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CITELINE REGULATORY

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Elzonris: A Case Study In Divergent Regulatory Decisions

by Ian Schofield

Stemline Therapeutics' Elzonris was approved for a rare cancer in Europe in January, following a long and arduous two-year journey through the EU regulatory process that included an initial rejection and a subsequent re-examination by the EMA. Its fortunes were very different in the US, where the review took just six months from filing to approval.

It's not unusual for drug regulators from different countries to take quite different stances on whether a new medicine should be approved for marketing. *Stemline Therapeutics, Inc.*'s orphan medicine Elzonris (tagraxofusp), whose EU authorization in January came two years after its approval in the US, is a striking example of just how far agencies' views can diverge.

Elzonris was initially granted accelerated assessment (AA) by the European Medicines Agency, but later lost this status because the number of questions raised by the regulator meant the AA timetable could not be met.

Then the product's marketing authorization application (MAA) for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) was turned down by the EMA on benefit-risk grounds. This decision was later reversed following a re-examination and the agency cleared Elzonris for approval, albeit with some restrictions.

For example, it is limited to first-line treatment because the benefit in the relapsed or refractory setting has not been

EU Drug Review Profiles

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Turalio: Why The EU Said No To The US-Approved Drug

established, and it does not have a pediatric indication. This contrasts with the US, where the therapy is approved for adults and children in first- and second-line settings.

The initial EU review found limitations in the design of the key study underpinning the MAA, methodological issues, non-comprehensive efficacy results, and uncertainties regarding the management of the safety profile.

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Real World Data Failed To Impress Kaftrio's European Reviewers

Elzonris was finally issued with an EU marketing authorization under exceptional circumstances in January this year, with the onus on the company to address numerous safety concerns raised during the evaluation process.

Not only that, Elzonris caused a split among the EU member state experts on the EMA's human drugs committee, the CHMP. Six of the 30-odd members disagreed with the committee's initial negative opinion, mainly on the grounds that no approved therapies were available at the time.

The whole process took exactly two years, from the filing of the MAA with the EMA on 7 January 2019 to approval by the European Commission on 7 January 2021. The procedure can normally be expected to last around 12-15 months, including the commission's 67-day decision-making process following a positive CHMP opinion. A timeline of the assessment process can be found at the end of this article.

By contrast, the US Food and Drug Administration took only six months to decide that Elzonris should be cleared for marketing – a quarter of the time taken by the EU. Filed in June 2018, the product was approved in the US in December that year, and enjoyed both breakthrough therapy status and priority review. It was launched in January 2019 as the first ever approved treatment for BPDCN.

The product has also hit hurdles in the UK, where the appraisal of tagraxofusp by the health technology assessment body for England, NICE, has been subject to repeated delays and was paused in March for corporate reasons. A marketing authorization filing for Elzonris with the UK regulator, the MHRA, is expected sometime this year. NICE appraisals generally begin before a new drug has been approved for marketing.

A Rare Disease

Before looking at the process that finally led to Elzonris's EU approval as monotherapy for the

first-line treatment of adult patients with BPDCN, it is worth examining the background to the decision, including the rarity of the condition and the lack of approved therapeutic approaches.

BPDCN is a rare blood cancer that is initially characterized by skin lesions and can later also affect the blood, bone marrow and lymph nodes.

The prevalence of the condition, as estimated in the data provided for the EU orphan designation for Elzonris, is 1.2 per 10,000 people, but the true incidence and prevalence are "not precisely known," according to the EMA.

BPDCN typically occurs in elderly patients between 60 and 70 years of age, but can present at any age, and is more prevalent in males (3:1 ratio male to female).

There are no medicines specifically authorized for the treatment of BPDCN, and no standard of care (SOC) has been established for patients with either first-line or relapsed/refractory disease.

Unmet Needs

Several treatments have generally been used to treat BPDCN patients, including multi-agent chemotherapy regimens, symptomatic approaches (such as local radiation), and intensive chemotherapy with allogeneic hematopoietic cell transplantation.

Chemotherapy regimens used for acute leukemia or lymphoma are often effective at inducing an initial response, but the duration of the response is typically brief, and recurrent disease is generally resistant to chemotherapy. While longer overall survival has been reported with allogeneic hematopoietic cell transplantation, many relapses have been observed after such transplants.

According to the *Public Assessment Report* (PAR) drawn up by the EMA for Elzonris, achieving high rates of durable response in patients with BPDCN while avoiding the morbidity and mortality observed with chemotherapy regimens "would be potentially very impactful in this disease."

[The PAR is a key part of the broader European public assessment report (EPAR), which includes other documents such as the medicine overview, the risk management plan summary, and the product information. In the case of Elzonris, the PAR runs to 207 pages.]

The Initial Assessment Of Elzonris

Despite the severity of the disease, the unmet medical needs, and the award of accelerated assessment, the CHMP was not initially convinced that Elzonris warranted a marketing authorization.

Tagraxofusp is a novel targeted therapy directed at the interleukin-3 (IL-3) receptor-α (CD123), which is present in a wide range of malignancies. As well as BPDCN, Stemline has been investigating the product in other indications including myelofibrosis and acute myeloid leukemia.

