**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Tagraxofusp for treating blastic plasmacytoid dendritic cell neoplasm**

**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 | Stemline Therapeutics | Yes, the remit broadly does reflect the intended license. | Comment noted. No change to the scope required. |
| Timing Issues | Stemline Therapeutics | Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare, highly aggressive and often fatal hematologic malignancy derived from plasmacytoid dendritic cells (pDCs). One of the main characteristics of BPDCN is high CD123 expression in cells. Patient with BPDCN have no curative treatment options, apart from allogenic stem cell transplantation, which is currently feasible in only ~10% of patients goal of treatment with a highly targeted treatment such as tagraxofusp that is able to deliver a high complete response rate, is to increase the likelihood of a successful allo SCT [1, 2].<br>BPDCN involves the bone marrow, bruce-like macules, nodular lesions and disseminated lesions and other organ sites and presents most commonly with skin lesions (90 percent of cases) with or without extramedullary organ involvement before leukemic dissemination. As a result of its clinical ambiguity, differentiating BPDCN from benign skin lesions or those of acute myeloid leukemia with leukemia cutis is challenging [3]. Reports show the aggressive | Comment noted. This appraisal has been scheduled into the work programme. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | nature of the disease, with death occurring in most patients within 6 months of diagnosis [4-6].<br>Early recognition of BPDCN can be challenging, because its clinical features can be heterogeneous and can overlap other hematologic malignancies [7-10]. There is often a significant delay between the onset of symptoms and diagnosis [11].<br>Currently there are no BPDCN-specific interventions which have undergone appraisal by NICE. Therefore, this appraisal should be reviewed by NICE, so that guidance is available to the NHS in a timely manner. | |
| | Leukaemia Care | There are no treatments current licensed for this condition, so this is a particularly urgent application for those with this indication. As stated in the scope, this disease has a high relapse rate from current treatments. | Comment noted. This appraisal has been scheduled into the work programme. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Background information | Stemline Therapeutics | According to the Surveillance, Epidemiology and End Results Program [12] Register (SEER), the estimated incidence of BPDCN in the US is 0.41 cases / 1,000,000 inhabitants. BPDCN occurs predominantly in the elderly (mean age at diagnosis 67 years) and affects predominantly men, with a ♂ : ♀ ratio of 2.2–3.0 : 1.0 [13, 14].<br>No independent surveys on the incidence or prevalence of BPDCN have been carried out for England so far. Based on various databases, Stemline Therapeutics estimates the patients population with BPDCN in England at around 107 – 143 new cases per year. | Comments noted. The background section includes the following text “BPDCN can occur in people of any age but the median age at diagnosis is between 60 and 70 years. Around 75% to 90% of cases occur in men”. It also |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | | includes the following text “the exact prevalence of BPDCN is unknown due to the difficulty of accurately diagnosing the disease and there are wide-ranging differences in reported prevalence and incidence rates”. No action required. |
| The technology/ intervention | Stemline Therapeutics | Tagraxofusp is a fusion protein targeting the cells that express CD123 (interleukin-3 receptor) on their cell surface.<br>Otherwise, the description of the technology is accurate. | Comment noted. The technology section of the scope has been updated. |
| Population | Stemline Therapeutics | Yes, the population has been accurately defined. | Comment noted. No change to the scope required. |
| Comparators | Stemline Therapeutics | The lack of a specific therapy for BPDCN is a major unmet need for patients. The archival therapies for BPDCN include aggressive non- Hodgkin lymphoma regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), ALL regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with methotrexate and cytarabine, or AML induction regimens (eg, MICE [mitoxantrone, idarubicin, cytarabine, and etoposide]; cytarabine and an anthracycline [7 + 3]; or FLAG-IDA [fludarabine, cytarabine, granulocyte colony stimulating factor, and idarubicin]). | Comments noted. The comparators section of the scope has been updated to reflect the discussion at the scoping workshop. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | However, after complete remission a relapse usually occurs, and a second remission is difficult to achieve with the previously applied chemotherapy regimen.<br>Stem – cell transplantation (SCT) cannot be considered as comparator, as it is the next step of the treatment and can be implemented when patients hits clinical response (CR). SCT does not introduce a CR. Achieving a high long-term remission rate in patients with BPDCN with a targeted agent that has the potential to bridge the gap to stem cell transplantation would be a major step in the treatment of this disease, with concomitant reduction of the morbidity and mortality observed on chemotherapy [15].<br>The draft scope should define what constitutes best supportive care (BSC). | |
| | Leukaemia Care | All possible comparators listed should be compared, as none are licensed or recommended as standard of care. | Comments noted. The comparators section of the scope has been updated to reflect the discussion at the scoping workshop. |
| Outcomes | Stemline Therapeutics | The outcome measures to be considered include:<br>• Response rate (including complete response rate, partial response rate, overall response rate and duration of response)<br>  ○ Circulating Blasts<br>  ○ mSWAT<br>• Overall survival<br>• Progression free survival<br>• Adverse effect treatment | Comments noted. Skin response has been added to the outcomes section of the scope to reflect the discussion at the scoping workshop. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Economic analysis | Stemline Therapeutics | We are in early stages of planning our economic case so cannot comment yet. | Comment noted. No change to the scope required. |
| Equality and Diversity | Stemline Therapeutics | There are no equity issues to raise. | Comment noted. No change to the scope required. |
| Other considerations | Stemline Therapeutics | None | Comment noted. No change to the scope required. |
