similar searches of the other relevant databases. Targeted searches of Google Scholar were also performed. No date restrictions were applied; search results were restricted to English language. We excluded conference abstracts, case reports, and studies in children. For evidence of efficacy, we excluded studies in which all patients had relapsed or refractory AML and studies in which AML groups were not stratified or reported by MRD status. Database searches were supplemented with searches of TRIP and Google Scholar, and citation searching of some included studies.

The clinical literature search identified 272 records, from which 29 duplicates were removed. The remaining 243 records were screened by title and abstract. The full texts of 22 studies were assessed for eligibility and 12 studies were identified to include in this report. See the PRISMA diagram in Appendix 1.

Gilteritinib

One randomised controlled trial (RCT) provides evidence of the efficacy, safety and quality of life for gilteritinib in the maintenance treatment of FLT3-ITD AML versus placebo (the MORPHO study), and one retrospective observational study. Five studies provide evidence of the safety of gilteritinib: two phase III RCTs (MORPHO and ADMIRAL), one meta-analysis, one retrospective study and one study of real-world evidence. All studies are discussed below.

Efficacy

MORPHO study (NCT: 02997202)

Levis et al. (2024) reported on this phase III RCT, which assessed the efficacy and safety of gilteritinib compared with placebo in the post-HCT maintenance therapy of

FLT3-ITD AML in adults in first remission; the study also aimed to detect if MRD could identify those patients who might benefit from gilteritinib treatment[3]. A total of 356 patients were randomised between day 30 and day 90 post HCT to receive either 120 mg gilteritinib (n = 178) or a placebo (n = 178) once daily for 24 months after HCT. Sixty percent of participants had received an FLT3 TKI pre-HCT. The primary endpoint was relapse-free survival (RFS); secondary endpoints included: overall survival (OS) and the effect of MRD before and after HCT on RFS and OS[3]. RFS was improved in the gilteritinib treatment arm: the two-year RFS rate was 77.2% (95% confidence interval [CI]: 70.1 to 82.8) for participants receiving gilteritinib and 69.9% (95% CI: 62.4 to 76.2) for those receiving placebo[3]. However, this did not meet the threshold for significance (hazard ratio [HR], 0.679 [95% CI: 0.459 to 1.005]; p = 0.0518). A pre-planned subgroup analysis of 180 patients with detectable MRD at a level of 1 x 10^{-6} or greater either before or after HCT showed significantly improved RFS with gilteritinib compared with placebo (HR 0.515; 95% CI: 0.316 to 0.838; p = 0.0065). No benefit of gilteritinib treatment was shown in those patients without detectable MRD (HR, 1.213 [95% CI: 0.616 to 2.387]; p = 0.575). OS was improved in patients with detectable MRD pre- or post-HCT in the gilteritinib arm but did not reach threshold for significance (HR, 0.614 [95% CI: 0.358 to 1.053]; p = 0.0731)[3].

Levis et al. (2025) reported a post-hoc analysis of data for the pre-specified subgroup of 341 participants in the MORPHO study for whom MRD analysis was performed before and after HCT[15]. Results showed that relapse of AML occurred in 66 participants: 46 (69.7%) in the placebo arm and 20 (30.3%) in the gilteritinib arm. The level of MRD detected correlated with RFS and relapse risk, and MRD detectable at any level negatively affected RFS. In the placebo arm, relapse occurred in 42.2% of participants with detectable FLT3-ITD MRD, compared with 13.4% for those without detectable MRD. The cumulative incidence of relapse showed that for patients who had any MRD detectable before or after HCT, relapse occurred in 14 of 86 patients in the gilteritinib group, compared with 35 of 88 patients in the placebo group (HR 0.338; 95% CI: 0.185 to 0.616). The probability of survival was significantly improved in the gilteritinib group compared with placebo for patients with MRD detectable pre-HCT (HR, 0.558 [95%CI: 0.336 to 0.924] p = 0.0215) and post-HCT (HR, 0.404 [95%CI: 0.191 to 0.855] p = 0.0143). Results showed the potential of FLT3-ITD MRD to guide therapy with gilteritinib for this subtype of AML[15].

Liang et al. (2025) conducted a retrospective study of 96 patients: 43 (44.8%) with primary refractory disease; 38 (39.6%) with recurrent AML;[16] and 15 patients were in first complete remission at transplant but had persistent MRD positivity during chemotherapy. At the time of transplantation, 30 patients (68.2%) in the gilteritinib group and 38 patients (73.1%) in the control group were in complete remission (either first complete remission or second complete remission). The remaining 14 patients in each group (31.8% and 26.9%, respectively) underwent transplantation with active disease. At time of transplantation 63 patients (65.6%) were MRD positive and 28 (29.2%) had active disease; MRD status post-HCT was not reported. All patients had received allogeneic HCT and were divided into two groups based on whether they received gilteritinib maintenance therapy after HCT (n = 44) or not (control group, n = 52). OS at 3 years was 79.1% (95% CI: 64.2% to 94.0%) for gilteritinib and 53.0% (95% CI: 36.5% to 69.5%) for the control group (p = 0.013). Median RFS was not reached in the gilteritinib group; three-year RFS was improved in the gilteritinib group: 67.2% (95% CI: 52.5% to 81.9%) compared with the control group 42.5% (95% CI: 27.2% to 57.8%; p = 0.026). Results were not reported

separately for MRD-positive patients, however, in univariate analyses MRD status at transplantation did not affect outcomes[16].

Liang et al. (2021) conducted an observational study of 36 adults with FLT3-ITD AML who underwent HCT at a centre in the USA between April 2019 and August 2020[17]. Twenty-nine patients (81%) received pre-HCT FLT3 TKIs, and 78% were in first complete remission at HCT. Median follow up after HCT was 14.0 months (range 4.6–25.7). Of the evaluable cohort, 9 (26%) experienced clinical relapse after HCT at a median of 4.2 months (range, 1.8–6.1), and 10 (29%) died: five from transplant-related mortality and five from AML[17].

