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

The EU Rejected The Drug A Year After Its US Approval

by Neena Brizmohun

Not everyone reviewing Daiichi Sankyo's EU marketing application for Turalio agreed that the potential tenosynovial giant cell tumor treatment shouldn't be approved.

Worries about unpredictable, potentially life-threatening effects of an orphan drug for treating a non-fatal condition. Missing data and uncertainty over the efficacy of the product even though it met its primary endpoint in a Phase III trial. A decision in the EU that contrasts sharply with the viewpoint in the US.

The statements all relate to Turalio (pexidartinib), Daiichi Sankyo's drug for tenosynovial giant cell tumor (TGCT), and the European Medicines Agency's recommendation that led to the product being refused pan-EU marketing authorization last October. The product had been approved in the US more than a year before.

The EMA advised the European Commission to reject the marketing authorization application (MAA) for Turalio in June 2020, around a year after the drug became the first medicine to be approved in the US for treating the non-cancerous but chronically debilitating condition of TGCT. (See chart below for the EU regulatory timeline relating to Turalio.)

EU Drug Review Profiles

This is the latest in the *Pink Sheet* series of EU drug review profiles. Previously published profiles can be accessed via the following links:

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In a brief statement at the time, the EMA said it did not believe the benefits of the drug outweighed the risks, which included potentially life-threatening effects on the liver.

Much more information on how the agency's human medicines committee, the CHMP, reached its decision is available in the 144-page European *public assessment report* for Turalio.

- *Piqray - What EU Regulators Saw And What They Wanted*
- *EU Indication Restricted For Novartis's Newly Approved Piqray*
- *Real World Data Failed To Impress Kaftrio's European Reviewers*

The decision was not unanimous. Six of the 30 plus members of the CHMP voted in favor of marketing approval.

The report also shows that Daiichi had agreed to restrict Turalio's indication to improve its chances of approval. In addition, the report explains why the EMA refused to fast-track the MAA.

> *"Based on the CHMP's opinion and the European Commission decision, pexidartinib will not be commercially available in Europe for the treatment of patients with TGCT." – Daiichi Sankyo*

Unusually, Daiichi did not ask the CHMP to re-examine its negative opinion. Companies often exercise their right to appeal and this sometimes, though rarely, results in the opinion being reversed in their favor.

It is not clear whether the company will pursue EU marketing approval for Turalio for TGCT at a later date. Daiichi told the *Pink Sheet* that "based on the CHMP's opinion and the European Commission decision, pexidartinib will not be commercially available in Europe for the treatment of patients with TGCT." It added that it remained "committed to the availability of pexidartinib for those currently in a clinical trial or compassionate use program."

Meanwhile, Daiichi stands by the safety and effectiveness of its drug and is pressing on with its global development of Turalio for TGCT. Studies are under way in Japan, Taiwan and China. Turalio is not yet approved for use in any country outside of the US.

Limited Options

TGCT – also referred to as giant cell tumor of the tendon sheath or pigmented villonodular synovitis – is a rare, slowly growing tumor that affects the synovium-lined joints, bursae and tendon sheaths. It results in swelling, pain, stiffness and reduced mobility in the affected joint or limb.

Surgery to remove the tumor has traditionally been the standard treatment for the condition.

While surgery usually produces good outcomes in patients with localized-type TGCT, it might not be suitable for patients with a recurrent, difficult-to-treat, or diffuse form of the condition where the tumor can wrap around bone, tendons, ligaments and other parts of the joint. In these cases, the tumor may be difficult to remove and/or may not be amenable to improvement with surgery. Multiple surgeries for more severe cases can lead to significant joint damage, debilitating functional impairments, reduced quality of life and, in very rare cases, amputation.

Different Agencies & Different Conclusions

Turalio is an oral small molecule that inhibits CSF-1R (colony stimulating factor-1 receptor), which is a primary growth driver of abnormal cells in the synovium that cause TGCT.

It was approved by the US Food and Drug Administration for use in certain patients with TGCT on 2 August 2019, albeit with a string of safety requirements including a boxed warning about the risk of serious and potentially fatal liver injury. Daiichi must also follow patients using the drug for at least a decade to determine whether there is a long-term risk of liver toxicity. *(Also see "Daiichi Must Follow Turalio Patients For 10 Years To Assess Liver Safety*" - Pink Sheet, 8 Aug, 2019.)

As Daiichi told the *Pink Sheet*, regulatory agencies sometimes reach different conclusions on the benefit-risk assessment of drugs, based on the same set of data.

What The CHMP Considered

The EU MAA was based on the company's pivotal, Phase III, ENLIVEN trial, a global, multicenter, 120-patient study in which Turalio met its primary endpoint, showing statistically significant improvement in overall response rate (ORR) compared with placebo. The ORR was 39% at week 25 compared with no response in patients who received placebo.

However, ENLIVEN also found that the drug was linked to the risk of serious hepatotoxicity.

As of January 2018, nine patients had been identified with mixed/cholestatic liver injury across the Turalio development program.

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In its review of the MAA, the CHMP also considered additional long-term follow-up data. In addition, it looked at US post-marketing safety data that had been collected as of 22 May 2020. Here, there were reports of six cases of serious hepatotoxicity among 125 registered TGCT patients treated with Turalio in the US Risk Evaluation and Mitigation Strategy (REMS) program.

As noted by the six CHMP members who voted in favor of approving Turalio, post-marketing data from US had not revealed any new fatal cases.

Daiichi told the *Pink Sheet* that "based on our post-marketing experience in the US the overall benefit/risk assessment remains positive."

No Accelerated Assessment

The CHMP started reviewing the MAA for Turalio on 28 March 2019, according to the public assessment report, which was published in December 2020.