| Innovation | Stemline Therapeutics | Tagraxofusp is a recombinant fusion protein, a novel biological targeted therapeutic that is aimed at CD123 (the interleukin-3 receptor IL-3R) ). Tagraxofusp consists of human IL-3 (the natural ligand of CD123) fused to a truncated diphtheria toxin (DT), wherein IL-3 replaces the native DT receptor binding domain. The treatment can be applied at any stage of the disease, but preferably as an initial treatment to prevent the condition from worsening. We expect patients' quality of life improvement based on the treatment.<br>On 11 November 2015, orphan designation (EU/3/15/1567) was granted by the European Commission to tagraxofusp for the treatment of blastic plasmacytoid dendritic cell neoplasm.<br>Tagraxofusp was granted Breakthrough Therapy Designation for the treatment of BPDCN on 22 August, 2016. | Comment noted. The committee will consider the innovative nature of tagraxofusp throughout the course of the appraisal. |
| | Leukaemia Care | Given that no other treatments are licenced in the UK for this condition, this has the potential to become standard of care for these patients immediately, and so is a massive step-change in the treatment of the condition. A licensed treatment can be accessed more quickly and easily than the process for applying to access unlicensed treatment allows. | Comment noted. The committee will consider the innovative nature of tagraxofusp throughout |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | | the course of the appraisal. |
| Questions for consultation | Stemline Therapeutics | Have all relevant comparators for tagraxofusp been included in the scope? Which treatments are considered to be established clinical practice in the NHS for blastic plasmacytoid dendritic cell neoplasm (BPDCN)?<br><br>*HCVAD, ALL-like regimens, AML-like regimens, CHOP, asparaginase*<br>*In the UK, there are no medicines specifically authorised for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) and no standard of care treatment has been established for patients with treatment-naïve (newly-diagnosed) or previously-treated (relapsed/refractory) disease.*<br><br>Is there a current standard of care for people with BPDCN? If so, please confirm what this is? *No standard of care treatment has been established for patients with treatment-naïve (newly-diagnosed) or previously-treated (relapsed/refractory) disease.*<br><br>Where in the pathway would tagraxofusp be used? Is it expected that tagraxofusp will be used to help people move onto haematopoietic stem cell therapy or would tagraxofusp be used as an alternative to haematopoietic stem cell therapy?<br>*Will be used in treatment-naïve and relapsed/refractory patients.*<br>*Tagraxofusp (TAG) may be used in lieu of hematopoietic stem cell transplant (HSCT) in cases where a complete response (CR) is achieved with TAG but the patient is unable/unfit for HSCT for clinical reasons or no matching donor is identified. In this case, TAG use can be continued.*<br><br>Have all the relevant outcomes been considered? Are all outcomes listed appropriate?<br>*As above.* | Comments noted. The comparators section of the scope has been updated to reflect the discussion at the scoping workshop.<br><br>Comments noted. Skin response has been added to the outcomes |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | | section of the scope to reflect the discussion at the scoping workshop. |
| | | Are there any subgroups of people in whom tagraxofusp is expected to be more clinically effective and cost effective or other groups that should be examined separately<br>*No; not defined, but some patients get into a CR very quickly.* | Comment noted. No change to the scope required. |
| | | Should people who proceed to haematopoietic stem cell transplant and those who do not be considered separately?<br>*Yes.*<br>*HSCT is very expensive, those that move on will have this cost associated.* | |
| | | Are there any other subgroups of people in whom tagraxofusp is expected to be more clinically effective and cost effective or other groups that should be examined separately?<br>*Not known at this time. In this ultra rare disease, subgroups, if any, are hard to identify*. | Comment noted. |
| | | Epidemiological sources report conflicting incidence and prevalence rates. What is the incidence and prevalence of BPDCN in the UK? Please provide the sources for the most relevant UK epidemiological data.<br>*See above (likely 1.5-2.0 per million). Incidence is estimated between 107-143 per year.* | Please see response to comment in “background information” section. No action required. |
| | | Do you consider tagraxofusp 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)? | Comment noted. The committee will consider |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | *Yes*<br>*There are no medicines specifically authorized for the treatment of BPDCN in the UK and no standard of care treatment has been established for patients with treatment-naïve or previously treated disease.* | the innovative nature of tagraxofusp throughout the course of the appraisal. |
| | Leukaemia Care | We are concerned about the choice of appraising this indication under the single technology appraisal process. The condition is extremely rare, affecting 25 people in the UK per year (based on the incidence as set out in the scope, although we appreciate this is difficult to predict). Conditions with more patients affected have been appraised previously; for example, the guidance for HST4, a treatment for Fabry disease, is estimated to applicable to 182 people. Another example would be HST9, which approved a treatment for hATTR, which was thought to be useful for 150 people.<br>As Sir Andrew Dillon, Chief Executive of NICE stated: “NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair.” To address this unfairness, NICE set up the Highly Specialised Technologies (HST) programme. However, this drug has been chosen to be appraised through the STA programme instead, which means it is highly likely to lead to this drug having limited or uncertain data available and a higher chance of not being approved.<br>This indication urgently needs a form of licensed treatment, fulfilling another selection criteria of HST in that there is the need for national commissioning. Again, this is shown as the rationale for most other HST appraisals, as set out the HST topic selection document available online. | Thank you for your comments. As discussed at the scoping workshop, a treatment must meet all the eligibility criteria in order for it to be routed to the highly specialised technology programme. Because it is unlikely that this treatment will be concentrated in very few centres in the NHS, and this treatment is not expected to be used exclusively in the context of a highly specialised service, this topic does not satisfy the criteria for a highly specialised technology assessment. |

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

None