Of 34 patients evaluable for post-HCT MRD analysis, 10 (29%) had detectable MRD within the first three months, while 24 (71%) remained MRD-negative[17]. Twenty-four patients (71%) received FLT3 TKI maintenance, initiated a median of 2.8 months after transplant (range 0.7–17.1 months); the median duration was 10.6 months (range 1.7–23.7). The most common FLT3 TKI used was gilteritinib (n = 15), followed by midostaurin (n = 9) and sorafenib (n = 5)[17].

The use of maintenance FLT3 TKIs led to a significantly superior progression-free survival (PFS) and OS ($p < 0.0001$ for both PFS and OS) in both MRD-negative and MRD-positive patients[17]. The use of early FLT3 TKIs post-HCT augmented PFS and OS in both MRD-negative and MRD-positive patients and effectively prevented clinical relapse in four patients with post-HCT MRD positivity[17].

Sorafenib

The main study providing evidence of the efficacy of sorafenib is an RCT (SORMAIN) comparing sorafenib maintenance with placebo after HCT for FLT3-ITD AML. A five-year follow-up of an RCT conducted in China and a retrospective analysis of real-world data from a German registry provide additional efficacy data for sorafenib maintenance.

SORMAIN study

Burchert et al. (2020) reported on the SORMAIN study, a randomised, placebo-controlled trial that investigated whether maintenance therapy with sorafenib can improve outcome after allogeneic HCT in high-risk FLT3-ITD-positive AML[18]. A total of 83 patients were randomly assigned to sorafenib maintenance (n = 43) or placebo (n = 40) post HCT. The dose of study medication was incremented from 400 mg to 800 mg per day and continued for 24 months or until occurrence of relapse or intolerable toxicity. The primary endpoint of RFS was calculated as time from randomisation to either AML relapse or death from any cause[18].

The median follow-up was 41.8 months; the median RFS was not reached in the sorafenib group and was 30.9 months in the placebo group[18]. Dose reductions were performed in 16 of 40 patients in the placebo group (40.0%) versus in 21 of 43 patients (48.8%) in the sorafenib group. The median duration of therapy was 54.36 weeks (range, 1.71–128.29 weeks) for placebo and 34.57 weeks (range, 1.29–106.86 weeks) for sorafenib. The most common reasons for treatment discontinuation were adverse events in the sorafenib group (n = 9; 20.93%) and relapse in the placebo group (n = 17; 42.50%)[18].

In SORMAIN, exploratory post-hoc analyses were conducted of MRD status pre-HCT and post-HCT[18]. Sorafenib demonstrated significantly improved RFS compared with

placebo for patients who were MRD-negative before HCT (p = 0.028), and for those who were MRD-positive after HCT (p = 0.015). For patients who were MRD positive pre-HCT and MRD negative post-HCT, improvements in RFS were not significant (latter showed a trend but small numbers may have affected ability to show a statistical advantage)[18].

Xuan et al. (2023) reported five-year follow-up data from a phase III open-label trial of sorafenib maintenance after HCT in 202 patients with FLT3-ITD AML[19]. The study provided results by MRD status, we report on patients who were MRD positive at HCT (n = 65) and MRD-positive post-HCT (n = 20). Sorafenib was administered at 30–60 days post-transplantation (initial dose was 400 mg orally twice daily) and continued until Day 180. Median follow-up for the whole group was 64 months[19].

Among patients who were MRD-positive at HCT, the 5-year OS was 61.3% (95% CI 42.0% to 75.8%) in the sorafenib group (n = 31), compared with 41.2% (95% CI 24.8% to 56.9%) in the control group (n = 34; HR 0.52; 95% CI 0.26% to 1.07%; p = 0.072)[19]. The 5-year cumulative incidence of relapse in these patients was 29.0% (95% CI 14.2% to 45.6%) in the sorafenib group, compared with 52.9% (95% CI 34.6 to 68.3%) in the control group (HR 0.39; 95% CI 0.18% to 0.87%; p = 0.030). The 5-year leukaemia-free survival (LFS) in patients who were MRD-positive at transplant was 58.1% (95% CI 39.0% to 73.1%) in the sorafenib group, compared with 35.3% (95% CI 19.9% to 51.0%) in the control group (HR 0.47; 95% CI 0.23% to 0.93%; p = 0.027)[19].

For 20 patients who were MRD-positive post-HCT, the 5-year OS was 55.6% (95% CI 20.4% to 80.5%) in the sorafenib group (n = 9), compared with 18.2% (95% CI 2.9% to 44.2%) in the control group (n=11; HR 0.38; 95% CI 0.12% to 1.25%; p = 0.097)[19]. The 5-year cumulative incidence of relapse in these patients was 33.3% (95% CI 6.5% to 64.2%) in the sorafenib group, compared with 72.7% (95% CI 31.6% to 91.6%) in the control group (HR 0.27; 95% CI 0.07% to 1.02%; p = 0.066). The 5-year LFS in patients who were MRD-positive post-HCT was 55.6% (95% CI 20.4% to 80.5%) in the sorafenib group, compared with 18.2% (95% CI 2.9% to 44.2%) in the control group (HR 0.32; 95% CI 0.09% to 0.99%; p = 0.049)[19].

Of the whole group, 28 patients in the sorafenib group died: nine due to leukaemia relapse, 11 due to infections, six due to acute or chronic graft-versus-host disease, one due to acute left heart failure (not related to sorafenib treatment) and one due to secondary malignant disease[19].

Massoud et al. (2026) conducted a retrospective study to assess the impact of FLT3 TKI maintenance on HCT outcomes by analysing data from 13 German transplant centres participating in the German Registry for Stem Cell Transplantation[20]. Of 523 adults with FLT3-ITD AML in first complete remission who underwent allogeneic HCT between 2011 and 2023, 116 (22%) received FLT3 TKI maintenance (49% with sorafenib; 37% with midostaurin; 5% with gilteritinib; unknown in 9%). Median treatment duration was 486 days (range 7–909 days) for sorafenib, 269 days (range 3–520) for midostaurin and 287 days (range 33–810 days) for gilteritinib[20].