The EU MAA for Elzonris in BPDCN was originally submitted by TMC Pharma (EU) Limited, although during the procedure the applicant was changed to Stemline Therapeutics.

The applicant requested an accelerated assessment and the CHMP agreed, saying it considered the product "could be of major public health interest" based on results in overall survival with manageable safety. The committee noted that no therapy for BPDCN was considered the standard of care, given the low incidence of the disease and poor durability of responses for most strategies used to date.

The CHMP began reviewing the MAA on 25 January 2019. However, during the assessment it concluded that it was no longer appropriate to pursue accelerated assessment. This was because the nature and complexity of the committee's major quality objections remaining at Day 90 of the evaluation process, and a request for consultation with an EMA scientific advisory group (SAG), no longer fitted into the accelerated procedure. A normal timetable for assessment was therefore implemented.

The Clinical Trial

The main evidence of the efficacy of tagraxofusp in patients with BPDCN was derived from study 0114. This was a Phase I/II non-randomized, open-label, single-arm study consisting of four stages.

Stage 1 was intended to determine the maximum dose of Elzonris that could be tolerated for use in Stages 2 to 4. Stage 2 evaluated patients with any type of BPDCN. Stage 3 (the pivotal cohort) evaluated patients not previously treated for BPDCN (first-line), while Stage 4 evaluated and treated seriously ill patients with BPDCN with no other treatments available.

> *"Contextualisation of the results was not possible" – Elzonris Public Assessment Report, European Medicines Agency*

Efficacy results obtained for the first-line BPDCN population, including patients from all stages, showed an acceptable rate of complete responses (72.4%, median duration not reached) in

patients who achieved bone marrow complete response, according to the PAR.

In addition, a large percentage of patients were bridged to stem cell transplantation, which "represents the best chance to obtain long-term remission and long-term survival," it says. "However, contextualisation of the results was not possible."

Positive results on overall survival (OS) were obtained, but the effect on OS "seemed to be driven by the stem cell transplantation itself more than the effect of tagraxofusp." Moreover, the single-arm trial design and the small sample size "do not allow to conclude on the efficacy profile of tagraxofusp and supportive efficacy data from stage 4 did not bring reassurance as a lower efficacy profile in the target population was shown," the report says.

Conclusions On Clinical Safety

On the safety side, the CHMP said tagraxofusp showed an "unfavorable safety profile with high incidence and high level of seriousness of the events reported, mainly related to hepatotoxicity, capillary leak syndrome (CLS) and hematological abnormalities." Hypersensitivity reactions, fatigue, pyrexia and pain were also frequent.

In particular, the potentially fatal CLS occurred frequently in the applicant-sponsored clinical trials. "Of the 26 CLS events, 9 patients (35%) experienced a grade ≥3 event. 3 of the 26 patients (11%) died from a CLS event."

Although mitigation strategies were implemented in the protocols after the first death due to CLS, it was not shown to be entirely preventable, with more deaths occurring after implementation, according to the PAR. The impacts of other potential risks, such as hepatotoxicity and excessive amounts of antibodies that might lead to severe immunogenicity reactions, "are still unknown."

The entire safety database was based on data from single-arm trials in different diseases, which meant that the causality of adverse events was difficult to demonstrate as they could be due to the drug effect, disease, aging or other factors.

Negative Opinion Issued

In reaching its initial recommendation on Elzonris, the CHMP also took account of the views expressed at a meeting of SAG/Expert Group/Working Party experts. On 23 July 2020, citing limitations in the study design, methodological issues, non-comprehensive efficacy results and uncertainties on the management of the safety profile, the committee issued a negative opinion on tagraxofusp.

Based on its review of data on quality, safety and efficacy for Elzonris as a monotherapy in the treatment of adult patients with BPDCN, the CHMP said it "considers by majority decision that

the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated and therefore recommends the refusal of the granting of the marketing authorization for the above mentioned medicinal product."

> *"It has been shown that tagraxofusp has clinically relevant activity and can be used to bridge patients to SCT" – dissenting CHMP members*

The six CHMP members who disagreed with the negative opinion said that BPDCN was an ultra-rare malignancy with a short survival time, where bridging to stem cell transplantation (STC) was the only way to induce longer term remission. They pointed out that there were no approved therapies, and those that were used in clinical practice were poorly documented.

"It has been shown that tagraxofusp has clinically relevant activity and can be used to bridge patients to SCT," the members said in their submission. "The toxicity profile is non-trivial, but in accordance with the SAG opinion, this is deemed manageable given risk mitigation strategies, and acceptable in the therapeutic context. In summary, B/R has been shown to be positive, though the precise wording of the indication would remain to be specified."

The Re-Examination

The applicant presented a number of reasons to justify a re-examination by the CHMP, addressing four grounds cited by the committee for its negative opinion.

These grounds included "important limitations" of the study, the fact that that the statistical analysis was planned only for cohort 3 of the study involving 13 first-line patients, and that it was not designed to detect a particular magnitude of effect in the BPDCN population as studied.

Another issue addressed by the applicant was the CHMP's assertion that the magnitude of the efficacy response was "highly heterogeneous across the four stages."

