**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Gilteritinib for treating relapsed or refractory acute myeloid leukaemia (ID1484)**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral) (revised June 2019)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

| Section  | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Wording | The National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, British Society for Haematology, and Royal College of Pathologists (NCRI, ACP, RCP, BSC, and RCPath) | Yes | Comment noted. The remit has been updated. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | Slightly amended wording“To appraise the clinical and cost effectiveness of gilteritinib within its marketing authorisation for treating adult patients with relapsed or refractory FLT3 mutation positive acute myeloid leukaemia.” | Comment noted. The remit has been updated. |
| Timing Issues | NCRI, ACP, RCP, BSC, and RCPath | A current standard of care does exist, similarly the evaluation of a comparable therapy is ongoing with NICE (Quizartinib ID1325) standard timing for evaluation is reasonable | Comment noted. Quizartinib (ID1325) has been removed as a comparator from the scope because the Anticipated publication date for ID1325 has changed and will not be considered established practice at the time of this appraisal.  |
| Leukaemia Care | Given the acute and often life-threatening nature of AML, there is always a need for urgency in the approval of potential new treatments, especially for those who have relapsed an may have no other options. | Comment noted. No action required. |
| Astellas Pharma Ltd | Marketing authorisation and launch of gilteritinib in a patient population where there are no approved treatment options available and where prognosis is poor | Comment noted. No action required. |
| Additional comments on the draft remit | NCRI, ACP, RCP, BSC, and RCPath | NICE ID1325- Quizartinib also needs to be considered as equivalent population under evaluation | Comment noted. Quizartinib (ID1325) has been removed as a comparator from the scope because the Anticipated publication date for ID1325 has changed and will not be considered established practice at the time of this appraisal.  |
| Leukaemia Care | n/a | No action required. |

Comment 2: the draft scope

| Section  | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Background information | NCRI, ACP, RCP, BSC, and RCPath | Broadly accurate.When the disease is relapsed or refractory the choice of salvage therapy is based a number of factors- dependent upon patients age, fitness/co-morbidity (and therefore their ability to tolerate further intensive therapy) previous therapy (challenge with alternative), prospect of proceeding to stem cell transplantation (donor availability and co-morbidity). In general where possible only long-term survival is achieved through indiucing remission and stem cell transplant- historically this has been through escalated conventional intensive chemotherapy. Therapy targeted at the specific FLT3 mutation has now been demonstrated to achieve complete responses (CR) facilitating an alternative approach to ‘bridging to transplant’. | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | We would suggest to add the sentence to the second paragraph“The FLT3 mutation is associated with poor prognosis because of the aggressive nature of the disease which results in relapse.” | Comment noted. The background section has been updated. |
| The technology/ intervention | NCRI, ACP, RCP, BSC, and RCPath | YesGilteritinib is also undergoing evaluation in combination with intensive and non-intensive chemotherapy, although these studies are still recruiting and no results have been reported. | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | No comments | No action required. |
| Population | NCRI, ACP, RCP, BSC, and RCPath | Yes | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | No comments | No action required. |
| Comparators | NCRI, ACP, RCP, BSC, and RCPath | Yes.The clinical trial compares gilteritinib to salvage chemotherapy of low dose cytarabine [LDAC]; azacitidine; mitoxantrone, etoposide, cytarabine (MEC) and FLAG-Ida;Additionally Quizartinib should be considered although there is no directly comparable data.The use of intermediate dose cytarabine (IDAC) is widely published and utilised internationally as salvage therapy- however rarely used in UK practice (considered inferior to intensive salvage such as FLAG-Ida).Whilst MEC is similarly infrequently used in the UK at salvage it is internationally recognised as a reasonable comparator- UK salvage uniformly utilises HDAC based regimens as the induction therapy is most like to have been DA (Daunorubicin and cytarabine at conventional doses). | Comment noted. Quizartinib (ID1325) has been removed as a comparator from the scope because the Anticipated publication date for ID1325 has changed and will not be considered established practice at the time of this appraisal.  |
| Leukaemia Care | Flag-Ida is the standard option for these patients in terms of chemotherapy following first relapse. MEC may be considered as a second treatment but are likely to only be an option if FLAG-Ida was administered first time round; this is unlikely to happen outside the context of a clinical trial. | Comment noted. No change to the scope required. |
| Astellas Pharma Ltd | Given the lack of treatments approved specifically for this population we would suggest amending the wording in line with other appraisals in this setting“Established clinical management without gilteritinib including, but not limited to cytarabine or azacitidine based chemotherapy. For some patients best supportive care may be their only option currently.”Astellas disagrees with the suggestion to include quizartinib in this section given that it does not have a licence, it is not an agent with established NHS practice in England, there is no NICE Guidance and cost-effectiveness has not been established | Comment noted. The comparators listed in the scope aims to be inclusive. Quizartinib (ID1325) has been removed as a comparator from the scope because the Anticipated publication date for ID1325 has changed and will not be considered established practice at the time of this appraisal.  |
| Outcomes | NCRI, ACP, RCP, BSC, and RCPath | Additionally hospital days and transfusion independence if available may be informativeThe frequency of ‘bridging to transplant’ should be specifically evaluated. | Thank you for your comment. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. These are also indirectly captured in the cost-effectiveness analysis. No change to the scope required. |
| Leukaemia Care | We are disappointed that the company has chosen not to record any quality of life outcomes in the trials associated with this technology. Changes in the quality of life of patients are as important as health-related changes, especially in the opinion of patients, as shown in the theme of many of our patient submissions. | Comment noted. No change to the scope required. |
| Astellas Pharma Ltd | No comments | No action required. |
| Economic analysis | NCRI, ACP, RCP, BSC, and RCPath | For therapy duration or until stem cell transplantation. Costs of transplant highly variable and not evident that there would be a robust analysis with such small numbers.All patients with AML are now assessed for FLT3 mutation- so this would no longer be routinely considered an additional evaluation at relapse | Comment noted. The economic analysis section has been updated. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | No comments | No action required. |
| Equality and Diversity | NCRI, ACP, RCP, BSC, and RCPath | No | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | Astellas Pharma Ltd is not aware of any issues of equality in the management of AML in England and Wales | Comment noted. No change to the scope required. |
| Other considerations  | NCRI, ACP, RCP, BSC, and RCPath | No | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | No comments | No action required. |
| Innovation | NCRI, ACP, RCP, BSC, and RCPath | The FDA’s approval of Gilteritinib was based on an interim analysis of the following endpoints in the ADMIRAL clinical trial: the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh); the duration of CR/CRh (DOR); and the rate of conversion from transfusion dependence to transfusion independence. The CR/CRh rate was 21%. The median duration of CR/CRh was 4.6 months. The rate of conversion from transfusion dependence to transfusion independence was 31.1% for any 56 day post-baseline period. For patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only.We await the final results to be published at a scientific meeting (Planned for AACR Atlanta March 2019) and ultimately in peer reviewed journal (submitted for review).However these reports (like Quizartinib) suggest that salvage therapy can be in the form of single agent oral therapy administered in an ambulatory setting -compared to the standard intensive combination approaches delivered in hospital these represent a potential new standard of care. | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | Given the lack of treatments licensed or NICE guidance for agents specifically for this population, Astellas believes that gilteritinib does represent an innovative therapy which confers a significant health-related benefit compared to current treatment Gilteritinib meets the NICE end of life criteria and delivers a significant improvement in efficacy, in terms of overall survival, compared to standard of care | Comment noted. Innovation and end of life benefits will be considered in more detail as part of the full appraisal. No change to the scope required. |
| Questions for consultation | NCRI, ACP, RCP, BSC, and RCPath | Stem cell transplantation is only considered appropriate for patient who achieve a disease response/remission- hence the need for salvage therapy. As a procedure it would generally not be considered an alternative to the technology.*Where do you consider gilteritinib will fit into the existing Blood and bone marrow cancers (2016) NICE pathway?*Currently the pathway for AML is in need of significant update for primary therapy. Gilteritinib could be incorporated as an option for patients With Relapsed or Refractory Acute Myeloid Leukemia (AML) With FMS-like Tyrosine Kinase (FLT3) Mutation although Qiuzartinib is seeking approval in the same patient population and there is probably more familiarity in the UK with this drug compared to Gilteritinib. There may be circumstances where one drug is ineffective but the other FLT3 inhibitor may be. This could arise when a FLT3 TKD emerges as a resistance mechanism to Quizartinib but is targetable by Gilteritinib | Comment noted. No change to the scope required. |
| Leukaemia Care | n/a | No action required. |
| Astellas Pharma Ltd | *Have all relevant comparators for gilteritinib been included in the scope?*Given the lack of treatments approved specifically for this population we would suggest amending the wording in line with other appraisals in this setting: “Established clinical management without gilteritinib including, but not limited to cytarabine or azacitidine based chemotherapy. For some patients best supportive care may be their only option currently.”Astellas disagrees with the suggestion to include quizartinib in this section given that it does not have a licence, it is not an agent with established NHS practice in England, there is no NICE Guidance and cost-effectiveness has not been established*Which treatments are considered to be established clinical practice in the NHS for treating relapsed or refractory FLT3-mutation positive acute myeloid leukaemia?* * Best supportive care
* Cytarabine based chemotherapy
* Azacitidine based chemotherapy
* FLAG-ida
* FLAG