In multivariable analyses, FLT3 TKI maintenance improved OS (HR 2.25; 95% CI: 1.28 to 3.95], p=0.005), RFS (HR 1.72; 95% CI: 1.05 to 2.81, p = 0.030), non-relapse mortality (HR 3.62; 95% CI: 1.08 to 12.11, p = 0.037), and graft-versus-host disease and relapse-free survival (HR 1.59; 95% CI: 1.06 to 2.40, p = 0.025), compared with

those patients who did not receive maintenance with FLT3 TKIs[20]. The cumulative incidence of relapse did not differ. In univariate analyses, OS benefits were observed in MRD-positive (HR 2.35; 95% CI: 1.04 to 5.31, p=0.025) and MRD-negative patients (HR 2.64; 95% CI: 1.05 to 6.68, p = 0.020). Sorafenib maintenance (n = 50) demonstrated superior efficacy with 5-year OS of 85% versus 62% (HR 2.979; p = 0.0045) and RFS of 84% versus 55% (HR 2.771; p = 0.0043) compared to no maintenance. The small number of patients who received gilteritinib maintenance precluded meaningful sub-group analyses for OS and RFS[20].

Safety

Gilteritinib dosing should follow instructions reported in the Summary of Product Characteristics (SmPC). If a grade three or higher toxicity occurs gilteritinib should be interrupted until toxicity resolves followed by resumption at a lower dose (80 mg or 120 mg). The modified Delphi consensus by Olivieri et al., also stated that it is advisable to lower the dose rather than discontinue the medicine[1].

The SmPC for gilteritinib describes adverse effects reported in patients with relapsed/refractory AML[4]. The most frequent serious adverse effects listed are: acute kidney injury (6.6%); diarrhoea (4.7%); alanine aminotransferase (ALT) increased (4.1%); dyspnoea (3.4%); aspartate aminotransferase (AST) increased (3.1%) and hypotension (2.8%). The SmPC also highlights several clinically significant adverse reactions including differentiation syndrome (2.2%), electrocardiogram QT prolonged (0.9%) and posterior reversible encephalopathy syndrome (0.6%). Regular electrocardiograms (ECGs) and monitoring of blood chemistry, including creatinine kinase are recommended before starting treatment and for the duration of treatment[4].

Clinicians in Wales say that the monitoring tests required for gilteritinib are routine and do not differ from monitoring with the use of sorafenib as post-HCT maintenance treatment. No haematologic disorders are reported as adverse events in the SmPC[4].

In the MORPHO study grade 3 or greater treatment-emergent adverse events occurred in 82% of participants[3]. The most common grade 3 or greater treatment-emergent adverse events occurring in more than 5% of participants receiving gilteritinib treatment were haematologic, with 36% of patients experiencing decreased neutrophil count; 21.3% had decreased platelets; 10.1% decreased white blood cell count and 9.6% had anaemia. Non-haematological grade 3 or higher adverse events in the gilteritinib group were creatinine phosphokinase elevation in 7.9% of patients; the rate was the same for increased ALT, increased AST, and hypertension at 6.2% of patients. In the gilteritinib treatment group, 52.8% of patients completed the 24-month treatment period, 52.2% of patients had dose reductions due to treatment-emergent adverse events, and adverse events led to treatment withdrawal in 19.7% of patients[3].

Perl et al. (2022) reported two-year follow-up data from a phase III trial (ADMIRAL) of gilteritinib maintenance treatment in relapsed/refractory FLT3 AML, which showed that the safety profile of gilteritinib was stable over a two-year period, with no new or clinically significant safety signals[21]. Twenty-six patients treated with gilteritinib remained alive for ≥ 2 years without relapse; 18 of these patients underwent HCT and 16 restarted gilteritinib as post-HCT maintenance therapy. The most common adverse events of interest during Years 1 and 2 of gilteritinib therapy were increased liver transaminase levels; adverse event incidence decreased in Year 2. Adverse events lead to dose reduction of gilteritinib in 5.7% of patients and discontinuation in

5.3% of patients. The study concluded that continued and post-HCT gilteritinib maintenance treatment sustained remission with a stable safety profile[21].

Kennedy et al. (2025) conducted a cohort study using administrative claims data to measure real-world treatment adherence to FLT3 TKIs as maintenance after HCT in patients with FLT3 AML in the USA[22]. Claims data were taken from adults with AML with ≥ 1 allogeneic HCT between January 2016 and June 2022 who received gilteritinib, midostaurin, or sorafenib as post-HCT maintenance. Of 162 patients, 41 received post-HCT maintenance with gilteritinib, 53 received midostaurin and 68 received sorafenib. Safety data for gilteritinib and sorafenib only are reported here. Across all patients, the Kaplan–Meier median duration of treatment was greatest for gilteritinib at 206 days (interquartile range [IQR] 129.0 to 550.0]), followed by sorafenib at 132 days (IQR 37.0 to 390.0)[22].

Results showed a higher risk of discontinuation for sorafenib (HR 1.74; p = 0.046) compared with gilteritinib[22]. After adjusting for pre-defined covariates, patients on sorafenib were approximately 75% more likely to discontinue compared with those on gilteritinib. The authors noted that discontinuation rates were markedly higher than seen in previous clinical trials of FLT3 TKIs as post-HCT maintenance. Their findings suggest that gilteritinib may have a better tolerability profile than sorafenib in the post-HCT maintenance population[22].

Majothi et al. (2020) conducted a systematic review and fixed effects meta-analysis of the efficacy and safety of FLT3 TKIs in AML[23]. Eight completed trials involving 2656 patients and assessing five different FLT3 TKIs, including sorafenib (2 studies) and gilteritinib (1 study). Safety data showed that the relative risk of grade 3 and above vascular, dermatological, respiratory and hepatobiliary adverse events was statistically significantly higher in the FLT3 TKI group compared to control groups, but the actual numbers of events were relatively small[23].

Real word evidence

Clinicians in Cardiff and Vale UHB haematology department provided data on discontinuation of sorafenib maintenance post-HCT due to intolerance. Of 17 patients treated to date 10 (59%) discontinued treatment due to toxicity; four stopped within one month of treatment, five within three months and one at five months. Gastrointestinal toxicities were the predominant effects leading to discontinuation.