On 4 November the EMA convened a SAG and asked the experts to provide their views on the CHMP grounds for refusal, taking account of the applicant's response. "Notwithstanding all the methodological weaknesses, potential selection bias, and need for a more precise understanding of benefits and harms in a wider population, the SAG agreed that benefit has been established and that the toxicity profile of Elzonris is acceptable," according to the PAR.

The CHMP then concluded that, based on the totality of the data, the grounds for re-examination and the advice from the SAG:

- The efficacy of Elzonris as shown in a small single-arm trial (SAT) in this rare, aggressive disorder with no approved treatment alternatives was considered relevant. "The side effect profile is non-trivial but acceptable in the context."

- The benefits in previously untreated patients outweighed the risks. "Benefit in the relapsed or refractory setting has not been established and the indication should therefore be restricted to first-line treatment only."

The CHMP recommended granting of a marketing authorization for Elzonris on 12 November, and the commission formally approved the drug in January 2021.

The committee agreed that the applicant would not be able to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication was so rare. It therefore recommended that the marketing authorization should be granted under "exceptional circumstances."

The applicant was asked to submit results from an observational study (eg, using a registry) of sufficient size and duration, including planned comparative matched analyses using relevant external controls. It was also required to complement these data with a clinical Post-Approval Safety Study (PASS), the design of which was agreed with the agency during review, based on the main safety concerns associated with tagraxofusp.

While the collection of further safety data was awaited, a number of measures were proposed to:

- Restrict the usage of tagraxofusp to patients consistent with those studied in clinical trials who have sufficient cardiac, renal and hepatic function prior to treatment.

- Manage potential adverse reactions that mainly occur at the start of treatment.

- Provide detailed safety information via routine pharmacovigilance.

The CHMP also recommended that an updated risk evaluation on the potential presence of nitrosamine impurities in Elzonris be conducted within six months of the marketing authorization. If a risk of presence of nitrosamines was identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorization or earlier if otherwise justified. If nitrosamine impurities were found to be present, appropriate risk mitigation steps should be

implemented.

The US Approval

By comparison, the US review of Elzonris appears to have gone without any major hitches. The biologics license application (BLA) submission was completed on 25 June 2018, and the FDA granted the product both priority review and breakthrough therapy designation, with a possible goal date of 25 February 2019. In the event the product was approved two months before that, on 21 December 2018.

In contrast to the EU, the product is approved in the US for adults and pediatric patients with either treatment-naïve or previously treated BPDCN.

The US approval was based on the same 0114 trial. The FDA cited the same adverse events as the EMA, including CLS, nausea, fatigue, peripheral edema, pyrexia, and weight increase. It also noted that out of 13 patients who had never been treated for BPDCN, seven patients (54%) achieved no evidence of disease (complete remission/CR) or no evidence of disease with some skin changes not indicative of active disease after treatment with Elzonris.

The US agency observed that out of 15 patients with worsening or resistant BPDCN, two experienced no evidence of disease (CR) or no evidence of disease with some skin changes not indicative of active disease after treatment with Elzonris.

Based on an evaluation of the trial data, the FDA was reassured the product had a positive benefit-risk profile and issued the approval.

The UK Situation

As the EU marketing authorization for Elzonris was granted after the end of the Brexit transition period on 31 December 2020, the product will need to be filed for approval in Great Britain (England, Scotland and Wales) with the UK's Medicines and Healthcare products Regulatory Agency. Under the Northern Ireland Protocol, EU centralized marketing authorizations are valid in Northern Ireland.

Menarini, which bought Stemline in June 2020, told the *Pink Sheet* that a filing by Stemline with the MHRA was planned sometime this year.

Meanwhile the product's evaluation by NICE, which carries out health technology appraisals of products intended for use on the National Health Service in England, has also been delayed.

Following a consultation on the proposed remit and scope of the appraisal in August and September 2019, NICE said in November that year that it would reschedule the appraisal to allow the company to include "important data" in its submission.

"This delay means that this appraisal will be removed from NICE's reporting targets for timeliness," the HTA body said. "In addition, as the delay will mean a NICE recommendation will not be available at the point of marketing authorization, the company accepts that this drug will consequently not be eligible to receive interim CDF [Cancer Drugs Fund] funding from the date of marketing authorization as no NICE recommendation will be made at that point."

At the time, NICE said it expected the appraisal to begin during early May 2020. However, on 30 September 2020 it said that "following on from advice received from the company the timelines for this appraisal have been revised. We now anticipate that the Technical Engagement stage of this appraisal will begin during the first half of February 2021 and we will write to stakeholders then about how they can contribute to this."

But the process has now hit a further delay. On 10 March 2021, NICE said the company had asked it to pause the appraisal because it was "in the process of merging with another company." As a result, NICE said, "technical engagement will not take place at this time and the appraisal committee meeting will not be in May 2021 as previously scheduled."

On 14 May, Menarini told the Pink Sheet that the integration with Stemline was still "ongoing, including also evaluation of the optimal way for patients to access Elzonris in the UK." It said a "NICE re-submission plan is within this scope and updates can be followed through the NICE website."

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