For patients who respond following the above treatments, they may be considered for a stem cell transplant*Is MEC (mitoxantrone, etoposide, cytarabine) a relevant comparator?*This combination is not included in BSH Guidelines and not licensed, however there does seem to be some low level usage*Would stem cell transplantation be a viable option at this point in the disease?* No, not at this point in the disease. When patients reach this point in their disease pathway, they may receive treatment with drugs if it is considered they may benefit from this. If they then respond to such treatment they may be viable for a stem cell transplant (also depending on general health status, previous transplant)*Are the outcomes listed appropriate?*Yes, the outcomes listed are appropriate*Are there any subgroups of people in whom gilteritinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?* None currently*Where do you consider gilteritinib will fit into the existing Blood and bone marrow cancers (2016) NICE pathway?* Gilteritinib should be considered within its anticipated licensed indication *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which gilteritinib will be licensed;* * *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
* *could have any adverse impact on people with a particular disability or disabilities.*

*Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*Astellas is not aware of any issues with this regard*Do you consider gilteritinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?*Given the lack of treatments licensed or NICE approved specifically for this population, Astellas believes that gilteritinib does represent an innovative therapy which confers a significant health-related benefit compared to current treatmentGilteritinib meets the NICE end of life criteria and delivers a significant improvement in efficacy, in terms of overall survival, compared to standard of care*Do you consider that the use of gilteritinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* No. Benefits will be captured in the QALY calculation *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*The HE model will calculate QALYs and it will show the detailed inputs regarding health outcomes and associated utility values*To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*Astellas is not aware of any major barriers*NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute’s Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).*Astellas agrees with this approach | Comment noted. The comparators listed in the scope aims to be inclusive. Quizartinib (ID1325) has been removed as a comparator from the scope because the Anticipated publication date for ID1325 has changed and will not be considered established practice at the time of this appraisal. Innovation will be considered in more detail as part of the full appraisal |
| Additional comments on the draft scope | Astellas Pharma Ltd | None | Comment noted. No change to the scope required. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

None