Comparative safety

Yeh et al. (2024) conducted a retrospective analysis to compare the efficacy and safety of gilteritinib to sorafenib maintenance in FLT3-ITD AML given post-HCT[24]. A total of 55 patients were treated with gilteritinib (n = 26) or sorafenib (n = 29) after HCT. There was no significant difference in progression-free survival (PFS) between groups but no subgroup analyses were provided for patients who were MRD positive at HCT. Both treatment groups had a high incidence of grade 3–4 adverse events whilst on treatment. No significant differences in adverse events were reported between the treatment groups. The most prevalent grade 3–4 adverse events were neutropenia reported in 45% of the gilteritinib group (34% in the sorafenib group; p = 0.6) and thrombocytopenia in 52% of the sorafenib group (30% in the gilteritinib group, p = 0.8). Skin toxicities of any grade were higher in the sorafenib group compared to the gilteritinib group (24% versus 7%; p = 0.09) as were incidences of grade 2–4 acute graft-versus-host disease (21% versus 11%, p = 0.3). Incidence of chronic graft-versus-host disease was higher in the gilteritinib group (19% versus 10%; p = 0.4). Dose reduction was required in 37% and 44% of patients in the gilteritinib and sorafenib groups, respectively. Maintenance treatment continued in 44% of patients receiving gilteritinib, and in 14% of patients receiving sorafenib[24].

Quality of life

Hamilton et al. (2024) reported an analysis of the effects of gilteritinib given after HCT versus placebo on the health-related quality of life (HRQoL) of patients in the MORPHO study[25]. Assessments used were: Functional Assessment of Cancer Therapy (FACT)-Bone Marrow Transplantation (BMT) measure, FACT-Leukemia (FACT-Leu) measure, and the EuroQOL-5 Dimensions (EQ-5D-5L). HRQoL was measured at post-HCT randomisation; day 29; months 3, 6, 12, 18 and 24; and/or end of therapy. There were no differences in HRQoL scores between the treatment groups at any time point. The EQ-5D-5L utility score for gilteritinib and placebo groups before HCT was 0.9, and after HCT it was 0.8. Despite higher treatment-emergent adverse effects with gilteritinib, response to the question of being "bothered by side effects of treatment" did not differ between groups. Subgroup analysis comparing MRD positive and negative patients also demonstrated no differences between groups[25].

Discussion

The main evidence comes from the results of the MORPHO study. However, the study did not meet its primary endpoint, because RFS was not significantly improved over placebo in the full cohort of patients eligible for treatment. A pre-planned subgroup analysis showed that gilteritinib maintenance treatment significantly improved relapse-free survival compared with placebo in patients who had detectable MRD after HCT[3].

The MORPHO study was conducted at centres in North America, Europe and Asia/rest of the world and subgroup analysis showed differences in outcomes between the geographic regions. Gilteritinib was beneficial in North America, of minimal benefit in Asia/rest of the world and had a mildly negative effect in Europe. There were distinct geographic differences between the study populations and practice patterns, such as, time from diagnosis to HCT, number of induction and consolidation courses, pre-HCT FLT3 TKI use, conditioning regimen and concomitant azole use. These might have contributed to regional differences, but multivariate regression models did not identify any single practice or group of practices that could explain the differences[3]. In addition, patients included in this study were restricted to those in first complete remission, whereas this assessment would not be limited to patients in first complete remission.

In a single-centre observational study of 36 patients with FLT3-ITD AML after HCT, 24 patients received post-transplant FLT3 TKI maintenance therapy (including gilteritinib in 15 patients). Maintenance FLT3 TKI therapy was associated with significantly improved PFS and OS overall, with benefits observed in MRD-negative and MRD-positive patients[17].

Patients in Wales who undergo HCT and have the presence of FLT3-ITD mutation at the time of diagnosis or AML relapse are eligible to receive maintenance therapy with sorafenib regardless of MRD status. There are no randomised clinical studies directly comparing gilteritinib with sorafenib in this indication. This is not unexpected, because both medicines are used off label for this indication.

Recent clinical guidelines, published since the results of the MORPHO study, recommend gilteritinib in preference to sorafenib for MRD-positive AML (NCCN; EMBT; ELN)[9,12,13]. The ELN recommends sorafenib maintenance treatment for FLT3

AML independent of MRD status. An ELN guideline also acknowledges that sorafenib is 'sometimes challenging to deliver'[8].

In the absence of any direct comparative data, efficacy data for sorafenib has been provided from the SORMAIN study. Clinical experts highlight several issues in using this study for comparison: the study pre-dates the routine use of FLT-3 TKIs pre-HCT; the study utilises a dose of 400 mg sorafenib twice daily (BD), in practice this dose is rarely tolerated; FLT-3 MRD technology has developed significantly since the SORMAIN study and patients who were classed as MRD negative may have had low level MRD positivity. Clinical experts who treat patients with sorafenib as maintenance post-HCT report that, all patients treated in Wales are treated with 200 mg BD due to the intolerability of 400 mg BD experienced in practice.

The safety profile of gilteritinib is known. No new safety signals were reported in the MORPHO study or other studies. More treatment-emergent adverse events were reported in the gilteritinib treatment group than in the placebo group; although there were no significant differences reported in patients' quality of life between the treatment groups.

Real-world treatment adherence data measured by administrative claims in the USA showed higher rates of discontinuation of FLT3 TKI maintenance than seen in clinical trials; the risk of discontinuing treatment was higher for sorafenib than gilteritinib[22].

Ongoing studies
A phase III randomised, controlled study (TROPHY-15) comparing gilteritinib with sorafenib as post-HCT maintenance therapy in FLT3-ITD AML is recruiting and expected to start in China in May 2026[26]. The MRD status of all 594 patients to be enrolled in the study will be tested by PCR-NGS method. The study is expected to complete in 2030[26].

Cost-effectiveness evidence

Review of published evidence on cost-effectiveness
A literature review conducted by AWTTC did not identify any studies evaluating the cost-effectiveness of gilteritinib compared with sorafenib as maintenance therapy in patients with FLT3-ITD mutated AML and MRD positivity after allogeneic HCT, the target population. However, two cost-utility analyses (CUA) were identified that evaluated gilteritinib compared with placebo or best supportive care in patients in the target population.

A published economic evaluation authored by individuals affiliated with the medicine manufacturer, compared gilteritinib versus placebo from a North American healthcare payer perspective using a semi-Markov model[27]. Over a three-year time horizon, gilteritinib was associated with an incremental cost of $224,432, and incremental gain of 0.18 quality-adjusted life-years (QALYs) and an incremental cost-effectiveness ratio (ICER) of $1,209,667 per QALY gained[27].