The drug was granted EU orphan drug status in March 2015, and the EMA had provisionally classified pexidartinib as new active substance.

Before submitting its MAA, Daiichi had asked the CHMP to review the application under the EMA's accelerated assessment mechanism. The CHMP said no, explaining that it did not consider Turalio to be of major public health interest. "This [decision] was based on the view that the strength of evidence was not convincing to support the claim that the product will fulfil unmet needs, considering that the tumor growth is slow and that its treatment needs to be well tolerated long-term," the assessment report said.

The EMA's accelerated assessment mechanism is reserved for drugs of potential major public health interest, particularly from the point of view of therapeutic innovation. In practical terms, fast-track review can cut a few months off the approximately 12 months it generally takes to review an application under standard EU centralized drug evaluation procedure timelines.

In contrast, US regulators granted Turalio priority review, a status under which the FDA aims to take action on a marketing application within six months compared with 10 months under standard review. Turalio was approved one day before its 3 August assessment goal. The product also received a US breakthrough therapy designation.

> ***"The strength of evidence was not convincing to support the claim that the product will fulfil unmet needs." – Turalio European public***

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assessment report

One of the ways in which Daiichi tried to address the CHMP's efficacy and safety concerns was by restricting Turalio's indication to cover a TGCT population with undisputable unmet medical need and for whom benefits relative to the risk of hepatotoxicity from the drug would be favorable.

The original indication sought was similar to that for which the drug is approved in the US – for treating adult patients with symptomatic TGCT that is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

The company told the *Pink Sheet* that it "worked very closely with the CHMP to identify a population that might have more heightened unmet medical need and derive more benefit."

The revised and restricted indication covered the use of Turalio as monotherapy for the treatment of adult patients with TGCT, which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability.

"[We] worked very closely with the CHMP to identify a population that might have more heightened unmet medical need and derive more benefit." – Daiichi Sankyo

This was not enough to allay the CHMP's concerns.

On 25 June 2020, the committee considered by a majority decision that the safety and efficacy of Turalio had not been sufficiently demonstrated and that the benefits of the drug did not outweigh the risks. The commission formalized the decision on 28 October when it published an implementing decision refusing the MAA.

CHMP decisions are usually adopted by consensus. This case was unusual in that several members of the committee officially disagreed with the overall decision, which was by majority. The reasoning for the divergent decisions is included in annexes to the European public

assessment report. The six dissenting reviewers who were in favor of Turalio being approved were from Denmark, Spain, Latvia, Malta, Lithuania, and Iceland.

Hepatotoxicity A Crucial Concern

In reaching its verdict, the CHMP had asked Daiichi to address the questions and concerns the panel had about the drug several times during the MAA review cycle. It sought advice from oncology experts from its Scientific Advisory Group. It also invited Daiichi to appear before it to address outstanding issues it still had towards the end of the review.

In the end, most of the committee members were concerned that although the main study found that tumors shrank in patients treated with Turalio, there was only a small improvement in symptoms such as pain and the ability to use the joint. It was also not clear how long this effect would last.

"The single pivotal study confirmed activity in terms of tumour shrinkage but did not establish that the activity was associated with relevant clinical benefit," the CHMP said in the public assessment report. "The measured clinical effects are lacking validity and relevance, and are uncertain due to missing data," it added.

Among the missing data mentioned in the report are "valid PRO [patient-reported outcome] data as a consequence of subject noncompliance and technical issues."

The hepatic toxicity of Turalio remained a "crucial concern" for the CHMP, which was also worried that a review of the hepatotoxicity cases did not suggest predictive factors.

> *"The mixed or cholestatic hepatotoxicity related to pexidartinib may be fatal and is likely not manageable." – Turalio European public assessment report*

The CHMP was troubled by the "potential mortality (or need for organ replacement) from this adverse reaction and the unpredictability of this adverse reaction, in the context of a disease that is chronically debilitating but does not reduce life expectancy."

"The mixed or cholestatic hepatotoxicity related to pexidartinib may be fatal and is likely not manageable because the mechanism of liver toxicity in animals and in humans is unknown and its occurrence cannot be predicted," the CHMP said. "Intensive monitoring of liver enzymes may

partly mitigate the severity and possibly the risk of severe hepatotoxicity, but even with monitoring the risk remains poorly predictable."

Daiichi had proposed a number of risk mitigation measures, but the CHMP said it was uncertain whether they would be able to effectively reduce the risk and severity of hepatotoxicity.

The Divergent Votes

The CHMP members who voted in favor of approving Turalio were of the opinion that "taken together, efficacy has been established and safety is well-characterized and could be acceptable in the proposed patient population."

They argued that the drug had met its primary endpoint in the Phase III study and that subgroup analyses had shown consistent favorable effects over most subgroups including disease location, joint size and type of TGCT (diffuse or localized). "Importantly, in an analysis across studies, at the latest data cut-off of May 2019 with continued pexidartinib treatment, the best objective response rate increased to 61.5%."

While they agreed that hepatotoxicity was the most important safety risk with the drug, they said that post-marketing data from US had not revealed any new fatal cases.

Four Months For Commission Decision

The European Commission has the final say on whether a product gets approved or not. In this case, it agreed – as it usually does – with the CHMP's recommendation.

Unusually, the commission took four months to issue its decision on Turalio; it is meant to do so within 67 calendar days of the CHMP adopting its decision. The commission told the *Pink Sheet*: "The adoption procedure was put on hold, as the Agency (EMA) had informed the Commission that the company would request a re-examination of the negative scientific assessment. However, in the end the company opted against such request. Nevertheless, it meant that we did not proceed until it was clear whether the company would exercise this legal right it has."

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