A Canadian Drug Agency (2026) HTA assessed a tumour group-submitted model comparing gilteritinib with best supportive care from a Canadian healthcare payer perspective[28]. Using the medicine list price in a mixed cure model over a lifetime horizon, the analysis reported incremental costs of $490,297 (CAD), an incremental

gain of 1.77 QALYs and an ICER of $277,163 (CAD) per QALY gained[28]. Neither analysis included sorafenib as a comparator, and costs can differ significantly between countries; therefore, their relevance to NHS Wales decision-making is limited.

Context

AWTTC's preferred reference case, a cost-utility analysis (CUA) was not considered appropriate for this assessment, based on an absence of comparative evidence.

AWTTC's analysis adopts a stepwise approach. A cost analysis compares oral off-label gilteritinib (120 mg once daily)[4] with oral sorafenib (400 mg twice daily)[29], as maintenance therapy following allogeneic HCT in patients with FLT3-ITD mutated AML and MRD positivity. A threshold analysis estimates the magnitude of health gain required for cost-effectiveness, and the plausibility of achieving the required QALY gains is assessed.

The cost analysis takes the form of a partitioned survival model, comprising 28-day cycles. The model adopts a three-year time horizon and an NHS Wales and Personal Social Services perspective. Costs are discounted at 3.5%. The model is characterised by three health states: RFS, relapsed, and death. Patients may transition to death from any health state. Patients in the sorafenib arm receive gilteritinib following relapse. In the base case analysis patients treated with gilteritinib do not receive a rechallenge with gilteritinib following relapse.

The efficacy data used to inform state membership are derived from the Kaplan–Meier curves published for the MORPHO trial for gilteritinib and by Massoud et al., 2026 for sorafenib[3,20]. The model estimates the incidence of treatment-related adverse events during the treatment period. Adverse events are included if they are grade 3 or higher and have a cumulative incidence of at least 5% in the relevant clinical studies informing the analysis. Event rates for gilteritinib and sorafenib are derived from the MORPHO and SORMAIN trials, respectively[3,18]. Where an adverse event is reported in one trial but not the other, the corresponding placebo-arm rate is used to inform the missing input. Clinical expert opinion informed both this approach and the assumed distribution of adverse events over time; 75% are applied in the first three months, with the remaining 25% spread equally across the remaining 21 months. It is assumed that their impact is temporary.

The model includes costs associated with medicine acquisition and administration, adverse events, ongoing healthcare resource use, and subsequent treatments. Medicine acquisition costs for gilteritinib and sorafenib are informed by confidential Welsh Patient Access Scheme (WPAS) prices. Treatment costs are modelled according to the dosing schedules evaluated in the MORPHO and SORMAIN trials[3,18]. In the absence of sufficient detail from trial data, treatment discontinuation and dose intensity reduction profiles are also partially informed by clinical expert opinion. Resource use associated with routine follow-ups (primary care contacts, outpatient and day unit attendance) is informed through consultation with clinical experts to align with NHS Wales clinical practice. Resource utilisation is applied according to time spent in the relapse-free and relapsed health states within the partitioned survival model framework. Adverse event management costs are primarily derived from NHS reference costs, inflated to current year pricing where required; graft-versus-host disease costs are sourced from the literature[30,31]. Continued care costs (primary care contacts, outpatient and day unit attendance, including

transfusions) are sourced from the Personal Social Services Research Unit (PSSRU) and NHS reference costs[30,32].

To inform plausibility assessments, health outcomes are accrued over time according to the proportion of patients occupying the relapse-free and relapsed health states. Health-related quality of life is captured using state-specific utility values informed by published evidence; specifically, MORPHO for the relapse-free health state and ADMIRAL for the relapsed health state[25,33]. The ADMIRAL trial is a phase III randomised controlled trial that evaluated gilteritinib versus salvage chemotherapy in patients with relapsed or refractory FLT3-mutated AML. Utility decrements associated with serious adverse events are applied separately within the model, with values sourced from the published literature and previous NICE technology assessments[5,34].

Deterministic and probabilistic sensitivity analyses test the influence of the uncertainty of individual parameters on the model results for the base case. The parameters tested, among others, included: utilities, serious adverse event rates, utility decrements, and healthcare resource use frequencies. Scenario analyses also explore alternative time horizons, subsequent treatments and alternative utility inputs. Extrapolation is required for durations longer than the Kaplan–Meier trial evidence. Observed data were fitted to a variety of common parametric distributions, and goodness-of-fit statistical tests were conducted. The exponential distribution was selected for the base case based on the statistical fit (AIC and BIC) and visual alignment.

Threshold analysis estimates the QALY gain required for gilteritinib to be considered cost-effective at a threshold of £20,000 per QALY gained. A subsequent assessment explores whether this gain is plausible based on the available evidence from MORPHO, SORMAIN, published literature and clinical expert opinion. Scenario analysis further evaluates the effect of alternative utility values on the required QALY gain and the associated plausibility assessment.

Results

The results of the base case cost analysis are detailed in Table 1. When compared with sorafenib, the incremental cost associated with gilteritinib over a three-year time horizon is [commercial in confidence text removed] per patient. The main cost differences can be attributed to medicine acquisition costs.

Table 1. Key results of cost analysis: cost per patient

Costs	Gilteritinib	Sorafenib	Difference
Medicine acquisition cost	¶¶	¶¶	¶¶
Relapse treatment cost	£0	¶¶	¶¶
Medicine administration cost	£498	£509	−£11
Adverse event cost	£1,700	£1,522	£178
Other secondary care costs	¶¶	¶¶	¶¶
Total cost	¶¶	¶¶	¶¶
¶¶ Commercial in confidence data removed			

The results of the univariate sensitivity analysis show that the incremental cost is most sensitive to the chosen time horizon for the analysis.

Table 2. Key scenario analyses results for the cost analysis

Scenarios	Incremental cost	Plausibility
5-year time horizon	¶¶	This is a plausible alternative to the base case, which uses the maximum amount of available within-trial data, and benefits from a longer horizon. However, the estimate remains subject to uncertainty due to the high degree of censoring.
40-year time horizon	¶¶	This is a plausible alternative to the base case; based on median age at start of treatment, it effectively offers a lifetime horizon, which is generally the preferred approach for HTA. However, this estimate is associated with a high level of modelling uncertainty, due to censoring, extrapolation and naïve comparisons.
Weibull extrapolation (40-year time horizon)	¶¶	The Weibull distribution provides a comparable visual fit to the base case but generates more favourable estimates for both treatment arms, AWTTC considers the base case to offer a more plausible and conservative estimate.
Gilteritinib rechallenge (gilteritinib arm)	¶¶	This is a plausible alternative to the base case, which increases the incremental cost of the gilteritinib arm.
¶¶ Commercial in confidence data removed HTA: health technology assessment		

The results of the threshold analysis for the three-year time horizon suggest that a gain of [Commercial in confidence text removed] QALYs is required for gilteritinib to

be considered cost-effective. AWTTC considers this gain to be implausible, given that the partitioned survival model estimates an incremental QALY gain of 0.03. The incremental QALY gains are predominantly driven by increased relapse-free survival. Scenario analyses suggest that this conclusion is maintained when alternative assumptions are applied to the cost analysis (see Table 3) and when alternative utility values are used in the threshold analysis. The use of alterative utility values in a scenario analysis results in an estimated incremental QALY gain of 0.02[35].

Probabilistic sensitivity analyses indicate that gilteritinib has a 0% probability of delivering sufficient QALY gains to be considered cost-effective, at a threshold of £20,000 or £30,000 per QALY gained.

Table 3. Key threshold analysis and plausibility considerations

	QALY gain required for cost-effectiveness at a threshold of £20,000 per QALY gained	Plausibility of achieving required QALY gain
Base case (3-years)	¶¶	Implausible. The total required QALYs exceed the modelled 3-year time horizon
Key scenarios		
5-year time horizon	¶¶	Implausible. The required QALYs exceed the modelled QALY gain estimate of < 0.01 QALYs.
40-year time horizon	¶¶	Implausible. The required QALYs exceeds the modelled QALY gain estimate of −0.12 QALYs.
¶¶ Commercial in confidence data removed QALY: quality-adjusted life-year		

4.4 Strengths and limitations of the AWTTC economic analysis

Strengths:

- The AWTTC analysis provides a transparent and pragmatic assessment of the likely cost implications of using gilteritinib in the target population, using data sources and unit costs relevant to NHS Wales.
- The stepwise approach provides a structured way to explore cost differences, the QALY gain required to achieve cost-effectiveness, and the plausibility of achieving that gain based on the available evidence.
- Extrapolation is inherently associated with uncertainty. To address this uncertainty, choice of distribution is guided by statistical tests, clinical expert opinion and the literature. To address the uncertainty associated with using the exponential distribution, sensitivity analysis explores alternative distributions.

Limitations:

- Relative treatment effects are informed by a naïve comparison of MORPHO and Massoud et al., 2026 rather than a direct or indirect treatment comparison. Differences in trial design, populations, geography, MRD assessment and definition, and follow-up may distort treatment effects,

meaning any inferred advantage of one treatment over the other may be misleading.
- The evidence used to inform serious adverse events, treatment discontinuation and dose intensity reductions is taken from the broader post-HCT AML population rather than the MRD-positive subgroup. However, clinical experts in Wales propose that adverse events are not expected to be influenced by MRD status.
- The MORPHO trial and Massoud et al., 2026 report immature OS data with few events and limited follow-up. This reduces statistical power and increases uncertainty in extrapolated survival estimates, potentially under- or over-estimating long-term benefit.
- Long-term survival estimates rely on parametric extrapolation from limited within-trial data. Small differences in curve shape can produce substantial differences in predicted survival, introducing uncertainty and potential bias into the cost, threshold and plausibility estimates.
- The Massoud registry data contained inconsistencies between the relapse-free survival and overall survival curves. The model therefore assumes that overall survival cannot be lower than relapse-free survival. This raises concerns about data quality and may affect the estimated relapse and overall survival outcomes for sorafenib.
- The Massoud study is retrospective and observational, with non-standardised treatment decisions and potential selection bias. This reduces confidence in the sorafenib outcomes relative to the trial-based gilteritinib data.
- Discontinuation is informed by aggregate trial summaries rather than time-to-event data. This may not accurately capture when patients stop treatment, particularly early discontinuation, which could affect medicine cost estimates and adverse event incidence.
- Several model assumptions are informed by clinical expert opinion where clinical trial evidence is unavailable. Although pragmatic, this introduces greater uncertainty than evidence derived directly from clinical trials.
- The model makes several pragmatic assumptions that simplify the treatment pathway. Limited evidence on continued care, and future treatments, for example subsequent (high cost) HCT, reduces alignment with expected real-world use, which limits the applicability of the analysis.

Budget impact

Context and methods

AWTTC estimates that, in 2026, two people will be eligible for gilteritinib maintenance treatment after HCT for AML in adults with FLT3-ITD mutation and evidence of MRD before or after transplant. This estimate is based on expert clinical opinion. Treatment discontinuation and dose intensity are informed by data from MORPHO and SORMAIN[3,18], and supplemented by clinical expert input on expected dose reductions, dose re-escalations, and the likely duration of treatment interruptions in NHS Wales practice. Medicine consumption with gilteritinib is spread across two years, reflecting the longer treatment duration and discontinuation profile, whereas sorafenib treatment is delivered entirely within the first year.

Based on clinical expert advice, patients treated with sorafenib are assumed to receive gilteritinib following relapse as next line therapy, while patients receiving gilteritinib are not rechallenged. Mortality assumptions are based on evidence from

the MORPHO trial for gilteritinib and Massoud et al. (2026) for sorafenib[3,20]. An assumed market share of 100% in Years 1 to 5 is further applied to estimate the number of people likely to be prescribed gilteritinib in Wales for the target indication. Table 4 provides a breakdown of how comparator medicines are likely to be displaced as a result. Sensitivity analyses explore an alternative dosing regimen for sorafenib, and alternative dosing intensity and discontinuation assumptions for both medicines.

Results

The budget impact is presented in Table 4. AWTTC estimates that introducing gilteritinib would lead to an overall cost of [Commercial in confidence text removed] in Year 1, increasing to [Commercial in confidence text removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of sorafenib. Sensitivity analysis exploring the impact of reducing the sorafenib dose to 400 mg daily increased the overall cost to [Commercial in confidence text removed] in Year 1, increasing to [Commercial in confidence text removed] in Year 5. Applying an assumption of no discontinuation or dose reductions for gilteritinib, while retaining base-case assumptions for sorafenib increased the net cost to [Commercial in confidence text removed] in Year 1 and [Commercial in confidence text removed] in Year 5. In contrast, applying an assumption of no discontinuation or dose reductions to sorafenib, while retaining base-case assumptions for gilteritinib, decreased the net cost to [Commercial in confidence text removed] in Year 1 and [Commercial in confidence text removed] in Year 5.

Table 4. Estimated costs associated with use of gilteritinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Population of eligible patients	2	2	2	2	2
Uptake of off-label medicine (%)	100	100	100	100	100
Number of patients receiving off-label medicine allowing for discontinuations	2	4	4	4	4
Medicine acquisition costs in a market without gilteritinib	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market with gilteritinib	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net next-line medicines costs	£0	£0	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence data removed					

AWTTC estimates that net resource implications arising from the introduction of gilteritinib will lead to a cost of £39,249. This is a consequence of increased secondary care costs. These medicine costs are included for potential planning purposes but may not be realised in practice.

AWTTC budget impact analysis strengths and limitations

- The analysis incorporates a broad range of relevant cost components, including medicine acquisition, administration, routine care, subsequent treatment and adverse event costs, thereby capturing the wider financial and resource implications of treatment adoption.
- Treatment costs and resource use account for relapse and mortality, drawing on the available clinical evidence and supporting a more comprehensive estimate of the budget impact.
- The clinical evidence informing the patient pathway and treatment discontinuation is derived from a naïve comparison which introduces uncertainty because potential differences in patient and study characteristics could influence key budget impact drivers.

- The reliance on clinical expert opinion to supplement the published literature for discontinuation and dosing intensity introduces uncertainty and the potential for bias. The budget impact estimates are highly sensitive to these variables. The impact of alternative assumptions has been explored through sensitivity analyses.
- The budget impact analysis also relies on clinical expert opinion to inform NHS resource use, which introduces uncertainty and the potential for bias for these estimates.
- The eligible patient population is uncertain. Minor changes in patient numbers could have a significant impact on the estimated budget impact.

Patient factors

Clinical experts in Wales consider gilteritinib to be more potent and better tolerated than sorafenib. Therapy targeted by MRD measurements would mean only those patients expected to derive benefit would receive maintenance treatment. Sorafenib is associated with significant toxicity resulting in dose interruptions and discontinuations. Unplanned hospital visits and additional monitoring are required for those patients who experience toxicity. Clinical experts in Wales expect the incidence of dose interruptions and unplanned hospital visits to be reduced if gilteritinib were to be used instead of sorafenib.

Equality and health impact assessment

AWTTC has completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that gilteritinib will have a significant potential negative impact on people based on the protected characteristics of the Equality Act 2010.

Additional factors

Prescribing unlicensed medicines

Gilteritinib is not licensed to treat this indication and is therefore prescribed ’off label’. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the medicine and has been published on the AWTTC website.

Information presented in this document can be reproduced using the following citation: All Wales Therapeutics & Toxicology Centre. Evidence Status Report. Gilteritinib for maintenance therapy after haematopoietic stem cell transplant for acute myeloid leukaemia in adults with FLT3-ITD mutation and evidence of measurable residual disease before or after transplant. Reference number: OW36. 2026.

Copyright AWTTC 2026. All rights reserved.

References

1. Olivieri J, Angelucci E, Cairoli R et al. A Modified-Delphi consensus on the management of patients with FLT3-mutated AML. *Cancers.* 2026;18(5):770.
2. All Wales Therapeutics and Toxicology Centre. Sorafenib film-coated tablets. Reference number: OW18. Appraisal information. Feb 2022 (reviewed Jun 2023). Available at: https://awttc.nhs.wales/accessing-medicines/one-wales-medicines-process/ow-decisions/sorafenib-for-acute-myeloid-leukaemia-aml-maintenance/. Accessed May 2026.
3. Levis MJ, Hamadani M, Logan B et al. Gilteritinib as post-transplant maintenance for AML with internal tandem duplication mutation of FLT3. *Journal of Clinical Oncology.* 2024;42(15):1766–1775.
4. Astellas Pharma Ltd. Gilteritinib Astellas. 40 mg film-coated tablets. Summary of Product Characteristics. Sep 2025. Available at: https://www.medicines.org.uk/emc/product/10832/smpc. Accessed May 2026.
5. National Institute for Health and Care Excellence. Technology Appraisal TA642. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia. Aug 2020. Available at: https://www.nice.org.uk/guidance/ta642. Accessed May 2026.
6. National Health Service. Acute myeloid leukaemia. Oct 2022. Available at: https://www.nhs.uk/conditions/acute-myeloid-leukaemia/. Accessed Jun 2026.
7. Lewis JFM, Daver NG, Robinson NJ et al. Prevalence of FMS-like tyrosine kinase 3 (FLT3) mutations in patients with acute myeloid leukaemia: a systematic literature review and meta-analysis. *Cancer Medicine.* 2025;14:e71205.
8. Dohner H, Wei AH, Appelbaum FR et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood.* 2022;140(12):1345–1377.
9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2026. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1411. Accessed Jun 2026.
10. National Institute for Health and Care Excellence. Technology Appraisal TA1013. Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3 ITD-positive acute myeloid leukaemia. . Oct 2024. Available at: https://www.nice.org.uk/guidance/ta1013. Accessed Aug 2026.
11. Welsh Cancer Intelligence and Surveillance Unit. Cancer incidence in Wales data 2002-2022. Available at: https://phw.nhs.wales/data/cancer-incidence-in-wales-data/. Accessed Jul 2026.
12. Cloos J, Valk PJM, Thiede C et al. 2025 update on MRD in acute myeloid leukemia: a consensus document from the ELN-DAVID MRD Working Party. *Blood.* 2025;147(11):1147–1167.
13. Sanz J, Bug G, Ciceri F et al. Measurable residual disease-guided interventions in patients with acute myeloid leukaemia undergoing allogeneic haematopoietic cell transplantation: best practice recommendations from the European Society for Blood and Marrow Transplantation Practice Harmonisation and Guidelines Committee. *The Lancet Oncology.* 2025;26:e586–e596.
14. Bazarbachi A, Bug G, Baron F et al. Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with FLT3-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica.* 2020;105:1507–1516.

15. Levis MJ, Hamadani M, Logan BR et al. Measurable residual disease and posttransplantation gilteritinib maintenance for patients with FLT3-ITD mutated AML. *Blood.* 2025;145(19):2138–2148.
16. Liang C, Yang D, Pang A et al. Gilteritinib maintenance after allogeneic hematopoietic stem cell transplantation for relapsed/refractory acute myeloid leukemia with FLT3-internal tandem duplication mutation. *Hematology.* 2025;30(1):2509353.
17. Liang EC, Chen C, Lu R et al. Measurable residual disease status and FLT3 inhibitor therapy in patients with FLT3-ITD mutated AML following allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant.* 2021;56(12):3091–3093.
18. Burchert A, Bug G, Fritz LV et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). *Journal of Clinical Oncology.* 2020;38(26):2993–3002.
19. Xuan L, Wang Y, Shao R et al. Sorafenib maintenance after allogeneic haemopoietic stem cell transplantation in patients with FLT3-ITD acute myeloid leukaemia: long-term follow-up of an open-label, multicentre, randomised, phase 3 trial. *Lancet Haematology.* 2023;10:600–611.
20. Massoud R, Flossdorf S, Hanke F et al. Impact of FMS-like tyrosine kinase 3 inhibitor maintenance on post-transplant outcomes in acute myeloid leukemia with FMS-like tyrosine kinase 3 mutations: a real-world German registry analysis highlighting sorafenib. *Haematologica.* 2026;Mar 5 Epub ahead of print. PMID: 41784041.
21. Perl AE, Larson RA, Podoltsev NA et al. Follow-up of patients with R/R FLT3-mutation–positive AML treated with gilteritinib in the phase 3 ADMIRAL trial. *Blood.* 2022;139(23):3366–3375.
22. Kennedy VE, Touya M, Spalding J et al. Real-world treatment adherence and persistence of FLT3 inhibitors as post-alloHCT maintenance therapy in patients with AML in the United States: a cohort study using administrative claims data. *Leukemia & Lymphoma.* 2025;66(14):2697–2707.
23. Majothi S, Adams D, Loke J et al. FLT3 inhibitors in acute myeloid leukaemia: assessment of clinical effectiveness, adverse events and future research — a systematic review and meta-analysis. *Systematic Reviews.* 2020;9(285).
24. Yeh J, Pasvolsky O, Saliba RM et al. Efficacy and safety of gilteritinib versus sorafenib as post-transplant maintenance in patients with FLT3-ITD acute myeloid leukemia. *Clinical Lymphoma, Myeloma and Leukemia.* 2024;24(11):e819–e826.
25. Hamilton BK, Pandya BJ, Ivanescu C et al. Health-related quality of life with gilteritinib vs placebo posttransplant for FLT3-ITD+ acute myeloid leukemia. *Blood Advances.* 2024;8(19):5091–5099.
26. The First Affiliated Hospital of Soochow University. NCT07463651: MRD-guided maintenance post-HCT: gilteritinib vs sorafenib (TROPHY-15). 2026. Available at: https://clinicaltrials.gov/study/NCT07463651. Accessed Jun 2026.
27. Huang T, Abel G, Cutler C et al. Cost-effectiveness of post-transplant gilteritinib maintenance in MRD-positive FLT3-ITD acute myeloid leukemia: a microsimulation model based on the Morpho trial. Presented at 67th American Society of Hematology (ASH) Annual Meeting. 6–9 Dec 2025. *Blood*. 146 (Suppl 1). DOI: https://doi.org/10.1182/blood–2025–4436 Accessed Mar 2026.
28. Canada's Drug Agency. Gilteritinib. Jul 2026. Available at: https://www.cda-amc.ca/gilteritinib. Accessed Aug 2026.

29. Zentiva. Sorafenib. 200 mg film-coated tablets. Summary of Product Characteristics. Sep 2025. Available at: https://www.medicines.org.uk/emc/product/13098/smpc. Accessed Mar 2026.
30. NHS England. National Cost Collection Data Publication: National Schedule 2023/24. Jul 2025. Available at: https://app.powerbi.com/view?r=eyJrIjoiNjI5YjA1OWMtOGNmOC00NGQzLWIxZDYtZDAyMDQ5YWVkZjU0IiwidCI6IjM3YzM1NGIyLTg1YjAtNDdmNS1iMjIyLTA3YjQ4ZDc3NGVlMyJ9. Accessed Mar 2026.
31. Kinsella F, Quignot N, Read SH et al. Quantifying the clinical and economic burden of graft-versus-host disease following allogeneic haematopoietic stem cell transplantation in England: a retrospective cohort study. *Advances in Therapy*. 2025;42(12):6012–6029.
32. Curtis L, and Burns A. Personal Social Services Research Unit (PSSRU). Unit costs of health and social care, 2024. Canterbury: University of Kent. Apr 2025. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/. Accessed Jul 2026.
33. Cella D, Qi CZ, Yang H et al. PCN306 Estimation of health state utilities in FLT3-mutated relapsed/refractory acute myeloid leukemia. May 2020; *Value in Health*, 23 (1), S77–S78; doi: https://doi.org/10.1016/j.jval.2020.04.1769 ; Accessed: Jul 2026.
34. National Institute for Health and Care Excellence. Technology Appraisal TA306. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. . Feb 2014. Available at: https://www.nice.org.uk/guidance/ta306. Accessed Jul 2026.
35. Joshi N, Hensen M, Patel S et al. Health state utilities for acute myeloid leukaemia: a time trade-off study. *PharmacoEconomics*. 2019;37:85–92.

Appendix 1. PRISMA flow diagram

